RISK FACTORS FOR CONGENITAL HEART DEFECTS IN SAUDI ARABIAN INFANTS

Thesis presented to the Faculty of Medicine

for the degree of Doctor of Philosophy

Amy Leona Sandridge

London School of Hygiene and Tropical Medicine

University of London

September 2006

Declaration of own work

I have read and understood the School's definition of plagiarism and cheating given in the Research Degrees Handbook. I declare that this thesis is my own work, and that I have acknowledged all results and quotations from the published or unpublished work of other people.

Signed: [redacted] Date: December 31, 2006

Full Name: Amy Leona Sandridge

Acknowledgements

I would like to thank the women who participated in the study. It was inspiring to see the courage of the case mothers with their very sick, beloved babies and the altruism of the control mothers: "there for the grace of God".

I thank the Research Centre of King Faisal Specialist Hospital, the Research Advisory Committee and especially, Sultan Al Sedairy, who understood that this study, with God's help, gave more to Saudi Arabia than it took. Thank you for your leadership.

Edward B. De Vol, Chairman, Biostatistics, Epidemiology and Scientific Computing, you are an excellent teacher, from whom I learned so much about statistics, needless to say, but also about Islam and getting along harmoniously.

I thank King Abdulaziz City for Science and Technology for funding the study and for being very polite in waiting patiently for the final report.

My friend and colleague, Abeer Al Harbi, acted as the intermediary between the CHD Registry and me. Ibrahim Al Khalifa, Riyadh Armed Forces Hospital was very gracious to allow the controls to be obtained from Family and Community Medicine. It was a pleasure to work with my co-investigators, Mansour Al Jufan, Wesam Kurdi, Hoda Kattan and Abdullah Al Rowais. The project benefited from the expertise of the BESC Data Management Section, especially, Abdullah Al Kurnas, my brother.

I am very grateful to my supervisor, Pat Doyle. I think we both learned that the adage "two countries separated by a common language" is definitely over-rated. Pat never asked for anything unreasonable, it was very brave of her to take on an old scarred epidemiologist like myself, and she gave excellent advice. She was right about so much – I see that now. Everything she predicted came true! I was very fortunate to do this "training exercise" with her.

Gregory Knell provided twelfth hour editorial advice. My parents, Jane Tollefson and Leonard Graham, sent me to good schools, had lots of books in the house and encouraged

my high aspirations. I thank two of my mentors for sending me up the academic ladder to this pinnacle I have now achieved: Jane McCusker, formerly of the University of Massachusetts and Mark Gould, Haverford College. You were right Mark, so easy to get a PhD!

At LSHTM, I have to say that the members of the EPH Computing Service run a class act – always friendly, most always in their office (that' night and day) and always able to solve the problem. And thank you Sue Teoh. From 2000 onwards, you have helped me leap the administrative, logistic and resource hurdles.

My darling daughters, Michael and Isis, were so good to me throughout these years. I hope I can return the favour one day.

And finally, thank you Bill. You encouraged me to start the process, you paid the fees, you bought software and hardware for me and you looked after the children. On top of which you wrote me some FORTRAN and talked me through regression not once but *three* times. So now, I guess we are two doctors?

Amy L. Sandridge
Doha, Qatar
sandridge@sandmews.demon.co.uk
October, 2006

Revised: December, 2006

Abstract

Two studies were undertaken. Firstly, congenital heart defect (CHD) data from the Saudi Arabian Congenital Heart Defects registry (CHD registry) were compared to data published by the Baltimore-Washington Infant Survey (BWIS) group and the European Surveillance of Congenital Anomalies registry (EUROCAT). Distributions of CHD diagnoses within the Saudi Arabian dataset (Riyadh region and Saudi Arabia as a whole) were similar to those from these more comprehensive efforts, providing evidence for the completeness and accuracy of the CHD registry, for Riyadh region in particular.

Secondly, an unmatched case-control study of risk factors for all structural congenital heart defects in children resident in Riyadh, Saudi Arabia was undertaken. The primary exposure of interest was consanguinity up to and including third cousins. Incident cases were identified from the CHD Registry from June 1, 2002 to December 31, 2004. Controls were obtained from the Well Baby Clinic, Riyadh Armed Forces (Military) Hospital. Using a detailed and reverse translated questionnaire, a face to face interview was conducted with 235 case and 247 control mothers by research assistants fluent in the local dialect. Mothers were asked to consider their exposure to risk factors within the period of 3 months prior to and 3 months post conception. Consanguinity was collected by phylogram method. The majority of mothers were interviewed when the infant was less than one year of age. Analyses were conducted using four different case groups: all cases, isolated cardiac cases, and embryological earliest and latest cases.

Twenty five percent of cases and controls were ***first cousins or closer***. Sixteen percent of cases versus 13 percent of controls were ***first cousins once removed*** or equivalent and 12 percent of both cases and controls were ***second or third cousins***. Consanguinity was not found to increase the risk of CHD in this population. The adjusted odds ratio for all cases was 1.0 (CI_{95}=0.7-1.7) and for isolated cardiac cases it was 1.2 (CI_{95}=0.7-2.0). Statistically significant associations were found for other exposures such as previous pregnancy losses, maternal age, multiplicity, maternal use of hair dyes and pesticides sprayed in the house, confirming findings from previous studies. It is unlikely that the findings for consanguinity can be explained by misclassification of exposure or, in the analysis of all cases, low statistical power.

Funding Source

This research was funded in part by a grant from the King Abdulaziz City for Science and Technology (KACST) and was supported by the Research Centre of King Faisal Specialist Hospital (KFSH&RC). This study received approval from the Ethics Committees of KACST, KFSH&RC, London School of Hygiene and Tropical Medicine and the Riyadh Armed Forces (Military) Hospital.

Table of Contents

List of Tables and Figures

Tables

Figures

Appendices:

Pocket:

Questionnaire with supplemental sheets

Pedigree paper: Sandridge AL (2000). Collecting pedigree information in an epidemiological context. Statistica – Anno LX – 2000, 4:745-751.

Abbreviations

BMI	Body mass index
BWIS	Baltimore Washington Infant Survey
CHD	Congenital Heart Defects
CPP	Collaborative Perinatal Project
DGS	DiGeorge syndrome
DS	Down syndrome
ECM	Extra-cardiac malformations
EPC	European Paediatric Cardiac System for coding CHD
EUROCAT	European Surveillance of Congenital Anomalies registry
GD	Gestational diabetes
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
IDDM	Insulin dependent diabetes
KFSH&RC	King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia
KSA	Kingdom of Saudi Arabia
MACDP	Metropolitan Atlanta Congenital Defects Program
NIDDM	Non-insulin dependent diabetes
PHCC	Primary Health Care Centre
PSCC	Prince Sultan Cardiac Centre

Congenital Heart Defect Abbreviations

ASD II	Atrial septal defect, secundum
AV	Aortic valve (as in AV stenosis)
AVSD	Atrioventricular septal defect
BAV	Bicuspid aortic valve
COA	Coarctation of the arota
DCRV	Double chambered right ventricle
DILV	Double inlet left ventricle
HLHS	Hypoplastic left-heart syndrome
HRHS	Hypoplastic right-heart syndrome
IAA	Interruption of aortic arch
PA	Pulmonary artery (as in PA stenosis or PA atresia)
PAPVR	Partial anomalous pulmonary venous return
PDA	Patent arterial duct or Patent ductus arteriosus
PV	Pulmonary valve (as in PV atresia or PV stenosis)
TAPVR	Total anomalous pulmonary venous return
TGA	Transposition of the great arteries
TOF	Tetralogy of Fallot
VSD	Ventricular septal defect

Glossary

Abaya - Arabic, a long outer cloak, worn by women. Often it is black or in a dark colour.

Coefficient of inbreeding - a measure of the degree of inbreeding in a population expressed as the expected proportion of homozygous loci in an individual at which both alleles can be traced back to the same ancestor called also *inbreeding coefficient*

DiGeorge syndrome - a congenital immunodeficiency characterized by abnormal facies; CHD (conotruncal abnormalities); hypoparathyroidism; cognitive, behavioral, and psychiatric problems; and increased susceptibility to infections.

Fuṣ'há (Arabic: فصحى pronounced "Fuṣ-Ḥá") - a collective term referring to the standard varieties of the Arabic language, as opposed to vernacular varieties of Arabic.

Heterotaxia – abnormal arrangement of organs or parts of the body in relation to one another.

Hiy' - Arabic, neighbourhood or local administrative area.

Homocysteine - a sulfur-containing amino acid. As a consequence of the biochemical reactions in which homocysteine is involved, deficiencies of the vitamins folic acid, pyridoxine (B_6), or B_{12} can lead to high homocysteine levels.

Homocysteinemia - an elevation of homocysteine level in blood. This condition has also been referred to as homocyst(e)inemia to reflect metabolites that may accumulate. It should not be confused with "homocystinuria" which is a disorder of methionine metabolism, leading to an abnormal accumulation of homocysteine and its metabolites in blood and urine where they are normally not found in appreciable quantities. A mild elevation of plasma homocysteine may exist without homocystinuria.

Hydraminos - an excess of amniotic flluid called also polyhydramnios.

Innominate artery -an artery that arises from the arch of the aorta and divides into the right subclavian and right carotid arteries. Also called brachiocephalic artery, brachiocephalic trunk.

Ivemark syndrome - characterized by CHD, the absence of the spleen and heterotaxia.

Marfan syndrome – an inherited connective tissue disorder which affects many structures, including the skeleton, lungs, eyes, heart and blood vessels with an estimated incidence between 1 in 5,000 and 1in 10,000 live births. They have a high incidence of heart problems.

McKusick codes - developed by Virginia McKusick and used to code birth defects.

Noonan syndrome – a genetic disorder that causes abnormal development of multiple parts of the body. Frequently-seen abnormalities include webbing of the neck, changes in the sternum (usually a sunken chest), facial abnormalities, and CHD, especially pulmonary stenosis. Noonan syndrome can be inherited in an autosomal dominant manner although it can also appear sporadically as a presumably new mutation. It affects at least 1 in 2,500 children.

Riyadh CHD Register – in this thesis, those 235 cases presented as the case control study

Saudi Arabian CHD Register – in this study, some of the data presented in Table 4.7 and Appendix 4C including all relevant cases registered by the Saudi Arabian CHD registered housed at KFSH&RC.

Shari'a – (Arabic: شريعة pronounced "Sha-rī'ah") refers to the body of Islamic law. The term means "way" or "path"; it is the legal framework within which public and some private aspects of life are regulated for those living in a legal system based on Muslim principles of jurisprudence. *Shari'a* law is based on the Qur'an and the life and words of Prophet Mohammed (the Sunnah).

Williams syndrome – estimated to occur in 1/20,000 births this genetic disorder causes medical and developmental problems. Most children with Williams syndrome are described as having similar facial features – often described as 'elvin'. Blue and green-eyed children can have a prominent "starburst" or white lacy pattern on their iris. These children often have a CHD, specifically supravalvular aortic stenosis.

Conventions

Many of the congenital heart defect names and the categories that are used for them are cumbersome. Where they could not be abbreviated and where in the text if, to the author, it was felt as though they were hampering the style then they were set off in italics to identify them. This principle holds for variable names as well. For the most part, in Chapter 1, Section 1.3 this was not felt to be necessary and therefore it was not performed. Foreign words are set off by italics. Quotes were only used to cite or as, on page 23.

CHAPTER 1 Introduction

This thesis reports a case control study designed and conducted between September 2000 and December 2004 in Riyadh, Saudi Arabia. The aim of the investigation was to explore risk factors for congenital heart defects in a population of Saudi Arabian infants.

1.1 Background of Saudi Arabia and its people

1.1.1 Geography

The Kingdom of Saudi Arabia (KSA) occupies the majority of a peninsula directly to the east of Africa in the Indian Ocean (Figure 1). It borders nine other Arabic countries including the causeway link to Bahrain. Its primary exports are petrochemical.

Figure 1.1: Map of the Kingdom of Saudi Arabia showing location of Riyadh, geographical position of Saudi Arabia in the Middle East

Riyadh

An arid, inland city, Riyadh rests on the Eastern edge of a plateau of altitude 2300 feet which slopes upwards towards the west. It is the capital and largest city and in the last 10-15 years has experienced tremendous migration of Saudi Arabians from the rural areas. A study conducted by the Higher Authority for the Development of Riyadh reported in 2005 that the growth rate between 1411-1417 *Hejira* (corresponding to 1990-1996 *Gregorian*)

was 8 percent. In the 1960's the population of Riyadh is estimated to have been 50,000 but now it has grown to 4.3 million. The ratio of Saudi Arabians to temporary immigrants who are brought in on all levels for industry is estimated to be 4.8:1 (CIA, 2006).

1.1.2 Political history

Saudi Arabia is a monarchy. The constitution is the religious teachings of the Holy Islamic *Shari'a*. There is no separation between mosque and state. It was established as a nation in 1750 by a regional ruler, Muhammad bin Saud and an Islamic cleric and reformer, Muhammad Abd Al-Wahhab. Over the next 150 years there were external conflicts with Egypt and the Ottoman Empire and internal conflicts between various Arabian families for control of the peninsula. By 1902 however Abdulaziz Al Saud had captured Riyadh and began a 30 year effort to unify the Arabian Peninsula. In his struggles he united the two geographical areas, the Najd (the central region) and the Hijaz (Jeddah, Mecca and Medina). In 1927 the United Kingdom recognized the independence of Abdul Aziz's realm as the Kingdom of Hijaz and Najd. In 1932 the name was changed to the Kingdom of Saudi Arabia (Nyrop, 1977).

Until the 1960's most of the population was nomadic or semi-nomadic (Bedouin) although there have always been urbanites residing in the villages, towns and cities. Since the development of the petrochemical industry and government initiatives the majority of the population has become urbanized. Nonetheless, many consider themselves ethnically Bedouin (Nyrop, 1977).

Saudi Arabians belong to tribes. Only the descendents of some male slaves or other unusual cases, like outlaws or unclaimed orphans, do not have a tribe. Some tribes are primarily Bedouin while others are Urban and some are mixed. Tribes are patrilineal in nature. There has not been a comprehensive recent attempt to document the tribes of KSA although the British Admiralty produced some detailed maps in 1946 (Naval Intelligence Division, 1946). Tribe is relevant to this thesis as it may impact on risk factors such as consanguinity, ethnicity and socio-economic status.

1.1.3 Culture

Presently, all Saudi Arabians follow Islam which in its ideal form, is a way of life rather than a religion. Some Islamic traditions are relevant to this thesis and will be described below:

Figure 1.2: Map of the Kingdom of Saudi Arabia showing roads and towns

Time

In KSA, the *Hejira* calendar is used (Muharram to Dhu Al Hijja) instead of the *Gregorian* (January to December). The current year is 1427 *Hejira* which corresponds to 2006/07 *Gregorian*. The 354 day *Hejira* year has 12 months, reckoned lunarly. Converting from Hejira to Gregorian and vice versa is possible by hand or by using printed calendars but software programs are generally used for precision and speed.

Ramadan and other religious, non-Ramadan, fasting days

One of the five pillars of Islamic faith is the observation of Ramadan, the 9th month of the *Hejira* year, with fasting. This is relevant to this thesis because one of the hypotheses tested is that pregnant women with a high background prevalence of diabetes may be more at risk to the wide variations in glycaemic control which occur during Ramadan.

During the 30 days of Ramadan adult Muslims abstain from all food and drink from dawn to dusk. Muslims look forward to Ramadan as a month of religious unity and spiritual renewal. Its purpose is to become more aware of God, of the poor and to develop discipline and self-restraint. Fasting is considered an honourable obligation. On the other hand, if a Muslim residing in Saudi Arabia did not fast they might be reluctant to admit it, as it is a socially mediated mandatory requirement of the religion.

Although the definition of "ill" would be self-defined, the ill as well as menstruating women are exempted. The observance is so revered that patients with major chronic diseases have been reported to endanger themselves rather than not participate (Aslam and Wilson 1992). For pregnant women fasting is optional but if it is not accomplished each day missed must be made up before the next Ramadan. Therefore, many pregnant women choose to fast. The woman herself decides whether she is able. Credit is lost for the entire day if the fast is broken prematurely, irrespective of reason.

The Ramadan day begins before sunrise with a heavy meal. At sunset the fast is broken traditionally with Arabic coffee, dates and some laban (similar to yoghurt). A second meal is eaten after sunset prayers. For some, Ramadan nights are 30 Christmas Day-like feasts in a row. Thirty nights of feasting with tremendous caloric intakes interspersed with thirty days of "famine". Of course, many have a more Spartan month where the variances in blood sugar from hypoglycaemic to hyperglycaemic levels will not be as dramatic. There are optional days of religious, non-Ramadan, fasting as well. Some Muslims daylight fast the thirteenth, fourteenth and fifteenth of the month as well as the Monday and the Thursday of each week. There are also 6 days in Shawwal (the tenth month), the first day of Ashurah (in Muharram, the first month) and the first day of Arafah (in Dhu al Hijjah, the twelfth month). Some of these additional fasting days may be associated with the more conservative Wahabi/Salafist sect of Sunni Islam and others are associated with Shi'a Islam (Wright, 2006; Sharon Peterson, Director, Palm Grove Bilingual School, Riyadh, Saudi Arabia, unpublished communication, 2005).

Inward migrations

Throughout history, the Arabian Peninsula has experienced waves of migrations bringing new blood into the population. The spice route cut north from the western most tip of the peninsula, to the Sinai Peninsula bringing settlers and exposure to outside cultures. On the

eastern coast, trade with the Persians is well documented throughout the last 2000 years. More recently, the Gulf Cooperation Council established by Saudi Arabia in 1981 reflects the close ties between Saudi and the other 5 members. Branches of Saudi Arabian tribes live across the peninsula and up into the Levant (Syria, Jordan, Lebanon) (Nyrop, 1984).

Marriage

Reproduction and production are fundamental components of a sustainable society. Traditionally, societies have controlled reproduction through the construction of marriage. Marital mores, among other things, govern who may marry whom in terms of sex, age, and biological relationship. In ancient Greek and Egyptian society, sisters could marry brothers. In Jewish and Hindu society uncles have married nieces. In Saudi Arabian society today, as in Europe and 19 states of the USA, the offspring of siblings can marry.

Endogamy is marrying within one's own group. Exogamy is marrying outside of one's own group. In tribal societies the "one's own" is usually within the tribe and may be further restricted to matrilateral or patrilateral marriage. "Outside one's group" would be outside the tribe. In Saudi Arabia a preference for patrilateral marriage has been noticed, but there is also matrilateral marriage and combinations thereof (e.g. a matrilateral first cousin who is simultaneously a patrilateral second cousin).

Juma'a

In Arabic, *juma'a* means "tribe". If a person marries someone from his or her *juma'a* then the couple is assumed to be distantly related but the exact connection is not known. Therefore, it is possible that there is no relationship at all. The concept is similar to that of *bradari* from the literature of Pakistani consanguinity (Bittles, Grant, Shami, 1993). Generally people of the same tribe will share the same last name although there are some tribes that are so large that there are clans with different last names within them.

The religious roots of marriage in Islam

Islam strongly advocates marriage. Unlike Christianity and Buddhism, chastity for religious reasons is not recognized. Marriage is a religious duty and considered moral protection against *fitna* (anarchy and chaos). Within traditional Islam the family is considered the fundamental unit of society and marriages are foremost strategic family

alliances. Through Prophet Mohammed it was revealed for Muslim men who they could not marry:

> Prohibited to you (for marriage) are: your mothers, daughters, sisters; father's sisters, mother's sisters; brother's daughters, sister's daughters; foster-mothers (who breast-fed you), foster-sisters (who breast-fed from the same woman as you); your wives' mothers; your step-daughters under your guardianship, born of your wives with whom you have consummated marriage, no prohibition if ye have not consummated; (those who have been) wives of your sons proceeding from your loins; and two sisters in wedlock at one and the same time, except for what is past; for Allah is Oft-Forgiving, Most Merciful. (Chapter 4, Sura' 23, the Qur'an)

As first cousin marriage was prevalent before Islam it continued afterwards although from a religious point of view, Islam neither encourages nor discourages the practice. Instead, Islam asks its followers to execute a thoughtful choice of a marital partner. The biological technicalities of human sexuality and reproduction are well understood within this formerly herding society. Parents are responsible for the genes transmitted to offspring. Therefore, if it were proven that consanguinity contributed significantly to adverse outcomes the practice would surely wane.

Arabic language

Arabic is a language that is complicated by three factors. First of all, religious scholars claim that the language of the Qur'an and the language that is spoken are similar. However, others believe that there are three types of Arabic. There is classical Arabic in which the Qur'an is written. It is sacred, inviolable and cannot be changed. The second is *fuṣ'há* and it is used in the newspapers and formal situations. The third is the local spoken dialect. In comparison with English, the classical Arabic is comparable to Chaucer (except for the addition of the solemnity of religious connotations); the *fuṣ'há* is comparable to the Queen's English and should be known and spoken by all educated persons; and the dialect is comparable to Dundonian or Cockney. While there is the recognized dialect of "Gulf Arabic" which some consider at the third level, in truth there are an unknown number of sub-dialects which may be specific to individual tribes or parts of the city. Possibly this phenomenon is exacerbated among some Saudi Arabian women because they may lead lives sheltered from non-family members and even from television. Some women of this study were so sheltered that one of the questions, "In what neighbourhood (*hiy'*) of the city do you live?" was difficult for them to answer because they did not know the name of the administrative area.

A second complication has to do with the written word. Although Saudi Arabians speak *fuṣ'há* or dialect Arabic, only *fuṣ'há* and classical are written. The questionnaire was written in *fuṣ'há*. It is impossible to write in dialect because the words have not been assigned a spelling. To some, because of the language's close relationship to the Qu'ran it would be blasphemous to misspell words that were revealed by God therefore control of writing is strictly maintained among Saudi Arabians.

Thirdly, because *fuṣ'há* grammar is difficult and exacting, even university educated Saudi Arabians, such as my research assistants, do not read or write as a hobby. It is not unusual to complete an Arabic secondary school without having read one entire Arabic novel (Sharon Peterson, Director, Palm Grove Bilingual School, Riyadh, Saudi Arabia, unpublished communication, 2005). My research assistant confessed to me that she had never written a letter in Arabic instead employing a scribe when necessary to write on her behalf. In sum, the distance between these three levels of Arabic is considered to be *comparable to* but *further than* the distance between the three English examples.

1.2 The Saudi Arabian health care system

Saudi Arabia is a modern paradox: a wealthy-developing nation. On the one hand the country has the largest proven oil reserves in the world. On the other hand they have an infant mortality rate of 14 per 1000 compared to Costa Rica's of 10 per 1000 or Jamaica's of 13 per 1000. The 2003 estimated literacy rate in Saudi Arabia was 71 percent for females and 85 percent for males, compared to 99 percent in the United Kingdom. A comparison of gross domestic product per capita reveals that Saudi Arabia is at $12,800 and Sri Lanka at $4,300 (CIA, 2006). The UK has a GDP of $30,300. As late as 1996 nine percent of births occurred outside a hospital or health facility (Khoja, Farid, 1996). A more recent report found that in remote areas the number could be as high as 24 percent (Khattab, 2000). There is large scale unemployment in Saudi Arabia and their economy is dependent on foreign workers for basic services such as health care, transportation and for the petrochemical industry. In many ways, their economic and political systems have more in common with feudalism rather than with the modern industrial nations (Nyrop, 1977).

Vital statistics for births and deaths are not routinely available even though birth registration is mandatory. Despite the fact that a census was conducted in 2004 the results

have yet to be released forcing reliance on estimates from the 1992 census. Death registration is not required. Autopsies are forbidden under *Shari'a* law and only performed in extremely unusual circumstances.

Despite the hurdles of a developing infrastructure Saudi Arabia has a robust national health care system. This system, the Ministry of Health, provides free medical care for nationals through the Primary Health Care Centres (PHCC). The PHCC refer cases as required to tertiary care facilities such as the JCIA[1] King Faisal Specialist Hospital and Research Centre (KFSH&RC). KFSH&RC is reputed to be the best health care facility in the Middle East outside of Israel.

Generally, the PHCC refers suspected cases of CHD to the KFSH&RC or to the Prince Sultan Cardiac Centre (PSCC) at the Military Hospital before birth or as soon as diagnosis is made. Foetal echocardiography is routinely performed between the 12th and 15th weeks and the 18th and 22nd weeks of gestation (W. Kurdi, Chair, Department of Obstetrics and Gynecology, KFSH&RC, personal communication, 2004). Of course, most of CHD is not detected pre-natally (Stumpflen et al., 1996). It is estimated that 50 percent of all cases of CHD are referred to each of these two tertiary care centres in Riyadh. The estimated prevalence of CHD in Riyadh in 1992 was 2.8 per 1000 for the one year old population (Sandridge, 2002).

The CHD Registry

To further develop the health care system the Ministry of Health requested that registries be formed to track the prevalence of diseases. The Congenital Heart Defects Registry was established in January 1998 with the goal of becoming a national registry by 2006. ALS designed and supervised the running of the CHD Registry from 1998 to 2002 (Mitri et al., 2002; Black and Sandridge, 2001; Molina and Sandridge, 2000, Molina and Sandridge, 1998). KFSH&RC was the first hospital to begin CHD registration and the PSCC was the second. Inclusion of these two hospitals is estimated to provide registration for over 95 percent of the cases of CHD born in the Riyadh region making this a regional based registry rather than a hospital based effort.

[1] Joint Commission International Accredited

1.3 Description of the normal and abnormal heart

The epidemiology of congenital heart defects requires caveats. The first is that it is not one disease but a spectrum of conditions which are often defined as any structural abnormality of the heart.

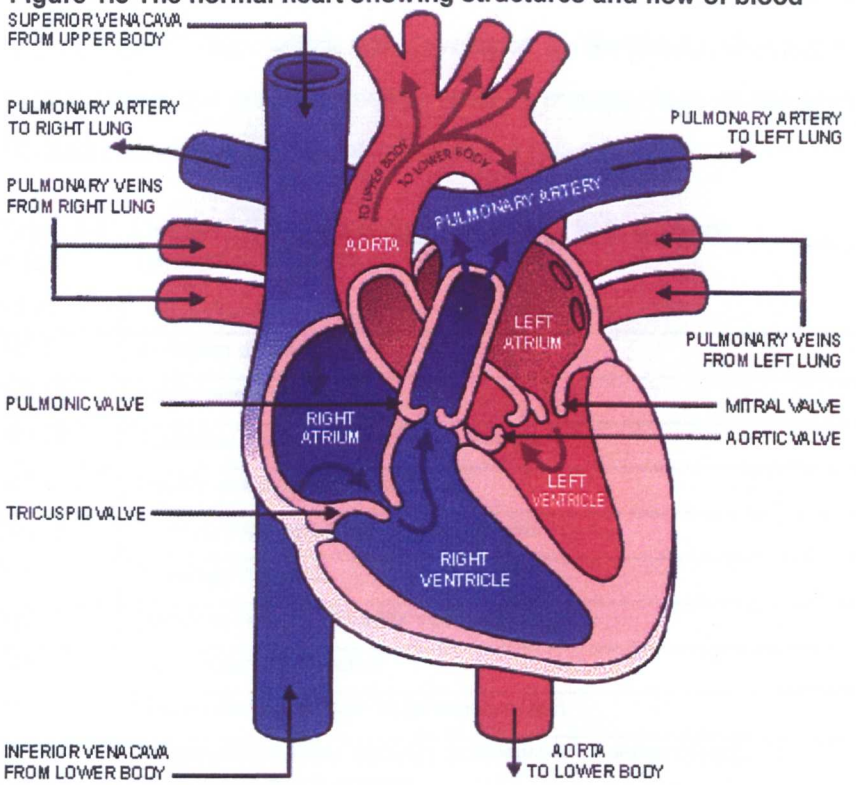
1.3.1 The normal heart

The normal heart, an organ little larger than the adult fist, comprises four chambers and four valves. It develops between days 17 and 50 of gestation (O'Rahily, 2001). After the primitive heart tube arises, this single tube folds, loops, rotates and differentiates into a four-chambered heart with valves that control blood flow from the atria to the ventricles and from the ventricles into the great arteries. The blood flows in only one direction, thanks to valves, by the pumping action of the coronary arteries which draw their blood from the aorta. Half of the blood (the blood on the left side) is oxygenated having just come from the lungs. The other half (on the right side) is deoxygenated having just circulated the body and then returned to the heart before going to the lungs. The Children's Heart Institute has good illustrations distinguishing the different heart defects. In one series, the heart is compared to a house with the chambers being rooms and the valves being doors (Abdallah, 1999).

Figure 1.3 is a classic picture of the heart showing the flow of blood. Each of the valves, except the mitral with two, has three flaps or leaflets. Heart defects are anomalies in this design. These defects are considered "congenital" when an infant is born with them and are considered "acquired" when the individual's heart was born structurally sound but then a valve, such as the mitral valve, becomes prolapsed and begins to leak.

Mitral valve prolapse is not generally "congenital" which demonstrates the imperfect nature of how congenital defects are defined. Marfan syndrome babies have a congenital anomaly manifested by a connective tissue disorder. Generally, these children acquire a defect in the mitral valve leading to mitral valve prolapse, but unless they have other specific heart defects they are not considered to have *congenital* heart defect. Aortic stenosis is another disease which can be acquired or congenital. When it is acquired it usually followed severe strep throat which developed into rheumatic fever.

Figure 1.3 The normal heart showing structures and flow of blood



From the Children's Heart Institute http://www.childrenheartinstitute.org/educate/heartwrk/bloodflw.htm

Three nosologies of the abnormal heart

Functionally, each abnormal heart defect can be classified as either acyanotic or cyanotic. However, these are not mutual exclusive categories with acyanotic and cyanotic defects existing simultaneously within the same infant's heart. Traditionally, the abnormal heart has been described in reference to the normal heart. Nosologies (systems of general classification) have been developed for this task. These nosologies are descriptive: what is seen by the describer is what the defect is called. There are three nosologies relevant to this project.

1. International Classification of Diseases (ICD)

Despite the fact that it was not designed for research, this system is the one primarily used in birth defects surveillance. ICD codes were originally developed to classify and code mortality data from death certificates and to assist with hospital re-imbursement in the USA.

This system has gone through several revisions since its creation. Some of the earliest work in CHD research was done in ICD 7 and ICD 8 although for the last decade ICD 9

has been used (USHHS, 1980) with certain modifications including ICD 9 CM which includes the 5th digit which was developed by the British Paediatric Associaition. The 5th digit is useful for specific entities such as *transposition of the great vessels* (745.10-12, 19) and *coarctation of the aorta* (747.10-11).

Table 1.1 List of ICD-9 diagnostic codes used in this study

ICD-9 Code	Description of structural defect	"Standard" abbreviation
745.0	Common truncus	truncus
745.01	Aortic septal defect	-
745.10	Complete transposition of great vessels	TGA
745.11	Double outlet right ventricle	DORV
745.12	Corrected transposition of great vessels	c-TGA
745.2	Tetralogy of Fallot	TOF
745.3	Common ventricle/Double inlet left ventricle	DILV
745.4	Ventricular septal defect	VSD
745.5	Ostium secundum type atrial septal defect	ASD II
745.69 745.61	Endocardial cushion defects / atrioventricular septal defect Atrial septal defect primum	AVSD ASD I
745.8	Sinus ASD	-
746.01	Pulmonary valve atresia	PV atresia
746.02	Pulmonary valve stenosis	PV stenosis
746.1	Tricuspid valve atresia and stenosis	TA
746.2	Ebstein's anomaly	-
746.3	Aortic valve stenosis	AV stenosis
746.4	Congenital insufficiency of aortic valve/Bicuspid aortic valve	BAV
746.5	Congenital mitral stenosis	-
746.7	Hypoplastic left heart syndrome	HLHS
746.81	Subaortic stenosis	-
746.83	Subvalvular pulmonic stenosis/Double chambered right ventricle	-
746.87	Dextrocardia	-
746.89	Mitral atresia	-
746.9	Hypoplastic right heart syndrome	HRHS
747.0	Patent ductus arteriosis	PDA
747.1	Coarctation of the aorta	COA
747.21	Interruption of aortic arch/Anomaly of aortic arch	IAA
747.3	Anomalies of pulmonary artery/ Pulmonary artery hypoplasia/stenosis	PA stenosis / atresia
747.41	Total anomalous pulmonary venous return	TAPVR
747.42	Partial anomalous pulmonary venous return	PAPVR
747.49	Other anomalies of great veins	-

Although ICD 10 is available for use, and promoted by the European Surveillance of Congenital Anomalies system (EUROCAT) most birth defects surveillance systems have remained with ICD 9 (CDC, 2001). Using ICD 9, including the sub-types, there are over 50 different diagnostic entities for CHD (ICD-9 745.0 to 747.9) however for the purposes of this study only the 31 listed in table 1.1 were considered although as will be specified in the methods no isolated cases of PDA were included. The 31 will be described in the section **Abnormal Defects** below. The approximately other 20 defects were either considered non-structural problems of the heart or were so rare that they were not seen in this live birth population.

2. *International Society for Cardiology (ISC)*

The International Society for Cardiology (ISC, 1970) developed a system of 800 codes available to describe the anatomic phenotypes. The system allocates a single three-digit number to each anatomic malformation and to certain complexes as well such as *transposition with ventricular septal defect in situs solitus*. Although it has not been revised in over 35 years it was developed by some of the great names in paediatric cardiology including V Rose and SC Mitchell. It was used to code the Baltimore Washington Infant Survey data to be discussed in Section 1.4.2. One difficulty with this system is that because of its fine distinctions it would be difficult for anyone except a paediatric cardiologist to use it to code CHD directly from medical records.

3. *European Paediatric Cardiac (EPC)*

The Association for European Paediatric Cardiology developed the European Paediatric Cardiac system (EPC) (Franklin et al. 1999; Stocker 2003). Its purpose is to facilitate comparisons of results between individual cardiac units specifically in the UK but it will allow international comparisons as well. The short list expands ICD 9 from 50+ codes into 126 codes however these can be collapsed into 10 major categories. It codifies the sequential segmental anatomy approach proposed by Tynan and co-workers in (1979). This approach describes the abnormal connections and associated abnormalities which require surgical treatment and may be ideal for standardization purposes. However, there will need to be a process of validating it in terms of inter-rater reliability. Additionally, it is currently only being used in a few centres in Europe although the intention is to expand its use internationally. It too is designed for paediatric cardiologists to determine codes.

In Appendix 1A the three coding systems are compared for two defects: endocardial cushion defect and single ventricle demonstrating the importance of the choice of coding system when interpreting results.

1.3.2 The abnormal defects

Using the ICD-9 nomenclature, 31 of the 50+ defects are described. Unless otherwise noted, the descriptions herein have been obtained from Anderson et al.'s Paediatric Cardiology (2002). The pattern is descriptive name, followed by "standard" abbreviation and synonyms, and ICD-9 code.[2]

1. *Ventricular septal defects* (VSD) (745.4)

A condition where there are one or more holes in the wall (septum) separating the right ventricle from the left ventricle. A VSD or VSDs can heal spontaneously and it (they) can be so minor as to be undiagnosed. The septum is of two substances, *membranous* on the side connecting to the atria and *muscular* on the posterior end. These two varieties of VSD are not separated according to the ICD-9 classification; however, the EPC and ISC do separate them and the Saudi Arabian CHD Registry has followed their lead. The terms "restrictive" (little blood) and "non-restrictive" (significant blood) can be used to indicate the severity of the defect. Restrictive VSD can heal spontaneously.

> *Ventricular septal defect, membranous* (aka *perimembranous*) (745.4_7) –
> A condition where the hole is located near the valves. The most common form of VSD, it accounts for 80 percent of defects.
> *Ventricular septal defect, muscular* (745.4_8) – A condition where the hole is in the muscular part of the wall. This type accounts for approximately 20 percent of defects.

2. *Atrial septal defect, secundum* (aka as ASD II, previously *auricular septal defect* because the atria resembles the human ear) (745.5)

A condition where a hole exists between the heart's two atria. Like VSD, this defect can heal spontaneously and can go undiagnosed. Also, it may be more common at high altitudes (Miao, Zuberbuhler, Zuberbuhler, 1988; Miao et al., 1988; Alzamora et al, 1953). They are termed *secundum* as opposed to *primum* defects because the defect is present at the site of the secondary embryonic foramen.

[2] Some defects do not have a "standard" abbreviation. These are marked with a "-" in Table 1.1.

A minor form of this defect is called *patent foramen ovale* (PFO). The foramen ovale is a small hole located in the atrial septum that normally closes at birth when increased blood pressure on the left side of the heart forces the opening to close.

3. *Sinus venosus ASD* (745.8)

A condition where the ASD involves the area of the atrial septum at the junction of the superior vena cava and the right atrium.

4. *Patent arterial duct* (PDA) (747.0)

A condition where the normal communication between the left pulmonary artery and the aorta does not close shortly after birth. During pregnancy although the foetal heart beats it is not responsible for oxygenation of the blood. Oxygen is provided by the maternal circulation via the placenta and the umbilical cord. This communication, the *ductus arteriosus*, between these two arteries normally closes a few hours after birth. However, if it does not close then it is said to be "patent" or still functioning. Clinically, PDA is defined as the persistence 10 days after birth of a normal foetal structure. It is more commonly found at high altitudes due to the ambient oxygen pressure not being sufficient to close it naturally (Miao et al., 1988; Miao, Zuberbuhler, Zuberbuhler, 1988; Alzamora et al., 1953, Penaloza et al., 1964). For research purposes generally the threshold for considering the defect a *congenital* defect is presence three months after birth.

5. *Complete transposition* (d-TGA for dextroposition, aka TGA or TGV (*transposition of the great arteries* or *ventricles*)) (745.10)

This condition is characterized by the aorta and the pulmonary artery being reversed sending deoxygenated blood to the body and oxygenated blood to the lungs. The aorta exits the right ventricle and the pulmonary artery exits the left ventricle. A VSD often complicates this defect.

6. *Corrected complete transposition* (l-TGA for levo or to the left, aka c-TGA for corrected) (745.12)

The alternate form to TGA where the aorta and the pulmonary artery are in the correct place but the ventricles are reversed. The aorta exits from the right ventricle and the pulmonary artery exits from the left ventricle. The left ventricle is below the right atrium

with the right ventricle being below the left atrium. Again, deoxygenated blood is sent to the body and oxygenated blood is sent to the lungs.

7. *Dextrocardia* (746.87)

A condition where the primitive heart tube folds to the left instead of to the right. Usually this defect is coupled with *situs inversus* where all the organ systems are reversed.

8. *Tetralogy of Fallot* (TOF) (745.2)

A condition once thought to have four components (thus "tetralogy"). Now it has been recognized that two of these are major (1.VSD and 2. constricted pulmonary valve) and two are minor (3. the aorta lies directly over the VSD causing the 4. right ventricle to develop thickened muscle making it larger in relation to the left ventricle). Kleinman (1997) has likened TOF to the top half of the heart not being set correctly on the bottom half.

9. *Double outlet right ventricle* (DORV) (745.11)

A condition where the pulmonary artery and the aorta arise from the right ventricle. Therefore only some of the deoxygenated blood flows to the lungs as it should while some returns to the body.

10. *Common truncus* (truncus) (745.0)

A condition similar to DORV where the one artery arises through a common arterial valve and will give rise directly to the systemic, pulmonary and coronary circulations. There is a large VSD leaving a "trunk" in the heart between the four chambers.

11. *Atrioventricular septal defect* (AVSD) (aka *endocardial cushion defect*) (745.69) often includes *atrial septal defect, primum* (ASD I) (745.61)

A condition characterized by deformities in the tricuspid and mitral valves combined with a hole in the atrial septum (ASD) and a hole in the ventricular septum (VSD). The key to their differentiation from other potentially related defects is the architecture of the atrioventricular junctions, including the structure of the fibrous skeleton of the heart. The holes lead to mixing of oxygenated and deoxygenated blood. This defect can be partial or complete. ASD I is considered to be one component of the partial form of AVSD.

Complete form – The complete form has three main components, a VSD, an ASD and a common atrioventricular valve.

Partial form – This form usually lack the VSD or the VSD is very small.

12. *Double inlet left ventricle* (DILV) (aka *single ventricle* or *common ventricle*) (745.3)

A condition where both atriums are connected to the left ventricle. Usually there is a hypoplastic right ventricle and the arteries and aorta may arise from the right ventricle and the pulmonary artery from the left ventricle or the right ventricle may be absent. Therefore, it is similar to the c-TGA because the right ventricle is on the opposite side of the heart from expected. *Pulmonary stenosis* or *atresia* and *coarctation of the aorta* may also be present (described below).

13. *Aortic septal defect* (aka *aorticopulmonary window* or *fenestration*) (745.01)

A condition where there is a small opening between the aorta and pulmonary artery just above the semilunar valves. This defect is included by EUROCAT in the *malformations of cardiac septa* group but not coded separately by the CHD Registry.

14. *Total anomalous pulmonary venous return* (TAPVR or TAPVC with "c" for "connection" or TAPVD with "d" for "drainage") (747.41)

A condition where the four pulmonary veins which normally bring the oxygenated blood from the lungs to the left atrium instead return the blood to the right atrium. There must therefore be an ASD II and possibly a VSD for the child to survive after birth.

15. P*artial anomalous pulmonary venous return* (PAPVR) (747.42)

A condition where less than four of the pulmonary veins lead to the right atrium.

16. *Other anomalies of great veins: Scimitar Syndrome* (747.49)

A condition of several components: TAPVR or PAPVR, hypoplasia and malformation of the pulmonary arteries and lung. There will be aortic-pulmonary artery collateral arteries to the hypoplastic lung.

17. *Ebstein's anomaly* (746.2)

A condition where the tricuspid valve does not move normally and therefore the blood leaks back into the right atria instead of progressing to the right ventricle. Often it is accompanied by an ASD II and associated with *Wolff-Parkinson-White* syndrome (WPW)

where there is an accessory conduction pathway and this in turn can lead to periods of abnormal fast heart rate (*supraventricular tachycardia* (SVT)).

18. *Tricuspid valve atresia and stenosis* (TA) (746.1)

A condition where there is no (or very little) connection between the right atrium and the right ventricle and therefore the blood is sent to the left atrium. The right ventricle is usually hypoplastic and survival depends on an associated VSD or a PDA. A single-ventricle defect, it is considered one of the more serious conditions.

19. *Pulmonary valve atresia* (PV *atresia*) (746.01)

A condition where there is no valve between the right ventricle and the pulmonary artery and therefore the blood is not able to flow to the lungs. The right ventricle is a *cul de sac* where deoxygenated blood collects. The tricuspid valve may also be poorly developed. *PV atresia* will be accompanied by an ASD II allowing the blood to exit the right atrium towards the left atrium. A PDA will also be present. The PDA remaining open is critical to the infant's survival.

20. *Pulmonary valve stenosis* (PV *stenosis*) (746.02)

A condition where one or more of the leaflets of the valve are malformed and the valve is stenotic or leaky.

21. *Pulmonary artery hypoplasia/stenosis* (PA *stenosis* or PA *atresia*) (747.3)

A condition where the pulmonary arteries narrow. The narrowing may occur in the main artery or in the left or right branches.

22. *Hypoplastic right-heart syndrome* (HRHS) (746.9)

A condition where the right side structures of the heart are underdeveloped. The major problem is PV *atresia*. Additionally there is a hypoplastic right ventricle, a small tricuspid valve and a hypoplastic pulmonary artery. The infant will be born with a PFO and a PDA. When the *PV atresia* exists with an intact ventricular septum then it is considered a single-ventricle defect (The Heart Institute, 2006).[3]

[3] ICD – 9 code 746.9 is *unspecified anomaly of heart* but the CHD Registry uses that code for HRHS. EUROCAT uses ICD-10 solely to code HRHS.

23. *Hypoplastic left heart syndrome* (HLHS) (746.7)

A condition where the aorta is reduced in size, the aortic valve is underdeveloped, the mitral valve is closed and the left ventricle is small. It is another single-ventricle defect. The blood flow from the lungs returns through an ASD II and the right ventricle pumps the blood into the aorta through a PDA.

24. *Aortic valve stenosis* (AV stenosis) (746.3)

A condition where the aortic valve is narrow preventing the blood from flowing from the left ventricle to the aorta and then to the body. It can occur congenitally or it can be acquired (rheumatic origin). *Hypertrophic cardiomyopathy*, (HCM) a heart condition but not a congenital heart defect because it is not structural, can be associated with AV *stenosis*. A cardiomyopathy is a condition in which the heart muscle does not function normally. The most commonly described are HCM and dilated cardiomyopathies (DCM). The main feature of the HCM is that the heart muscle is thickened. With DCM, the leading cause of sudden death in children, the heart becomes enlarged and is not able to pump efficiently.

25. *Coarctation of the aorta* (COA) (747.1)

A condition where the aorta is constricted and blood flow to the lower body is obstructed.

26. *Bicuspid aortic valve (BAV)* (746.4)

A condition where the aortic valve, which should have three flaps, only has two. The valve becomes stenotic making it more difficult for blood to flow. This condition is sometimes conflated with AV *stenosis* (above). It is rarely problematic at birth and is often under diagnosed. However, by adulthood more cases appear.

27. *Interruption of aortic arch* (aka anomaly of aortic arch) (IAA) (747.21)

A condition where part of the aortic arch is missing. There are three types:

Type A: the interruption occurs just beyond the left subclavian artery. Approximately 33 percent of the defects are of this type.

Type B: the interruption occurs between the left carotid artery and the left subclavian artery. It is the most common type and accounts for 66 percent of the cases. It is often associated with the chromosomal abnormality DiGeorge syndrome (DGS).

Type C: the interruption occurs between the innominate artery and the left carotid artery. It is the least common only occurring in 1 percent of the reported cases.

The defect is thought to occur towards the end of gestation between days 35 and 49. The defect is almost always associated with a large VSD. The PDA provides sufficient oxygen to the infant but as it closes symptoms begin to appear (Loffredo et al., 2000; Chin, 2006; Gruber, Epstein, 2004).

28. *Sub-aortic stenosis* (aka subvalvular aortic stenosis or sub-aortic membrane) (746.81)

A condition where there is a membrane or obstruction immediately upstream, or prior to, the aortic valve. It may occur spontaneously or as part of Williams syndrome (Singh, 2006).

29. *Double chambered right ventricle* (746.83)

A condition where the right ventricle is divided into two: a high pressure inflow chamber and a low pressure infundibular chamber. If a VSD is present it usually communicates with the high pressure inflow chamber.

30. *Mitral atresia* (746.89)

A condition where the mitral valve is missing.[4]

31. *Congenital mitral stenosis* (746.5)

A condition where the mitral valve is narrowed restricting blood flow between the left atrium and ventricle.

Meta-Nosologies used in research

In three years of data collection the CHD Registry recorded 855 unique combinations of cardiac diagnoses among 4362 Saudi Arabian patients (Black and Sandridge, 2001). This aspect of CHD, many unique combinations, is well known. In order to analyze such a large number of categories, systems have been developed to group. Six of these systems, the ones most commonly used in the literature, will be discussed here. No systematic review has compared and contrasted these six systems clinically; nor are all of them well

[4] ICD – 9 code 746.89 is "*Other congenital anomalies of the heart/Other*" but the CHD Registry codes *mitral atresia* here.

enough documented so that their use can be easily replicated. Nevertheless, the literature provides some clues for their implementation.

1. Isolated versus parallel

This system has been used by some in order to present "pure" results (Martin, Adams, Mortensen, (1990) for some analyses; McLaren, Lachman, Barlow (1979) and Ferencz et al., (1997)). Analyses are stratified by individual isolated diagnoses and parallel diagnoses (where there is more than one CHD simultaneously) might be excluded. This has merit in terms of purity of illness. Or, analyses of this type can take advantage of the four manifestations of CHD and present the data either as four groups, or some combination thereof, or some exclusion thereof. However, as many as 41 percent of CHD cases potentially suffer from parallel defects (Pradat, 1992a). Additionally, since some defects are required for survival "isolated" must be defined as to whether it can include that type of defect or not (as in *interrupted aortic arch* with VSD).

The four manifestations of CHD[5]:

1. ***in isolation*** - one CHD diagnosis.
2. ***in parallel*** - at least two different CHD simultaneously neither of which are required for the sustainability of life.
3. ***in isolation***, as above, with ***one or more extra-cardiac malformations*** (ECM).
4. ***in parallel***, as above, ***with one or more ECM*** (chromosomal syndromes are often found in this group). It has been proposed that these infants always have an underlying chromosomal anomaly even if it is not yet identified (CA Moore, Centers for Disease Control, unpublished communication, 2002).

In this thesis, an ECM is any malformation that is not a cardiac problem but is a congenital problem.

2. Predominant lesion (aka clinically dominant, hemodynamically most serious)

This method is especially in use in the developing world with the exception of Laursen's work (1980) (Denmark); Scott et al. (1984) (UK) and Grech (1998) (Malta). None of the studies have provided enough information for replication: Bannerman and Mahalu

[5] Ambiguity exists as to whether this should include adaptative defects (i.e., PFO, PDA, or occasionally a VSD) without which the case would not be seen live born. These adaptative defects sustain life and therefore might not be counted as defects if defect is defined as something which is a *deficiency*.

(1998), Becker et al. (2001); Laursen (1980); Subramanyan et al. (2000); Grech (1998), Sung et al. (1991); and Scott et al. (1984).

3. Lesion analysis

This well documented method (EUROCAT, 2005b) has been chosen by European Register of Congenital Anomalies (EUROCAT) among others. It compares groups of lesions. The number of lesions, given that some cases have more than one, will be greater than the number of cases. The data are presented by EUROCAT in two ways:

Firstly, the data are presented in four groups[6]:

1. malformations of cardiac septa (*septa*)
2. malformations of great arteries and veins (*arteries and veins*)
3. malformations of valves (*valves*)
4. anomalies of cardiac chambers and connections (*chambers*)

Secondly, EUROCAT presents 6 individual defects: TGA, AVSD, COA, TOF, HLHS and *truncus*. Please note that although an individual may be counted in more than one group (i.e., *septa* and *valves*) the individual will not be counted twice within the same group. Conversely, the category AVSD as defined by EUROCAT includes all patients with ICD-9 745.6: (AVSD (745.69) and ASD I (745.61)).

4. New England Regional Infant Cardiac Program (NERICP)

Each patient registered in the six New England states from 1969 until 1977 was included for a total of 3626 infants in nine years. The live birth prevalence was 2.4. Each infant was assigned a single diagnosis which best represented the patient. When a patient had several diagnoses an arbitrary hierarchical system was devised to permit assignment of a diagnostic category (Fyler, 1980). This method has been used by Francannet et al., (1993), Zierler et al., (1988) and Kidd et al., (1993).

5. Complex, significant, minor

This method is described by Abu-Harb, Hey and Wren (1994). It was developed primarily to study survival from CHD and to estimate how many deaths could be avoided for minor defects with improved intervention.

[6] The specific ICD-9 codes for these categories are specified in table 4.6

6. Embryological

This method was used by BWIS (Ferencz et al., 1985; Ferencz et al., 1993; Ferencz et al., 1997), Fixler et al. (1990) and Martin, Adams, Mortensen (1990) for some analyses. It was developed using the ISC coding system which is more detailed than ICD-9. This method is alternatively referred to as "hierarchical" and "mechanistic". After reviewing the New England Regional Infant Cardiac Program's (NERICP) methodology the BWIS paediatric cardiologists combined the current understanding of embryologic development, teratogenic timing of cardiac malformations and a pilot of 719 infants to develop a hierarchical and embryological system. They worked closely with Clark (1987, 1990) to develop a system where CHD was categorized by cellular and physiologic developmental mechanisms. It has been particularly useful for dividing the largest phenotype (VSD) into four distinct groups and identifying certain lesions which may be related to the abnormal migration of cells from the primitive neural crest (Kirby, 1987). It is hoped that the method orders the defects chronologically with those in category 1 arising earlier in gestation than those in category 6 or 7. If this method achieves this goal then it will be easier to restrict the timing of the specific insult which caused the defect thereby bringing researchers closer to identifying the etiology of a particular CHD lesion or a particular group of CHD.

As described by BWIS (Ferencz et al., 1993) the embryological system classification is as follows:

1. Defects of laterality and cardiac looping
2. Defects of the ventricular outlets and arterial trunks
3. Extracellular matrix defects
4. Targeted growth defects
5. Cell death defects
6. Hemodynamic defects
7. Cardiomyopathies.

Further descriptions of these categories are found in Section 4.2 and table 4.4.

Pradat (1992a, b); Kallen (1999); Storch and Mannick (1992); Tikkanen and Heinonen (1990) and Grabitz et al. (1988) have analysed their data using an embryological system.

The embryological system, categories 1 to 6, has been used for parallel defects in this research. Cardiomyopathies, category 7, are not included as they are not structural defects.

Table 1.2 presents a review of 41 selected studies published from a variety of geographical regions since 1985 comparing nosology, method of analysis for parallel diagnoses and isolated diagnoses, and prevalence. This table demonstrates the poor quality of the CHD literature. These studies were assessed on nosology, meta-nosology, percent of ECM, percent isolated CHD (as opposed to in parallel or with an ECM), and reported prevalence per 1000 live births. Only 2 of the studies (Pradat 1992a, 1997; Stoll 1989) reported data in all categories. Only slightly more than half of the studies reported the nosology they used for classifying the defects (22 of 41). Only 63 percent reported the prevalence of CHD in the population they were studying. Twenty-two percent did not report the meta-nosology that they used. Only 4 of the 41 studies analyzed the data using more than one meta-nosology.

Seven studies performed lesion analysis. Two analyzed by complex, significant, minor. Four compared isolated to parallel and/or syndromic. Four used the Fyler (1980) NERICP system. Six used predominant lesion and eleven used an embryological system. One reported all lesions individually instead of using a meta-nosology because the sample size was so small (n=34) (Miao, Zuberbuhler, Zuberbuhler, 1988).

Summary of features which make CHD difficult to research

Features of CHD which make it particularly difficult to study are

- its varied manifestations
- naming conventions are inconsistent. Examples include:
    - VSD is often analyzed as one homogenous group rather than being divided into 2 to 4 categories
    - the three types of ASD are not always differentiated (ASD II, sinus venous, ASD I)
    - ASD I is not always differentiated from AVSD
    - VSD+ASD in some work appears synonymous with AVSD

Table 1.2: Comparison of Nosology, Treatment of Multiple Diagnoses, Isolated Diagnoses and Prevalence in the literature for selected literature published since 1985

	Study	Geographic Region	Study Design	Nosology	Meta-nosology: Treatment of parallel diagnoses	ECM %	Percent Isolated	Reported Prevalence/ 1000 live births
1	Abbag (1998) Cases=335	Southwestern, Saudi Arabia	Case series	NR	NR	NR	NR	NR
2	Abu-Harb, Hey, Wren (1994) Cases=1074	Cumbria, Northumberland, Tyne and Wear, Durham, Cleveland, England, UK	Cohort	same as NRFAS[1]	Complex, significant, minor	NR	NR	4.7
3	ABDCC[2]: Lian et al (1986)	Atlanta, USA	Case control	ICD 8	Lesion Analysis	NR	NR	NR
4	Boneva et al. (1999)		Case control	ICD 9 CM	Embryological	NR	NR	NR
5	Watkins and Botto (2001)		Case control	ICD 9 CM	Embryological Isolated vs Parallel/Syndromic	NR	NR	NR
6	Botto, Mulinare, Erickson (2000) Botto, Lynberg, Erickson (2001)		Case control	ICD 9 CM	Embryological Isolated vs Parallel/Syndromic	NR	NR	NR
7	BWIS[3] (Ferencz et al., 1985, 1993, 1997) Cases=664	Baltimore - Washington, DC, USA	Case control	ISC	Embryological Isolated vs Parallel/Syndromic	27	NR	3.7 All 2.4 Severe
8	Araneta et al., 2003 Cases =6863 Gulf War Veterans	Arkansas, Arizona, California, Georgia, Hawaii, Iowa, USA	Prevalence	MACDP	Isolated defects	NR	NR	VSD=1.9 PV atresia/stenosis=0.9
9	Cases =17,922 Non Deployed Veterans					NR	NR	VSD = 2.5 PV atresia/stenosis=0.6 Dextrocardia=0.4 COA=0.4
10	Bannerman and Mahalu (1998)	Zimbabwe	Case series	NR	Predominant lesion	NR	NR	NR
11	Bassili et al. (2000) n=894 x 2	Alexandria, Egypt	Matched case control	NR	Lesion Analysis	4	81	NR

[1] Northern Regional Fetal Abnormality Survey
[2] Atlanta Birth Defects Case-Control study. Cases collected by the MACDP surveillance program.
[3] Baltimore Washington Infant Survey

	Study	Geographic Region	Study Design	Nosology	Meta-nosology: Treatment of parallel diagnoses	ECM %	Percent Isolated	Reported Prevalence/ 1000 live births
12	Becker et al. (2000)	Saudi Arabia	Case series compared to national data	NR	Predominant lesion	NR	NR	NR
13	Bitar et al (1999) 883 patients collected 1980 – 1995	Beirut, Lebanon	Hospital based prevalence	NR	NR	NR	NR	11.5
14	BCHSR[4]: Olshan, Schnitzer, Baird (1994) N=4110 live births identified 1952-1973	British Columbia, Canada	Case control	ICD 9	Lesion Analysis	6	NR	5.2
15	Child Cardiology Registry (CCR) Pradat (1992a, 1997) 1605 cases of 573 422 births	Sweden	Cohort	ISC	Embryological Lesion Analysis	31	54	2.8
16	Pradat 1992b		Case control	ISC		NR	NR	2.3
17	Kallen K (1999) 3384 cases of 1,413811 births		Case control	ISC	Embryological	NR	NR	2.4
18	El Hag (1994) Cases = 96	Khartoum, Sudan	Case series	NR	NR	NR	NR	NR
19	EUROCAT:Cordier et al. (1997) Bouche du Rhone, France Paris, France Emilia Romagna, Italy Toscana, Italy Glasgow, United Kingdom Groningen, the Netherlands	Europe		ICD 9	Lesion Analysis	NR	NR	NR
20	Fixler et al. (1990) 2509 cases from 379,561 births	Dallas County, Texas, USA	Prevalence Study	ISC	Embryological	NR	NR	6.6 All 3.15 Severe[5]
21	Grech (1999)	Malta	Case series	NR	Predominant lesion	NR	NR	8.8
22	ICBD[6]: Francannet et al. (1993) New South Wales, Australia; Central-east, France; Strasbourg, France; Emilia-Romagna, Italy; Sweden	Europe and Australia	Cohort	ICD 9 (6digit)	NERICP	NR	NR	0.2 (HLHS) 0.3 (TGV) 0.2 (TOF)

[4] British Columbia Health Surveillance Registry
[5] Rate calculated from data in article
[6] International Clearinghouse of Birth Defects

	Study	Geographic Region	Study Design	Nosology	Meta-nosology: Treatment of parallel diagnoses	ECM %	Percent Isolated	Reported Prevalence/ 1000 live births
23	Jaiyesimi, Ruberu, Misra (1993) Cases = 320	Buraidah, Saudi Arabia	Case series	NR	NR	NR	NR	NR
24	Khalil et al. (1994) Cases = 43 of 10 964 live births	New Delhi, India	Cohort	Mitchell Method	NR	18	NR	3.9
25	Kidd, Lancaster, McCredie (1993) 1479 cases from 343,521 births Jan 1981-Dec 1984	Australia	Cohort	BPA[7]	NERICP	NR	NR	4.3
26	Kramer, Majewski, Trampisch, Rammos, Bourgeois (1987)	Dusseldorf, West Germany	Case series	NR	Isolated vs Parallel/Syndromic	13	NR	NR
27	MACDP Martin, Adams, Mortensen (1990)	Atlanta, USA	Cohort	ICD 9 (6digit)	Embryological	NR	NR	0.4 (COA) 0.05 (IAA) 0.06 (Hypoplasia)
28	Adams, Mulinare, Dooley (1989) Cases = 83 Controls = 1303	Atlanta, USA 1976-1980	Case control	ICD 8	NR	NR	NR	Truncus 0.10 TGA 0.50 TOF 0.29
29	Montana et al. (1996) 1,589 from 194,754 live births	Atlanta, USA 1990-1994 Prevalence	Cohort	NR	Embryological	35	52	8.1
30	Meberg et al. (1999) 353 from 35,218	Vestfold, Norway	Case series	NR	NERICP	NR	NR	10
31	Miao, Zuberbuhler, Zuberbuhler (1988) 34 from 1,116 children	4 cities in China	Cohort	NR	Reported all conditions	NR	6	28.7
32	Mikhail, Walker, Mittendorf (2002) n=7 cases and 144 controls Only studied 'isolated' defects	Chicago, Illinois African-Americans	Cohort	NR	NR	NA	NA	NR
33	National Perinatal Databases of the Netherlands Anthony, Buitendijk, Dorrepaal, Lindner, Braat, den Ouden (2002) N=314 605 controls, 4224 cases Data from 1995-1996	Netherlands	Cohort	NR	NR	NR	NR	5

[7] British Paediatric Association coding system

	Study	Geographic Region	Study Design	Nosology	Meta-nosology: Treatment of parallel diagnoses	ECM %	Percent Isolated	Reported Prevalence/ 1000 live births
34	Robida, Folger, Hajar (1997) 610 cases of 49 887 births / 11 yrs	Qatar	Cohort	NR	NR	NR	NR	12.2
35	Samanek, Slavik, Zborilova, Hrobonova, Voriskova, Skovranek (1989) 91,823 with 589 cases of CHD	Bohemia	Cohort	NR	Predominant lesion	NR	NR	6.4
36	Savitz, Schwingl, Keels (1991) Cases = 86 of 14 685 live births	San Francisco, California, USA	Cohort	ICD 7	NR	NR	NR	3.2 (VSD) 1.2 (PS) 0.7 (AS)
37	Stephensen et al. (2004)	Iceland	Cohort	ICD 9	Complex, significant, minor	12	NR	17
38	Stoll et al. (1989) 105,374 consecutive births and stillbirths	Bas-Rhin France	Cohort	ISC	Lesion Analysis	11* 14 ECM	74	7.6
39	Storch and Mannick (1992)	Louisiana, USA	Cohort	ICD 9	Embryological	NR	85	2.2
40	Subramanyan et al. (2000)	Oman	Cohort	NR	Predominant lesion	NR	NR	7.1
41	Sung et al. (1991)	Hong Kong	Cohort	NR	Predominant lesion	NR	NR	6.4
42	Tikkanen and Heinonen (1990, 1992) N=408 with 583 defects	Finland	Cohort	Mitchell method	Embryological	NR	66	3.1
43	Zierler et al. (1988)	Massachusetts	Ecologic Case control	NERICP	NERICP	NR	NR	NR

NR=Not reported
NA=Not applicable
NB, Where the study was a case series but a prevalence is reported the data generally came from a clinic population and the number of cases was applied to the relevant area live birth statistic. Where the study was a case control study prevalence was calculated from a cohort study in which the case control study was nested or from a relevant area live birth statistic.

- the fact that some conditions (e.g., PDA and PFO) are normal features of the foetal heart which disappear at or shortly after birth
- some of the defects such as ASD II and VSD can be sufficiently minor that they will heal themselves or
- be missed until after childhood; and
- some of the defects, such as a VSD found in *truncus* or an ASD II found with TAPVR may be considered as "functional" defects rather than "congenital" defects. These functional defects are necessary for life given the "true" congenital defect. This being the case there may be additional combinations of defects where there is a functional component rather than congenital which have not yet been recognized.

1.4 Epidemiology of congenital heart defects

1.4.1 Prevalence at birth

Although the frequency of congenital heart defects (CHD) was not the topic of this study some basic prevalence statistics will give an idea of the magnitude of this health problem. CHD are one of the most common groups of birth defects affecting between 4 and 12 per 1000 live births (Hoffman, 2002). The EUROCAT system found CHD to be the most common system defect with an overall prevalence (live births, foetal deaths and induced abortion) of 6 per 1000 (EUROCAT, 2005a). The UK Congenital Malformations Registration Scheme (ONS, 2001) found it to be the third most common defect.[7]

In the Middle East, Alabdulgader (2001) reported an incidence of 11 per 1000 live births in the referral centre for the Al Hassa region, Saudi Arabia. One of the three major hospitals of the Abu Dhabi Emirate in the United Arab Emirates (UAE), a population similar genetically to the KSA population, belongs to the International Clearinghouse for Birth Defects Monitoring Systems. They purport to be a population based effort. Their 1998 data reported no cases of *TGA*; rates of 2.67 per 10,000 live births for *TOF* and for *HLHS*. The rate for *COA* was 1.33 per 10,000 live births (ICBD, 2000). In a separate study they report an overall CHD incidence of 6 per 10,000 live births (Al-Gazali et al. 1995).

[7]Despite the fact that the passive reporting system used by ONS results in serious under-ascertainment of CHD.

In Oman, CHD was detected (using the clinically dominant lesion method in cases of parallel defects) in 992 live births from 139,707 registered from 1994-96 (incidence 7/1000) (Subramanyan et al., 2000). In Qatar, Robida et al., (1997) found a prevalence at live birth of 12.23 per 1000.

1.4.2 Risk Factors for CHD

The literature review for risk factors for CHD was systematic. Using the search history in table 1.3 the titles, and abstracts where necessary, of the 991 articles were hand-searched for relevance. Additional articles were identified from the Baltimore Washington Infant Survey reference list of 288 references (Volume 4) and 462 references (Volume 5) and the two volume tome edited by Anderson et al. (2002).

Table 1.3 Search History for CHD prevalence and risk factor data

#	Search History	Results
1	.*Heart Defects, Congenital/cl di, ep [Classification, Diagnosis, Epidemiology]	1435
2	Limit to Human and English language	991

From this initial set of references the reference lists of the relevant papers were also searched. From this effort 140 risk factor articles on CHD and 41 articles with prevalence data were reviewed (Appendix 1B and table 1.2, respectively). The CHD literature on diagnosis, treatment and survival was not considered in depth. Where possible only articles with a primary focus on CHD were selected although some researchers studied congenital malformations and then reported on CHD as a sub-type.

This review indicated that the Baltimore Washington Infant Survey (1981-1989) was the best, recent study (Ferencz et al., 1993; Ferencz et al., 1997). For the most part, studies previous to the BWIS, while interesting historically, are not described here because the BWIS built on their legacies.

Baltimore Washington Infant Survey (BWIS)

The Baltimore Washington Infant Survey thoughtfully followed previous studies building on the successes of the Collaborative Perinatal Project (CPP) of 56,000 births (Mitchell et al., 1971), the Toronto Heart Registry (Rose, Hewitt, Milner, 1972) and the New England Regional Infant Cardiac Program (Fyler et al., 1980). The BWIS was a case control study

drawing participants from a large regional population in the USA: the state of Maryland, Washington, D.C. and six counties of northern Virginia. The area population was approximately 6 million with 100,736 annual live births (mean). All 53 local obstetric and paediatric services were approached and all their live births were included. Cases were those for whom a CHD was confirmed before 1 year of age by echocardiography, cardiac catheterization, surgery or autopsy. The only cases of CHD not included were those premature infants (less than 38 weeks gestation) with PDA. The BWIS literature reports on 4,390 cases and 3,572 controls, however, this figure includes cases of PDA and cardiomyopathy which were not included in this Saudi Arabian study. Comparable to the types of CHD analyzed for this project, there were 3,885 BWIS structural anomalies.

BWIS case ascertainment was thorough. With the exception of one region, all death certificates of infants who died under 1 year of age were reviewed. Cases were coded by the paediatric cardiologist for the participating centre from a written description of the CHD and any ECM. ECM were coded and heritable syndromes were assigned McKusick codes (McKusick, 1998). Cases were reviewed by a second paediatric cardiologist to resolve inconsistencies in diagnostic coding. One year after birth all cardiac and non-cardiac diagnoses were confirmed using available data.

Control selection adhered to a strict random methodology. The number of infants chosen from each hospital was determined proportionally to the total number of annual regional deliveries. One control was selected as well as four potential alternates. A reference "time frame" of 6 months prior to and 9 months following the last menstrual period (LMP) and a "critical period" of 3 months prior to the LMP and 3 months following LMP were established. Interviews were conducted in the home of the respondents where possible. Intensive interviewer training was conducted. For practical and ethical reasons, the interviewers were not blinded to case-control status. One strength of the study was that all case mothers were approached for interview even if the infant died previous to the interview.

While the BWIS is the most comprehensive study and has advanced our understanding of CHD, even it has limitations. Firstly, the authors failed to justify their use of the ISC coding system, which is clearly less popular than ICD-9. In the 22 studies reviewed in table 1.2 for which this data were reported ISC was used 23 percent of the time versus 59 percent for ICD-9. Secondly, the structure of the two BWIS volumes is not clear and the

index is inadequate. While it succeeds in documenting the findings of that particular study, it does not provide sufficient information to replicate the work. For example, the distinctions between the hierarchical, embryological and mechanistic systems are not clear. When to prefer one to the others is also not described. Some of the decisions for grouping and exclusions of cases from particular analyses were not well justified. And there are some mistakes, for example, in table 3.2 the numbers do not add up which makes it difficult to compare (Ferencz et al., 1993).[8] Lastly, the book has vast numbers of odds ratios and confidence limits and it is difficult to know which ones are preferred. The summary chapter in Volume 5 (Ferencz et al., 1997), *Risk Factor Analysis: a synthesis* is helpful but does not consistently present all the information.

In large part, this study was an attempt to replicate Ferencz et al.'s work in Saudi Arabia. During the planning stages ALS contacted Drs. Ferencz and Adolfo Correa-Villasenor for advice especially regarding coding issues. Nevertheless, despite these efforts to build on the BWIS legacy the blueprints provided were incomplete. Therefore, the embryological coding decisions used in this analysis may differ slightly from those of the BWIS.

Summary of results from BWIS and other studies

Numerous results from the BWIS are reported in two volumes of the Perspectives in Pediatric Cardiology Series (Ferencz et al., 1993; Ferencz et al., 1997). These results will be described where they fit into the following schema. The literature review is presented according to broad categories which will generally be followed throughout the thesis:

- Consanguinity
- Infant characteristics
- Maternal characteristics
- Paternal characteristics
- Index pregnancy characteristics
- Previous pregnancy characteristics
- Environmental risk factors
- Socio-economic characteristics

CONSANGUNITY

Consanguinity is the property of being related by blood from a common ancestor, near or far. Marriage between people who are related is often referred to as a consanginous marriage. Descriptions of the levels of relatedness, and how these are measured, is presented in section 1.5.

[8] The numbers add up to 4157 but they should add up to 4065.

Individuals who are related will share more of their genome than individuals who are not related. According to the Mendelian laws of inheritance, when relatives reproduce, their offspring are more likely to be homozygous for any given trait than the offspring of unrelated parents. Recessive alleles are only expressed phenotypically in the homozygous condition, which increases the probability that recessive traits (either positive or negative) will be present in the offspring of consanguineous, compared to non-consanguineous, parents. Such reasoning applies also to traits determined by more than one gene, the so-called multi-factorial traits.

Consanguinity is thus often used as a proxy measure for genetic aetiology. Few studies have been conducted on single gene aetiology diseases to explore the increased risk of the condition in the offspring of consanguineous parents because such an outcome would be expected according to Mendelian theory. Indeed, consanguineous populations are often used as a source of rich material with which to identify the locus of the gene responsible for a disease (Sundin et al., 2006; Oberti et al., 2004; Tlili et al., 2005) Recent work has suggested that single gene mutations may cause a variety of rare cardiac defects, but the aetiologies of more common conditions remain largely unknown (Ransom et al., 2007).

It is likely that the cause of most CHD will be a complex mixture of both environmental and genetic factors. Care has to be taken when interpreting the results of studies using consanguinity to investigate disease aetiology. Parents who are related may also be more likely to share non-genetic behavioural and environmental exposures than parents who are not. Theoretically at least, exposure from both the male and female may increase risk through a "dose" effect. Alternatively, consanguineous parents may have different patterns of behavioural and environmental exposures than parents who are un-related.

Consanguinity is a risk factor uniquely prevalent in the Middle East. It has been studied extensively and a further review of it will be found in Section 1.5 below. Only the eight studies of the effect of consanguinity on CHD are reviewed here.

Gev, Roguin, Freundlich (1986) studied an Arab Israeli population and found an elevated relative ratio of 2.6 associated with first cousin consanguinity. The relative ratio was calculated by ALS but there was not enough detail to calculate confidence limits. It was odd that this cohort study from a population of 1,546 reported no cases from diabetic

mothers and no cases of CHD in the parents. There was no sibling CHD and only one case of Down syndrome (DS). The authors reported no CHD in parallel and they collected consanguinity using the hard coded method which only allowed for first and second cousins thus there is the possibility for misclassification of exposure.

Hassan, Haleem, Bhutta (1997) in a population of 8,331 Pakistani live births in a case control study found no association between CHD without chromosomal abnormalities and consanguinity (OR =1.0, CI_{95}=0.7-1.4). The research was conducted by medical record review. However, their method of collection of consanguinity was not defined and they did not describe the degree of consanguinity in the cases.

Stoll et al. (1989) found no association between consanguinity and increased incidence of CHD. Their analysis was conducted on a dataset collected under the auspices of the Northeastern France Birth Defects Monitoring System. From a population of 105,374, there were 801 cases of CHD. Nine cases of consanguinity were identified.

Bassili et al. (2000) found an association between CHD and consanguinity using the case control method with an adjusted odds ratio of 2.4 (CI_{95}=1.9-3.0) in a case population of 894. They found that VSD was associated with consanguinity with an adjusted odds ratio of 2.7 (CI_{95}=2.0-3.5) and ASD II had an adjusted odds ratio of 2.4 (CI_{95}=1.6-3.5). This study found a variety of other associations which will be discussed below. However, they also included cousins more distantly related than second. Furthermore, they included cases diagnosed from birth to 15 years of age which suggests that non-incident cases were included which would contribute to bias (survivor). On the other hand, they used the phylogram method and they carefully explained their method of data collection.

Nabulsi et al. (2003) studied 759 infants selected from the Children's Cardiac Registry Center (CCRC) in Beirut, Lebanon using the embryologic meta-nosology. They only included cases of CHD that were structural and in parallel, excluding cases with ECM. They compared these to those from the National Collaborative Perinatal Neonatal Network. The proportion of first cousin marriage was 20 percent. This was statistically significantly higher than the 13 percent in the background population ($p<0.0001$).

Roodpeyma et al., (2002) studied CHD in a case control study with 346 cases and 346 controls collected between 1995 and 2000 in Tehran, Iran. They did not find an association with consanguinity. They authors reported a remarkably low number of maternal diabetes (2 cases and 3 controls). The authors did not state that they excluded multiple siblings from the same family from the analysis and they did not define their method of ascertaining consanguinity, however.

Badaruddoza et al., (1994) performed a cross-sectional study of 1,721 infants in North India and found that of the 37 cases of CHD, 3.4 percent were consanguineous. The relative risk was 2.8. However, such an extremely high prevalence of CHD (21 per 1000) suggests that possibly families with sick children were more likely to present than the general population. The 95% confidence interval was not presented.

Becker and Al-Halees (1998) whose study was a precursor to this one, reported on 891 cases of CHD abstracted from the Saudi Arabian CHD Registry. She and her colleagues reported a significant association between first cousin consanguinity and defects such as ASD, VSD, AVSD, PV stenosis and PV atresia (Becker et al., 2001). However, the study classified cases according to the predominant lesion method of categorization of parallel defects which was not described by the authors and is thus unlikely to be replicable. They did not collect a control population but compared the proportions of consanguinity in the predominant lesion categories to those proportions of consanguinity from one publication by El-Hazmi (1995). Consanguinity was hard-coded and therefore at risk of misclassification. The interviewer was not a native Arabic speaker and the coding system for region was embryonic and prone to misclassification bias (S. Becker, unpublished communication, 1999).

INFANT CHARACTERISTICS

Familial history of cardiac malformations or extra-cardiac malformations

From the Baltimore-Washington Infant Survey data Loffredo et al. (2000) reported an association between a familial history of extra-cardiac malformations (ECM) and Type B, IAA with DGS (OR=7.2, CI_{95}=1.5-39.2). This strongly significant result was found despite the fact that there were only 32 cases.

Tikkanen and Heinonen (1992) identified that CHD in the father, mother's mother, mother's sister or mother's brother were associated with ASD in the child. This team, working with the Finnish births registry dataset, used the embryological method for classifying parallel diagnoses in one child. The results for the three risk factors were robust with significant, albeit wide, confidence limits: father - OR=10, (CI_{95}=1.6-61), maternal grandmother - OR=5, (CI_{95}=1.6-16), maternal sister or brother - OR=2.5, (CI_{95}=1.1-5.9). The results follow a dose response curve.

Race

Using the BWIS dataset, Correa-Villasenor et al. (1991b) found a positive association between CHD and the white race for Ebstein's anomaly, AV stenosis, PV atresia, COA, dTGA and AVSD. For AV stenosis there was interaction between race and SES. Additionally, a positive association was seen between CHD and the black race for PV stenosis and heterotaxia.

Sex

One of the conclusions expressed by the investigators of the Toronto Heart Registry was that sex was a potential determinate for etiological CHD studies (Rose, Hewitt, Milner 1972). Rotherman and Fyler (1976) found in a descriptive study using the NERICP Registry that there was a differential sex ratio in PDA with 115 of 179 (63%, $CI_{90\%}$ = 30-42) girls affected. In boys, there were three defects that were more common: AV stenosis (78%, $CI_{90\%}$ = 66-87); COA (59%, $CI_{90\%}$ = 53-66); and TGA (66%, $CI_{90\%}$ = 61-70). They used the predominant lesion method for classifying parallel CHD.

Gensburg, Marshall, Druschel (1993) looked at data from the upstate New York congenital malformation registry using an embryological methodology and found that males tended to predominate in the earlier diagnostic groups. They used the BWIS method for categorization and closely modelled their work on the BWIS efforts. The latest diagnostic group (septal defects) was primarily female. There was a relative excess of females in the endocardial cushion defect group.

In a cohort study of 664,218 live births conducted in Bohemia, Czech Republic, Samanek (1994) found a higher proportion of boys than girls with DORV, HLHS, TGA, AV stenosis, PV atresia, TA, COA, and c-TGA. There were significantly more girls than boys with PDA, Ebstein's anomaly, truncus, AVSD and TOF.

Birth weight

Rosenthal et al. (1991) using the BWIS data set, found that all case groups other than TGA had greater percentages of births in the low birth weight category (≤ 2500 gm). Tikkanen, Heinonen (1992) reported data from a case control study of 132,993 infants born in Finland during 1982-83. The two national registries identified 408 cases of ASD (defined as an opening in the atrial septum not covered by a valve). Birth weight was found to be significantly associated with ASD (OR=2.5, CI_{95}=1.1-5.9).

Gestational age less than 37 weeks and placental weight

Two other findings from the Tikkanen, Heinonen ASD study were that gestational age less than or equal to 37 weeks was associated with an odds ratio of 2.9 (CI_{95}=1.3-6.5) and placental weight greater than 600 gm was associated with an odds ratio of 2.7 (CI_{95}=1.5-4.9). Rosenthal et al. (1991), using the BWIS data set, analyzed each CHD type separately and found that all of the defects had a higher percentage of infants born before 37 weeks of gestation than controls except for TGA and minor VSD.

Multiplicity

Tikkanen, Heinonen (1992) in their case control study of 408 infants found the risk of twin birth for ASD to be elevated to an odds ratio of 7.8 ($CI_{95\%}$ = 1.4-44). Pradat (1992a) reported twinning of 2.8 percent in his Swedish CHD population. Berg et al., (1989) found, using the BWIS dataset, that there was an excess of case twins compared with control twins. However, the relative rates of monozygous and dizygous twins were as expected. Looping abnormalities occurred in 4 (18.2%) of 22 monozygotic twins, but only 1 (2.5%) of 40 dizygotic twins. Among the co-twin pairs, only 6.2 percent had a co-twin with CHD but when there was a co-twin the defect was mechanistically concordant. However, this analysis is limited by the fact that there is naturally greater foetal loss in one or more of the foetuses in a multiple gestation therefore there is a likely to be a differential selection bias. Kuehl and Loffredo (2003), using the BWIS dataset, found an excess of twin gestations in c-TGA with odds ratio of 1.4, ($CI_{95\%}$=1.0-19.4) which increased in strength after removing Ivemark syndrome infants to an odds ratio of 5.8 ($CI_{95\%}$ = 1.3-26.1).

MATERNAL CHARACTERISTICS

Maternal age

Using the NERICIP data, Rothman and Fyler (1976), after controlling for Down syndrome, reported that TGA is associated with increasing maternal age. The study found that mothers older than 30 years of age had 2.3 times greater likelihood of giving birth to a child with TGA than mothers younger than 20. They used the predominant method for classifying the lesion. Tikkanen and Heinonen (1992) in their Finnish case control study of ASD demonstrated a borderline maternal age effect in crude analysis (OR=1.8, $CI_{95\%}$ = 1.0-3.2) which disappeared in adjusted analysis (OR=1.2, $CI_{95\%}$ = 0.6-2.4).

Pregnancy Complications

(Pradat, 1992b) reported on 1,324 cases of CHD collected from 1981-1986 in Sweden and 2,648 controls. He found that foetal-pelvic disproportion (OR=1.4, $CI_{95\%}$=1.1-1.9) and hydramnios (OR= 8.0, $CI_{95\%}$=3.8-17.0) were associated with CHD.

PATERNAL CHARACTERISTICS

Paternal age

Lian, Zack and Erickson (1986) in a case control study using data selected from the Metropolitan Atlanta Congenital Defects Program (MACDP) found an increased risk for TGA if the father was older than 45 (OR=3.6) adjusted for maternal age and race. However, confidence limits were not presented and the number of cases was only 117 in a 12 year period. TGA was hierarchically defined in the case of parallel defects. There were more than 300,000 controls. Zhan et al., (1991) reported that paternal age of less than 25 was independently associated with increased risk of CHD (OR=2.8, $CI_{95\%}$ = 2.2-3.5) in a population of Chinese infants using the case control study design. However, they accepted cases up to 5 years of age (non-incident cases), did not address the issue of parallel CHD and the study was hospital based.

Savitz, Schwingl and Keels (1991) investigated a population of live births collected from the Kaiser Foundation Health Plan members who participated in the Child Health and Development Studies between 1959 and 1966. The participants, from the San Francisco area of the USA, were predominantly white (65%) although African-Americans were a sizeable minority (24%). A range of socioeconomic levels were represented. Of the 20,530 eligible pregnancies 19,044 resulted in live births. These authors demonstrated

that fathers aged 30-34 (OR=4.3, $CI_{95\%}$ =1.1-16.1) and 35-39 (OR=7.5, $CI_{95\%}$ =1.6-36.3) were at increased risk of having a child with PV stenosis after adjusting for mother's age, race, education and smoking.

Olshan, Schnitzer and Baird (1994) demonstrated an increased risk for ASD to fathers 45-49 with an odds ratio of 2.7 ($CI_{95\%}$ = 1.3-5.8) and for PV stenosis to fathers 35-39 with an odds ratio of 2.0 ($CI_{95\%}$=1.0-4.0). A total of 4,110 individual cases of CHD were identified from the British Columbia Health Surveillance Registry born in the study period 1952-1973. The data were analyzed as lesions. Cedergren, Selbing, Kallen, (2002a) studied 277 cases of severe cardiac defect with two controls per case in Sweden identified between 1982 and 1996. The cases were from a population of 175,768 live births in the 8 year period for a prevalence of 1.6 per 1000. They found no effect for maternal age on the risk of a cardiac defect in the infant but they did find that the paternal age group of 30-34 was protective (OR=0.7, $CI_{95\%}$ = 0.5-1.0).

However, in Stoll et al., (1989) no association was found between advanced paternal age and isolated CHD (OR=0.7, $CI_{95\%}$ = 0.5-1.2); CHD with ECM (OR=0.7, $CI_{95\%}$=0.4-1.2) or in recognized syndromes (OR=0.6, $CI_{95\%}$=0.3-1.0). Similar odds ratios and 95% confidence intervals were found when looking at isolated VSD or ASD. This study also used the lesion analysis method. Bassili et al. (2000) performed a case control study very similar to this one in Alexandria, Egypt. They found an increased adjusted odds ratio of 2.0 ($CI_{95\%}$=1.4- 2.7) for fathers greater than 40 years of age. However as mentioned above the study likely suffers from survivor bias. Pradat (1992c, 1992b) reported in a letter the paternal age results from his Swedish case control study. After stratifying for maternal age and parity he found no relationship.

INDEX PREGNANCY CHARACTERISTICS

Artificial reproductive technologies

In 2002, Anthony et al. demonstrated an increased risk for CHD (OR=1.6, $CI_{95\%}$ =1.1-2.2) with artificial reproductive techniques (ART). However these results should be viewed cautiously as there were concerns over multiple testing, the small numbers which made it impossible to control for confounding and the Hawthorne effect due to the increased surveillance for ART conceptions.

Time to pregnancy/Involuntary childlessness

Pradat (1992b) could not find a relationship between involuntary childlessness and CHD (OR=1.1. $CI_{95\%}$ = 0.8-1.5) or a time to pregnancy of 6 months and CHD (OR=0.4, $CI_{95\%}$ = 0.2-1.1). Cedergren, Selbing, Kallen (2002a) in their case control study did not find an elevated risk (OR=1.3, $CI_{95\%}$ = 0.7-2.4) for involuntary childlessness.

High altitude

Although Alzamora made the observation in 1953 that both PDA and ASD were more likely to be found in infants born at high altitudes, only one analytical study has investigated the relationship between birth at high altitude and CHD. Miao, Zuberbuhler, Zuberbuhler (1988) (also, Miao et al., (1988)) reported that ASD and PDA were found more frequently at high altitudes (OR of 4.6) but it is unlikely that this is congenital. Instead, these occurrences of the defect are hypothesized to be due to compensatory placental mechanisms for pressure differentials which take longer to adjust in some infants than others.

Vaginal bleeding

Using the BWIS dataset, Loffredo et al. (2000) found that vaginal bleeding during pregnancy was higher in Type B IAA without DGS (OR=3.7, $CI_{95\%}$ = 1.4-11.4) than in controls. Tikkanen and Heinonen (1992) found an increased risk associated with maternal bleeding with an odds ratio of 1.9 ($CI_{95\%}$ =1.3-2.8).

Use of female hormones (oral contraceptives)

Although there has long been interest in a relationship between female hormones and CHD, Ferencz et al. (1980) could not find an association between maternal hormone intake and CHD of the conotruncal type (TOF, DORV, and truncus) with a dataset collected prior to BWIS. Although later, (Ferencz et al., 1997) using the BWIS dataset, they reported an increased risk for progesterone use in a multivariate analysis for transposition and normal great artery groups (OR=2.5, $CI_{95\%}$ = 1.1-15.8). For TGA with intact VSD and TOF with PV stenosis in multivariate analysis they also found an association (OR=3.0, $CI_{95\%}$ = 1.0-8.6). Bassili et al. (2000) found a relationship between

female hormone exposure until the eighth week of gestation and the risk of CHD with an adjusted odds ratio of 1.7 ($CI_{95\%}$ =1.1-2.6).[9]

Extra-cardiac malformations (ECM)

Overall the understanding of extra-cardiac malformations is hampered by the fact that they are not always well defined in the literature. While some researchers separate chromosomal anomalies from other ECM and others do not state their methods clearly. The most common ECM associated with CHD is Down syndrome (DS). The number of children with CHD and DS has been reported to be as low as 5 percent (Kenna et al., 1975) and as high as 9 percent (Ferencz et al., 1993).

CHD is also highly associated with DS. Gordon (1990) reported that 45 percent of DS infants have CHD although his was a non-incident population of 190 patients. In Dallas, Texas, USA, Fixler and Threlkeld (1998) reported 52 percent of cases of DS had a CHD. Their population was identified through various sources supporting infants with DS including the two cytogenetic laboratories in the area. They found AVSD most commonly in these infants, a result supported by others (Gordon, 1990; Samanek, 1999; Dickinson, 1981). This strong association of AVSD with trisomy 21 prompts the speculation that the genes on chromosome 21 may determine some important function of growth or adhesion of the endocardial cushions (Anderson et al., 2002).

Kramer et al., (1987) documented the ECM found in 1016 German children with CHD up to 16 years of age in 1981 to 1982. They found that in the non-syndromic patients (e.g., without Down, Noonan, Marfan, Williams, etc) 7 percent had a major ECM, 41 percent had a minor ECM and 53 percent had no ECM. TOF had significantly more ECM than any other CHD. However, the cases were non-incident and they did not state their nosology or how they classified in the case of parallel lesions. Pradat (1997) found 397 (15%) with ECM in 2,618 cases of cardiac anomalies.

Eskedal et al., (2004) reported results from 3,257 Norwegian live born infants registered from 1990 to 1999 from a population of 450,000 live births in this period. The team found a higher percentage of ECM in the CHD population. Thirteen percent had an ECM

[9] Heinonen et al., (1977b) reported an association in the CPP dataset, Wiseman and Dodds-Smith (1984) later suggested that their study suffered from misclassification bias of the cases.

excluding DS. Seven percent had DS alone. Three percent had DS and at least one other ECM. The BWIS group (Ferencz et al., 1989) reported that 28 percent had an ECM.

Maternal weight

Watkins and Botto (2001) found that low pre-pregnancy weight (BMI <16.5) was protective against a major isolated heart defect (OR = 0.6, $CI_{95\%}$ = 0.4-1.0). The odds ratio was elevated among overweight women (BMI > 26) although not statistically significant (OR = 1.4, $CI_{95\%}$ = 0.9-1.9). Although a strength of the study was that the data were from the MACDP, a weakness was that weight was self-reported. Another weakness was that unrecognized diabetics may have been included in the exposure group. On the other hand, they used a hierarchical classification for CHD and they excluded syndromic cases to achieve greater homogeneity of cases. For specific types of CHD they found in adjusted analyses an increased risk for BMI of 16.5 to 19.8. For isolated septal defects (VSD, ASD) the adjusted odds ratio was 1.5 ($CI_{95\%}$ = 1.0-2.3) and for isolated plus parallel cardiac defects the adjusted odds ratio was 1.4 ($CI_{95\%}$ = 1.0-2.0).

In a hospital based case control study from the University of Chicago, Mikhail, Walker, Mittendorf (2002) studied isolated cardiac malformations in infants born to African-American women and found an odds ratio of 6.5 ($CI_{95\%}$ = 1.2-34.9) for infants born to obese (BMI $\geq$ 27) women. They excluded those with possible confounding exposures such as maternal age greater than 35, all forms of clinical diabetes, multiple gestations, maternal seizure or psychiatric disorders (to rule out exposure to teratogenic drugs), maternal radiation, maternal TORCH[10] infection and alcohol abuse. However, the sample size was small (7 CHD and 144 controls) and measurement of pre-pregnancy weight was not described. Cedergren, Selbing, Kallen (2002a) in their case control study found an increased risk for women with BMI $\geq$ 29 with an odds ratio of 1.5 ($CI_{95\%}$ = 1.1-1.9).

Diabetes

This is one of the risk factors most consistently found to be associated with congenital anomalies in general and CHD in particular. In Macintosh et al., (2006) it was determined that women who were diabetic pre-gestationally (*overt diabetes Type 1 or Type 2*) were more likely to deliver an infant with CHD (prevalence ratio 2.7 ($CI_{95\%}$ = 2.5-4.6)). Their population was 2,359 pregnancies to overt diabetic women delivered between March

[10] TORCH=toxoplasma, rubella, cytomegalovirus, herpes

2002 and February 2003 in England, Wales and Northern Ireland. The data were collected through the confidential Enquiry into Maternal and Child Health (CEMACH) and the numbers compared to expected numbers obtained from EUROCAT based on 2002 age-specific rates adjusted for the maternal age distribution.

Other teams have researched diabetes' relationship to the risk of CHD. Pradat (1992b) found that the risk was increased with overt maternal diabetes (OR = 2.7, $CI_{95\%}$ = 1.4-5.0). Among patients with septum defects (ASD and VSD) the odds ratio increased to 6.2 ($CI_{95\%}$ = 2.0-19.5). For *truncus* the odds ratio was 3.7 ($CI_{95\%}$ = 1.9-7.4). Cedergren, Selbing, Kallen, (2002a) in their case control study found an increased odds ratio of 2.4, ($CI_{95\%}$ = 1.4-4.2).

Becerra et al. (1990) analyzed data from the MACDP dataset and found different results for non-insulin dependent (NIDDM), insulin dependent (IDDM) and gestational diabetes (GD) for CHD. For NIDDM they found a relative risk of 9.7 ($CI_{95\%}$ = 2.7-35.3), For IDDM mothers (n=28) they found a relative risk of 18 ($CI_{95\%}$ = 3.9-82.5). Relative risks for specific defects (analysis by lesion) for IDDM mothers were presented. For *truncus* (n=2), the relative risk was 17.9 ($CI_{95\%}$ = 2.4-132.6), for VSD (n=5) the relative risk was 20.2 ($CI_{95\%}$ = 3.8-108.1), for *dextrocardia* (n=1) the relative risk was 56.9 ($CI_{95\%}$ = 4.1-794.1) and for *PA atresia* the relative risk was 61.1 ($CI_{95\%}$ = 4.7-791.3). For those with GD (n=12) the relative risk for *truncus* was 76.0 ($CI_{95\%}$ = 6.8-843.9), TGA 57.1 ($CI_{95\%}$ = 5.4-598.9) and VSD 32.6 ($CI_{95\%}$ = 2.5-434.4). While the confidence limits are wide for all the findings, these are strong point estimates with the lower bounds indicative of a risk. However, the investigators took the lesion approach to CHD diagnosis. A second concern is that with a case control study the exposure definition is retrospective and subjects may have been misclassified. Additionally, if the mother did not report DM then her medical record was not reviewed. The prevalence of GD was unexpectedly low. Additionally, the authors could not measure metabolic control during the first trimester.

The BWIS group took great interest in this risk factor and studied it in a variety of analyses. They reported results in 1990 which showed that overt maternal diabetes was indicative for increased risk with odds ratio of 3.2 ($CI_{99\%}$ = 1.3-7.8) and in GD there was an odds ratio of 1.5 ($CI_{99\%}$ = 0.9-2.2). For subgroups they found that for DORV there was an odds ratio of 21.3 ($CI_{99\%}$ = 3.3- 136.3), for *truncus* an odds ratio of 12.8 ($CI_{99\%}$ = 1.4-114.6), for TOF an odds ratio of 6.2 ($CI_{99\%}$ = 1.4-27.4) and for VSD an odds ratio of 3.5

($CI_{99\%}$ = 1.0-11.3). However, as they state in their limitations because of the rarity of diabetes and the rarity of CHD especially by subgroup, the definitive study is very difficult to conduct.

Loffredo, Wilson and Ferencz (2001c) reported more results of data analyzed embryologically. They found that embryologically early CHD (defined as hierarchical groups 1-3) was found to have an odds ratio of 4.7 ($CI_{99\%}$ =2.8-7.9) associated with diabetes. Laterality CHD had an increased odds ratio of 10 ($CI_{99\%}$ =3.7-27.0). An association was also found between major cardiac outflow problems with TGA (OR=3.0, $CI_{99\%}$ =1.1-8.7) and without TGA (OR=6.6, $CI_{99\%}$ =3.2-13.3). For complete AVSD the association was 22.8 ($CI_{99\%}$ =7.4-70.5). On the other hand, Stoll et al., (1989) and Gev, Roguin, Freundlich (1986) did not find an association between CHD and diabetes.

Prevalence of diabetes in females of reproductive age

Becarra et al., (1990) reported that the overall adjusted prevalence of IDDM in a population of American women was 8 per 1000 and for GD it was 28 per 1000. The CDC (1998) reported a prevalence of any diabetes during pregnancy for white non-Hispanic women aged 20-24 of 17.8 per 1000 singleton live-born infants; aged 25-29 of 24.5 per 1000 singleton live-born infants; aged 30-34 of 30.3 per 1000 singleton live-born infants; aged 35-39 of 41.3 per 1000 singleton live-born infants and aged 40-49 of 56.1 per 1000 singleton live-born infants.

The overall diabetes prevalence in reproductive-aged women is necessary for later comparisons. Warsy and El-Hazmi (1999) reported an estimated background diabetes prevalence of 8 per 100 for reproductive-aged Saudi Arabian women (table 1.4).

Table 1.4 Prevalence of diabetes mellitus in Saudi Arabian women of reproductive age

Age group	Type I Diabetes Mellitus / 100	Type II Diabetes Mellitus / 100	Impaired Glucose Tolerance / 100
14-29	0.320	0.987	0.420
30-44	0.265	5.030	1.552
Total	0.585	6.017	1.972

Maternal diet

Although the relationship between maternal diet and CHD would be an interesting area of study, only one team has tried to look at it and their work is more than 40 years old. Pitt

and Samson (1961) found that control infants had more grams of protein (72 gm as compared with 59 gm) in the maternal diet than those of the CHD children and more calories (2453 to 1989). Control mothers also consumed more mg of iron (10.7 mg compared to 8.6 mg), more Vitamin C (86 mg compared to 57 mg) and more niacin (12 mg compared to 9 mg). However the sample size was very small with only 11 cases of CHD out of a total of 99 congenital malformations and a control group of 99.

In 1976, Stein and Susser produced results from an ecologic study investigating problems of the central nervous system related to the famine of September, 1944 to May, 1945 in Western Holland. During this period of the war the official rations were as little as 4 to 5 hundred calories per day. They found a relative risk of 2.0 with eight cases of spina bifida and hydrocephalus where four were expected. It is likely that severe birth defects like spina bifida and early embryological congenital heart defects are different manifestations evolving from the same mechanisms which could arise from early insults such as inadequate diet.

The BWIS group collected data on maternal diet and promised in their 1993 effort to analyze it. To date, only Scanlon et al.'s (1997) report looking at folic acid, described below, has been published from the BWIS data source.

Caffeine

Rosenberg (1982) looked unsuccessfully for an association between CHD and caffeine containing beverages. However, they considered "use of caffeine-containing drugs" as a confounder rather than adding it to the estimate of exposure. The BWIS group did not find an association either (Ferencz et al., 1993).

Maternal multivitamin use

Related to diet is the issue of maternal multivitamin use. Botto et al. (2000) found that maternal multivitamin use was protective against CHD. This study defined CHD hierarchically. However, they did not attempt to control for background adequacy of the mother's diet. From a population of 113 mothers who used peri-conceptional multivitamins and 1,179 mothers who did not, they found a reduced odds ratio for all heart defects of 0.8 ($CI_{95\%}$ =0.6-1.0), TGA 0.4 (0.2-1.0) and VSD 0.6 (0.4-1.0). In the same group's 1996 publication they found a decreased risk with peri-conceptional use for isolated *truncus* and

for those with TGA. They found in the earlier study that timing of use was essential with only peri-conceptional and early use being protective.

Folic acid

Scanlon et al. (1997) in their analysis of the BWIS data found that if adequate diet was provided then in defects of the outflow tract (hierarchical group 2) there was no difference in those who consumed supplemental folic acid $\geq$ 400 mg per day and those who did not 1.0 ($CI_{95\%}$=0.5-2.2).

Homocysteine

Kapusta et al. (1999) showed in a case control study among a population of 27 Dutch mothers of 29 children with CHD recruited between June 1996 and September 1997 that fasting hyper-homocysteinemia was more prevalent in CHD mothers 3 to 6 months after delivery than in non-CHD mothers (OR = 5.1, CI_{95}=1.8-14.4). However, homocysteine was measured after the CHD diagnosis in the infant. Since homocysteinemia levels are stress related the mother of a child with CHD might be predicted to have a higher level.

In a study of avian embryos, Rosenquist, Ratashak and Selhub (1996) demonstrated that an increase in homocysteine increased the risk of VSD. Twenty-three percent of embryos suffered VSD after an exposure to a teratogenic dose of homocysteine.

Nausea during pregnancy

Boneva et al. (1999) found that early onset, daily frequency and long lasting nausea during pregnancy were associated with a lower odds ratio for CHD (0.8, $CI_{95\%}$=0.7, 1.0). In fact, women with any nausea who took any medications, or Bendectin in particular, were found to be protected against CHD. For Bendectin there was an odds ratio of 0.7 ($CI_{95\%}$=0.5, 0.9).

PREVIOUS PREGNANCY CHARACTERISTICS

Pregnancy losses/spontaneous abortion

In a BWIS analysis, previous stillbirths and spontaneous abortion were found to be associated in a population of infants with Type B IAA without DGS (Loffredo et al., 2000) with an odds ratio of 9.4 ($CI_{95\%}$=1.3-53.1). Pradat (1992b) however found no associations except in the *truncus* group with an odds ratio of 3.9 ($CI_{95\%}$=2.0-7.6) and an overall odds ratio of 1.2 ($CI_{95\%}$=1.0-1.5).

Stillbirths

Pradat (1992b) found an association between stillbirth and all CHD with an odds ratio of 1.9 ($CI_{95\%}$=1.2-3.0). Loffredo et al., (2000) reported in their study of IAA that previous stillbirth was associated with an OR of 4.6 ($CI_{95\%}$ =1.2-3.0) for all IAA (n=46) and an odds ratio of 7.5 ($CI_{95\%}$ =1.7-32.7) for Type B cases. Tikkanen and Heinonen (1992) found a strong significant result with ASD of an odds ratio of 265 ($CI_{95\%}$=34-546).

ENVIRONMENTAL FACTORS

Hair treatments

Blackmore-Prince et al., (1999) looked for a relationship between chemical hair treatments and outcomes of pre-term delivery and low birth weight and could find no association. The study was of 188 preterm infants and 156 low birth weight infants from 123 mothers. Controls were 304 women who delivered term and normal birth weight infants. The mothers were African-American who delivered in North Carolina, USA. In analyzing the BWIS dataset Kuehl and Loffredo (2003) found that mothers who used hair dyes in the plus and minus 3 month window period had an odds ratio for c-TGA of 3.7 ($CI_{95\%}$= 1.6-8.5). After the Ivemark syndrome infants were removed the odds ratio strengthened to 5.6 ($CI_{95\%}$= 2.3-13.7). For severe *PV stenosis* an association was identified with an adjusted OR of 3.7 ($CI_{99\%}$ = 1.5-9.0).

Maternal Illness

Analyzing data from the Atlanta Birth Defects Case-Control Study conducted in 1982-83 (which is part of the MACDP) Botto, Lynberg, Erickson (2001) found an increase in the risk of non-syndromic heart defects for any respiratory infection with fever with odds ratio of 1.9 ($CI_{95\%}$ =1.4-2.6). The result for all heart defects was an odds ratio of 1.8 ($CI_{95\%}$ =1.4-2.4); and for all right obstructive defects 2.7 ($CI_{95\%}$=1.2-4.2). For TA the odds ratio was 5.2 ($CI_{95\%}$=1.3-20.2); for *AV stenosis* it was 6.9 ($CI_{95\%}$=1.0-14.8), for COA it was 2.7 ($CI_{95\%}$=1.2-6.0) and for VSD it was 1.8 ($CI_{95\%}$=1.1-2.9).

Influenza

Ferencz et al. (1997) found associations between influenza and CHD for a variety of CHD sub-types. For right-sided outflow tracts they found an odds ratio of 2.7 ($CI_{95\%}$=1.2-6.0) and for *PV stenosis* the odd ratio was 2.5 ($CI_{95\%}$=1.3-4.6). Also, for those with TA they found an odds ratio of 4.3 ($CI_{95\%}$=1.9-9.8).

Epilepsy

Although Ferencz et al. (1997) found associations between maternal epilepsy and CHD for COA with an elevated odds ratio of 6.5 ($CI_{95\%}$ =1.8-23.0) the risk for epileptic mothers and the medications associated with that disease have been difficult to assess because of the rareness of the disease. However, Pradat, (1992b) found 9 cases of CHD from 1,324 cases with epilepsy versus zero cases of 2,648 controls. Cedergren, Selbing, Kallen (2002b) found an association between antiepileptic drugs and CHD with 3 of 269 cases having exposure and none of the 524 referents having exposure. But Stoll et al., (1989) found that 0.4 percent of case mothers and 0.4 percent of control mothers had epilepsy.

Thyroid disease

Similarly, thyroid disease is difficult to explore as a risk factor. Cedergren (2002) found a suggestion of elevated risk with 3 of 269 cases versus 2 of 524 controls yielding an odds ratio of 2.9 with an insignificant confidence interval ($CI_{95\%}$= 0.3-35.4). Pradat (1992b) too found no association with thyroid disease but the case numbers were extremely low: 3/1324 versus 1/2648. The BWIS group found that thyroid disease was associated with an odds ratio of 3.0 ($CI_{95\%}$= 1.2-2.7) for moderate PV stenosis.

Medications

Ferencz et al. (1997) report several significant findings with respect to medications consumed in the critical period.

Benzodiazepines and Metronidazole

These include an adjusted odds ratio of 3.3 ($CI_{99\%}$ = 1.3-8.2) for TGA and an adjusted odds ratio of 2.4 ($CI_{95\%}$ = 1.1-5.3) for l-TGA with use of benzodiazepines. For metronidazole in l-TGA they found an adjusted odds ratio of 5.5 ($CI_{95\%}$ = 1.1-26.8). Similar significant results were found for VSD, TOF with PV stenosis, and left sided obstructive defects.

Gastrointestinal medications

Gastrointestinal medications were associated with Ebstein's anomaly in univariate analysis with an odds ratio of 3.0 (1.1-8.5) (Ferencz et al., 1997).

Antitussives

For defects of laterality and looping Ferencz et al., (1997) reported an increased odds ratio of 4.6 ($CI_{95\%}$ = 1.4-15.5).

Aspirin/Ibuprophin

Loffredo et al., (2000), using the BWIS dataset, found that maternal exposure to aspirin in Type B of IAA with DGS was significantly associated with CHD with an odds ratio of 4.7 ($CI_{95\%}$ = 1.5-14.2). Ferencz et al. (1997) found that for TGA with intact VSD the odds ratio was 2.5 ($CI_{95\%}$=1.2-4.5); for BAV they found an odds ratio of 3.8 ($CI_{95\%}$ = 1.7-8.6), for membranous VSD they found an odds ratio of 1.5 ($CI_{95\%}$ = 1.0-2.3) and for AVSD an odds ratio of 2.5 ($CI_{95\%}$ = 1.4-4.3). Mothers in the AVSD group had taken the ibuprophin for menstrual pain with their last menstrual period.

Sulfonamide

In urinary tract infections treated with sulfonamide Ferencz et al., (1997) found in increased odds ratio for defects of laterality and looping of 7.5 ($CI_{95\%}$ = 2.1-26.6).

X-ray exposure

Stoll et al. (1989) were not able to demonstrate an association between exposure to x-rays and CHD. However, Bassili et al., (2000) identified an association between maternal irradiation until the eighth week of gestation and increased risk of CHD with an odds ratio of 6.5 ($CI_{95\%}$ = 1.4-44.0).

Maternal smoking

Kallen (1999) identified maternal smoking during pregnancy as having an association with three sub-diagnoses: *truncus*, with odds ratio of 1.2 ($CI_{95\%}$=1.0-1.5); TGA with odds ratio of 1.3 ($CI_{95\%}$=1.0-1.7); and ASD with odds ratio of 1.6 ($CI_{95\%}$=1.0-2.6) in a case control study of 3,384 cases of CHD from a population of 1,413,811. She did not demonstrate a dose response but the analysis was controlled for year of birth, maternal age, parity and educational level. It was not controlled for maternal diabetes, epilepsy, rubella infections or alcohol use. However, neither Stoll et al., (1989) nor Pradat (1992b) were able to find an association between maternal smoking and an increased risk of any type of CHD.

Paternal smoking

Zhang et al. (1992) looking at birth defects in general found a modest effect for smoking between 1 and 20 cigarettes per day with an odds ratio of 1.2 ($CI_{95\%}$ = 1.0- 1.5) in a case

control study using data from the Shanghai Birth Defects Monitoring Program. From 1986 to 1987, 1,012 cases and 1,012 controls were recruited. They limited the time frame of exposure from 28 weeks gestation to 1 week postpartum and obtained exposure information of paternal smoking from the mother. Savitz, Schwingl, Keels (1991) however could not demonstrate an association with paternal smoking (or alcohol consumption).

Pesticides[11] (includes insectcides, rodenticides, herbicides)

Correa-Villasenor et al., (1991a) found that pesticide use was associated with TAPVR (OR=2.1, $CI_{99\%}$ = 0.82-5.2); when coupled with familial ECM the odds ratio increased to 6.3 ($CI_{99\%}$ = 2.2-18.1) and with familial cardiac disease it increased to an odds ratio of 19.1 ($CI_{99\%}$ = 3.6-102.0). With both familial ECM and familial cardiac disease it increased even further to an odds ratio of 58.3 ($CI_{99\%}$ = 5.1-662.8). Loffredo et al (2001b) analyzed the BWIS data and found that TGA was associated with the use of rodenticides and herbicides. The odds ratio for any exposure to pesticides during the critical period was 2.0 ($CI_{95\%}$ = 1.2-3.3). In multivariate analysis: herbicides were associated with TGA with an odds ratio of 2.8 ($CI_{95\%}$ = 1.2-6.9) and rodenticides with an odds ratio of 4.7 ($CI_{95\%}$ = 1.5-14.2), An earlier study by Adams et al., (1989) had used the agricultural trades as a proxy for pesticides use for truncus and found an odds ratio of 16 ($CI_{95\%}$ = 3.1-85.5).

Maternal occupation

Interest has been raised in maternal occupational exposures. While Stoll et al., (1989) could not find an association, the BWIS found several. They found an association for TAPVR with maternal exposure to soldering (as a proxy for lead) of an odds ratio of 15.5 ($CI_{99\%}$ = 2.0-122.7) and maternal exposure to paint and paint stripping materials (as a proxy for lead) with an odds ratio of 3.0 ($CI_{99\%}$ = 1.1-7.7) (Correa-Villasenor et al., 1991a). Exposure to organic solvents was found to increase the risk of TGA with an odds ratio of 3.2 ($CI_{95\%}$ = 1.4-7.1). And maternal use of arts and crafts increased the risk of IAA, type B without DGS to an odds ratio of 4.8 ($CI_{95\%}$ = 1.3-17.4) (Loffredo et al., 2000). Tikkanen and Heinonen (1990) investigated chemicals, dyes, lacquers and paints

[11] Rodenticides (includes pellets, powders or food imitators but not traps). Herbicides kill weeds.

and found associations with conal septal malformations (TOF, TGA, *truncus*, DORV and *PV atresia*) with an odds ratio of 2.9 ($CI_{95\%}$ = 1.2-7.5). In a second publication in 1992 they showed an association with ASD II with an adjusted odds ratio of 1.9 ($CI_{95\%}$ = 1.1-3.4). However, Cordier et al., (1997) could not demonstrate an association between maternal exposure to glycol ethers and endocardial cushion defects, septal defects, malformations of the cardiac outflow tract, HLHS or valve anomalies. However, their analysis was lesion-based and they limited their cases to those identified within the first week of life. Correa-Villasenor et al. (1993) found an association between jewellery making and ASD II with an odds ratio of 12.6 ($CI_{95\%}$ =2.3-68.6).

Anesthetic gases

In an early study Pharoah et al., (1977) found that the prevalence of malformations of the heart and great vessels reported for offspring of women anaesthetists was 13.8 per 1000 versus 3.6 per 1000 for other physicians and 6.6 per 1000 for the National Child Development Study background population. The data were collected on the outcome of 5,700 pregnancies to women physicians first registered in England and Wales in 1950 or later. However, their exposure information was completely self-reported and they used a reference control population. Furthermore, their response rate was only 72 percent. Nevertheless, the respondents were all medically trained and data on all participants' pregnancies were collected.

Paternal occupation

Olshan, Teschke and Baird (1990) reported an increased risk for certain CHD in children whose fathers were fire-fighters as compared to controls or policemen although no hazardous exposure measurement was made. They used the Clark group "flow lesions" and found an odds ratio of 4.0 for VSD ($CI_{95\%}$ =1.3-12.2) and 5.7 for ASD II ($CI_{95\%}$ =1.2-28.0). The study was a linkage effort and as such left many questions unanswered such as the fact that there were only 281 live births to firemen in 21 years and the policemen were recorded as having had three times as many births. Also, since ASD II runs in families (Bizarro et al., 1970) the authors should have noted that they only included one case per parental pair. Additionally, there was no measurement of the hazardous exposure load. Bassili et al., (2000) found an adjusted odds ratio of 1.2 but the confidence limit crossed one for paternal occupational exposures to all CHD ($CI_{95\%}$ =1.0-1.6).

Air pollution

Ritz et al. (2002) found in an ecological study that maternal exposure to ambient air pollution increased the risk of isolated aortic artery and valve defects with an odds ratio of 2.7 ($CI_{95\%}$ = 1.2-6.1). A dose response for VSD was found to exposure to carbon monoxide in the second month. They found that at 1.1-1.6 ppm the odds ratio was 1.6 ($CI_{95\%}$=1.1- 2.5); at 1.6-2.4 ppm the odds ratio was 2.0 ($CI_{95\%}$ = 1.1, 3.7) and >2.3 ppm the odds ratio was 3.0 ($CI_{95\%}$=1.4, 6.1). In a multiple-pollutant model they found in the group exposed to greater than 2.9 ppm of ozone an odds ratio of 2.9 ($CI_{95\%}$=1.0, 8.7). These odds ratios were adjusted for decade of birth, infant sex, maternal race, maternal age, single versus multiple birth, parity, prenatal care, maternal education and season of conception.

Water contamination

Bove et al. (1995) identified an increased odds ratio of 2.8 ($CI_{90\%}$=1.4, 6.1) for major cardiac defects and VSD in 6 cases where there was a level of 1,2-dichloroethane that was above the contaminate level. Goldberg et al., (1990) found in an ecologic study in Arizona in the south west of the United States that 35 percent of children with CHD (n=707) had exposure to water contaminated with trichloroethylene, dichloroethylene and chromium versus 10 percent of the two control groups. Additionally, after the clean-up the proportion of CHD in those areas reduced to the average for the area.

Environmental pollution

Abushaban et al., (2004) found that the annual incidence per 10,000 live births of CHD increased from 40 pre-invasion to 103 post-liberation ($p<0.001$) in Kuwait. They attributed this increase to the oil fires that burned for 10 months in 1991 in that area. However they were not able to distinguish between those mothers who remained in Kuwait during the invasion by Iraq and those who left. They were also unable to identify those babies with PDA of prematurity.

SOCIO-ECONOMIC CHARACTERISTICS

Residence

Bassili et al. (2000) found that semiurban residence was associated with an adjusted odds ratio of 1.5 ($CI_{95\%}$ =1.2-1.9). Rural residence was associated with an increased adjusted odds ratio of 3.0 (2.3-4.0). Cedergren, Selbring, Kallen (2002b) found that rural residence was associated with an increased adjusted odds ratio of 1.4 ($CI_{95\%}$ =1.1-1.8) for one of the

two groups studied however city residence showed elevated risk for the reference counties (OR= 1.3, $CI_{95\%}$ =1.1-1.5).

1.5 Consanguinity and health

1.5.1 Consanguinity

This definition of consanguinity is the one geneticists use – marriage to a blood relative. Using a schematic diagram, called a phylogram, consanguineous relationships can be described without ambiguity. Anthropologists have used this method to describe the general endogamous and exogamous marriages allowable within a society and geneticists have used the phylogram (aka as a pedigree) to identify disease affected and unaffected members of an extended family. This project has used the phylogram to help mothers identify their relationship to their spouse to avoid misclassification bias.

Using the phylogram to document consanguinity

This first example (figure 1.4) uses the phylogram nomenclature to describe a non-consanguineous partnering. X represents males and O represents females. Figure 1.5 is of patrilineal first cousin marriage. Double cousins occur when a sibling pair marries a sibling pair (figure 1.6). Figure 1.7 shows that two brothers (the X's in Generation II) have married two sisters (the O's in Generation II). The double cousin marriage is as close genetically (F=0.125) as uncle-niece marriage which is not seen in Saudi Arabia or any Islamic society. Additionally, other marriages which are closer than first cousin are allowed. For example, figure 1.7 presents a child whose parents are triply related: (1) first cousin once removed (O_{IIa3}, O_{IIa2}, X_{IIIa2}); (2) first cousin once removed (O_{IIa3}, X_{IIa1}, O_{IIIa1}); and the parents of O_{IVa1} are first cousins (figure 1.7).

Figure 1.4 Example of a non-consanguineous relationship between Generation III X and O with offspring in Generation IV

Generation	Couple A	Couple B	Couple C	Couple D	
I	O_A + X_A	O_B + X_B	O_C + X_C	O_D + X_D	• Four couples: A-D. • Each couple has at least one offspring. • X_a marries O_b and X_c marries O_d • X is not related to O. • Offspring of X and O is the product of a non-consanguineous relationship.
II	X_a	O_b	X_c	O_d	
III	X		O		
IV	Offspring				
Offspring has 8 biological great-grandparents (the maximum). (O_A+X_A, O_B+ X_B, O_C+ X_C, O_D+ X_D)					

Figure 1.5 – Example of a first cousin relationship between Generation III X and O with offspring in Generation IV

Generation	Couple B	Couple A	Couple C
I	O_B + X_B	O_A + X_A	O_C + X_C
II	O_b	X_{a1}	X_{a2} O_c
III	X		O
IV	Offspring		

- Three couples: Couple A-C.
- Couple A has at least two offspring. X_{a1} and X_{a2} (brothers).
- X_{a1} marries a non-relation O_b and X_{a2} marries a non-relation O_c. (Couples A, B and C may of course have other offspring.)
- X, a son of X_{a1}+O_b marries O, a daughter of X_{a2}+O_c.
- The parents of Offspring are patrilateral first cousins.

Instead of 8 great-grandparents (the maximum) Offspring (Generation IV) has 6: (O_A and X_A, O_B and X_B and O_C and X_C)

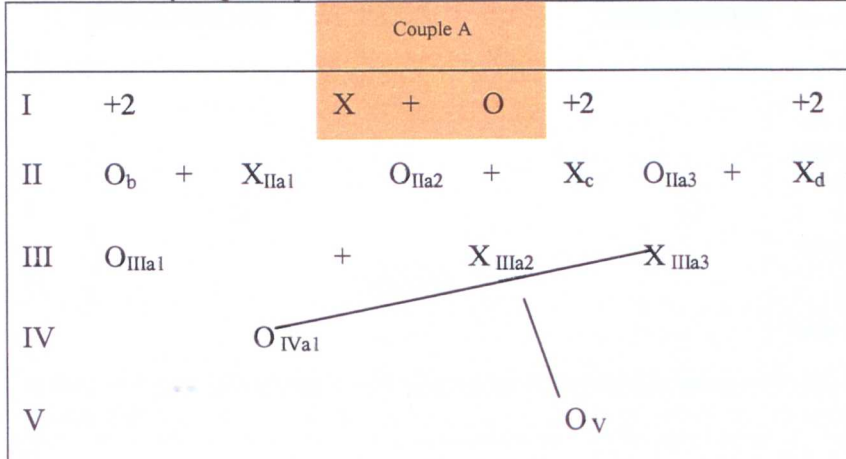
Figure 1.6 Example of a double first cousin relationship between Generation III X and O with offspring in Generation IV

Generation	Couple A	Couple B
I	X_A + O_A	X_B + O_B
II	X_{a1} X_{a2}	O_{b1} O_{b2}
III	X	O
IV	Offspring	

- Two couples: Couple A and Couple B.
- Each couple has two children. In this example they are brothers, but they could be sisters or one boy and one girl. The two brothers (X_{a1} and X_{a2}) and two sisters (O_{b1} and O_{b2}) marry one of the other pair. (Couple A and B may of course have had other children. Additionally, as many as 30 years of age could separate X_{a1} and X_{a2} (or O_{b1} and O_{b2}) if O_A were 15 at the birth of X_{a1} and 45 at the birth of X_{a2}.)
- An offspring of X_{a1} + O_{b1} marries an offspring of X_{a2} + O_{b2}.
- The parents of Offspring are double first cousins.

Instead of 8 great-grandparents (the maximum) Offspring (Generation IV) has 4: (X_A and O_A) and (X_B and O_B)

Figure 1.7 Example of a triple cousin relationship between Generation III X and Generation IV O with offspring in Generation V



- Couple A has 3 (or more) children. X_{IIa1}, O_{IIa2}, O_{IIa3}
- They marry non-related O_b, X_c, X_d, respectively.
- Offspring O_{IIIa1}, X_{IIIa2}, X_{IIIa3}.
- O_{IVa1} is offspring of O_{IIIa1} and X_{IIIa2}
- O_{IVa1} marries X_{IIIa3}
- The parents of O_V are related in two ways and the parents of O_{IVa1} are first cousins.

Instead of 16 great-great-grandparents (the maximum) Offspring (Generation V) has 8 (Generation I). Instead of 8 great-grandparents (the maximum) Offspring (Generation V) has 6. There are three relationships: 2 first cousins once removed and mother's parents are first cousins.

Or, conversely, the relationship can be less close because of the acceptance of polygamy, divorce and remarriage as in figure 1.8. X and O in generation III are half-first cousins. The offspring has 7 rather than 6 great-grandparents. Half-first cousins once removed, half-second cousins and so forth also exist.

The schematic development process was iterative. The four examples of full first cousins and the two examples of full double first cousins were drawn firstly.[12] Following this as the phylograms were collected new patterns were added to the schematic. Whenever a new phylogram was brought in it was compared with the old and assigned a number. Figures 1.4 to 1.8 are therefore real patterns as well as theoretical. Over 3000 phylograms have been collected as a consanguinity sub-project (Sandridge, 2005).

Some examples found in the sub-project helped avoid problems in collecting the data for this project. For example, problems in translation where a couple defined themselves verbally as "first cousins" but through the phylogram they revealed a different relationship such as third cousin but the partner was the "first" born. Another example is the "milk cousin" phenomenon referred to in the passage from the Qur'an quoted in Section 1.1.3 where the persons are not related by blood but would describe themselves as

Figure 1.8 Example of a first half-cousin relationship between Generation III X and O with offspring in Generation IV

	Marital Unit B	Marital Unit A	Marital Unit C
I	O_B + X_B	O_{A1} + X_A + O_{A2}	O_C + X_C
II	O_b	X_{a1} X_{a2}	O_c
III	X		O
IV		Offspring	

- Marital Units A-C. Marital Unit A is one man who has been married twice and has had children with both women: X_{a1} and X_{a2}. They are half-brothers.
- X_{a1} marries a non-relation O_b and X_{a2} marries a non-relation O_c. Unless specifically asked, X_{a1} and X_{a2} will not mention that they have different mothers.
- X, a son of X_{a1}+O_b marries O, a daughter of X_{a2}+O_c.
- Offspring's parents are patrilateral half- first cousins.

Instead of 8 great-grandparents (the maximum) Offspring (Generation IV) has 7: (O_{A1}, X_A and O_{A2}, O_B and X_B and O_C and X_C).

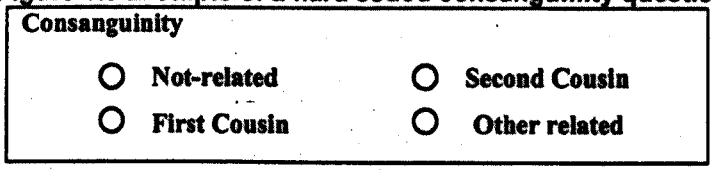
[12] First cousin 1) matrilateral, 2) patrilateral, 3) crossed, 4) crossed crossed; 5) double first cousin, and 6) crossed double first cousin.

such. Milk siblings are created when two people are breastfed three times by the same woman. This makes them siblings (unable to marry) and their children cousins (milk cousins) who, naturally, are allowed to marry. Unless specifically asked, the milk cousins would define themselves as consanguineous.

The alternative to the phylogram – hard coding

The alternative to the phylogram is hard-coding the response at the point of contact or possibly even from the medical record. The question would be asked, "Are you related to your spouse in any way besides marriage," and the response would then be coded to one of the choices in figure 1.9.

Figure 1.9 Example of a hard coded consanguinity question



Other codes (such as first cousin once removed) could be included for more detail however it appears that the onus is on the interviewee to relay to the interviewer the correct category. My research has indicated that Saudi Arabians, while they know they are related to a relative, do not have the precise category in mind and therefore need an instrument to describe the relationship accurately. The phylogram provides the assistance needed in identifying the category to which the couple belongs.

Genetic studies

Genetic studies are certainly also possible to determine the relationship between two parents. However, in Saudi Arabia they are not culturally appropriate.

Interest in consanguinity as an epidemiological risk factor

Animal breeding indicates that inbreeding yields genetic strengths as well as genetic weaknesses (Patterson, 1991; Pyle, Paterson, Chacko, 1976). In human society marrying relatives was widespread until as recently as 120 years ago. In the United Kingdom, the practice was accepted under Roman Catholic law until the eleventh century after which time papal dispensations were required. After a period of prohibition, it was formally approved shortly after the succession of Queen Elizabeth I in 1558. Currently, although it is legal in the UK, it is not common practice (Ottenhiemer, 1996).

In the United States inbreeding at least at the level of first cousin is prohibited in 31 of the 50 states (Ottenheimer, 1996). In Europe, though legal, the practice comes under public scrutiny. In Britain this may have been expressed by proposed changes in immigration laws (BBC news, 2004). An advantage associated with marrying a relative found in the Japanese culture (Schull, and Neel, 1972) and the Hindu society of Andhra Pradesh (Dronamraju and Meera Khan, 1963; Govinda Reddy, 1988) was maintenance of family property. Khlat et al., 1986 found psycho-social benefits including familial unity, decreased pressures on the new wife in her new home, less abuse against women and a stronger marital bond with less risk of divorce. Jaber, Shohat, Halpern (1996) reported also that there was greater compatibility of the bride with her husband's family and found that property retention were also important reasons. However, consanguinity has also been accused of preventing efforts of "national building" (Sailer, 2003) by enhancing political unity among the family and the clan (Barth, 1954) rather than shifting the strength of the alliance to the elected government. Ottenheimer argues that marriage between relatives allows the effective transmission of the culture of a group from generation to generation thereby creating social stability (1996) which in a period of turmoil and change could have collateral benefits. No recent, comprehensive surveys have been conducted to investigate the reasons for choosing to marry consanguineously.

Nonetheless, concern has been raised over the practice in the Middle East. The main genetic implication of inbreeding is that there could be an increase in the birth rate of homozygotes for recessively inherited Mendelian characteristics in relation to the gene frequency which could bring about a decrease in the overall fitness of the population (Khoury, Beaty, Cohen, 1993). For the Middle East the concern has been expressed that because they are isolated that they suffer greater from genetic diseases not only because of genetic drift, but possibly founder effect and inbreeding (Khoury, Beaty, Cohen, 1993).

1.5.2 Diseases studied

The search for literature on consanguinity and health with specific reference to Saudi Arabia was systematic. Using the key words "consanguinity" and "Saudi Arabia" 134 articles were identified. Of these, 16 were relevant, but many which were known to ALS were missing. Searching by the keyword "consanguinity" returned 7268 articles. Therefore it was decided to refer to a compendium by Bittles (1998), one of the experts in the field of consanguinity, of relevant articles. From this collection of articles, 10 diseases

(plus CHD) were identified as potentially revealing information about consanguinity. Once the 11 disease areas were identified each was searched individually ("Consanguinity and CHD", Consanguinity and reproductive wastage", etc.) to identify relevant articles. Table 1.5 reports the results of these searches. Please note that not all articles were identified through the search strategy. Additional articles found via other sources, including Bittles, were included as appropriate. A detailed description of these studies can be found in Appendix E.

Table 1.5 Searching strategy for literature concerning relationship between consanguinity and disease

Disease	Search results	Suspected to be relevant after review of abstract	Reviewed in this Thesis
CHD	186	14	14
Reproductive wastage, fertility, stillbirth	10	8	14
Under 5 mortality	338	9	2
Hearing loss	288	8	5
Cognitive disability	11	4	5
Down syndrome	73	12	6
Sleep apnea	14	1	1
Malformations*	560	10	10
Pre-Reproductive death	117	2	4
Schizophrenia	47	4	3
Breast Cancer	16	3	2

* Initial search returned 2206. After limits applied reduced to 560.

Reproductive wastage, fertility, stillbirth, infant mortality

In a cross-sectional study of 2007 couples randomly selected from the entire Jordanian population, Khoury and Massad (2000) found that stillbirth was more frequent in consanguineous couples (controlled for year of marriage) than in non-consanguineous couples with 11 per 1000 live births versus 6 per 1000 live births ($p< 0.05$). The consanguinity data were well collected and the consanguinity itself was well-defined.

In a population collected by the Norwegian Registry, Stoltenberg et al., (1999) compared 629,888 non-consanguineous births to 3,466 births to related parents with the outcome of recurrent stillbirth and infant death. The analysis was restricted to first cousin consanguinity and the index case had to have a previous sibling born in Norway between 1967 and 1994. The method for determining the category of "first cousin" was not described. For unrelated parents, the risk of still birth and infant death was 17 per 1000 if the first child survived and 67 per 1000 if the previous child died before 1 year of age. For first cousins the risk of early death was 29 per 1000 if the previous child survived and

116 per 1000 if the previous child died. Analyses were adjusted for sibling number, maternal age, mother and father's educational level and year of birth. In an earlier study Stoltenberg et al., (1997) restricted the population to 7,494 children born to two parents of Pakistani origin. These data were collected as part of a cross-sectional survey between 1967 and 1993 again in Norway. The authors found an adjusted elevated odds ratio of 1.4 ($CI_{95\%}$=1.2-1.6) for birth defects in general.

In a study of perinatal, neonatal and post-neonatal mortality, Dorsten, Hotchkiss and King (1999) found that among 1,777 singletons born from 1917 to 1988 to Amish families in Pennsylvania, USA, that the more consanguineous the marriage the greater the chances of dying during the first year for infants who survive the first week of life.

Jain et al., (1993) conducted a hospital based case control study in Pondicherry, India where they collected 400 cases and 1000 controls between 1988 to 1989 with the endpoint of reproductive wastage. They found a relative risk of 2.0 but did not present confidence intervals and their data were not independent as they accepted multiple children from the same consanguineous union. Additionally, they did not define their method for collecting consanguinity data.

Bittles, Grant and Shami (1993) performed a cross-sectional study of 9,250 families in Punjab, Pakistan from 1979 to 1985. The stillbirth rate was 9 percent for double first cousins, 4 percent for first cousins, 3 percent for first cousins once removed, 4 percent for second cousins and 3 percent for those non-related. Their study was well conducted with adequate exposure data. An earlier study by Shami, Schmitt and Bittles (1989) presented data from 3,329 interviews conducted door to door in seven cities in the Punjab over the period 1980 to 1983. It is not clear whether these data are a part of the later study. The interviews collected information about labour and delivery. Using a regression equation the authors were able to demonstrate that mortality under random mating was lower than death ascribed to inbreeding measured as lethal equivalents per gamete ($p<0.001$). The authors were unable to control for SES and there was noticeable variation between the seven cities.

A cross-sectional study of 5,007 randomly selected women in Kuwait in 1983 (Al-Awadi et al., 1986) was not able to demonstrate a significant difference between consanguineous and non-consanguineous unions with respect to reproductive wastage.

Al-Abdulkareem and Ballal (1998) using a cross-sectional design of 944 ever married female Saudis and 363 males found that there was no difference between consanguineous and non-consanguineous offspring with the outcome reproductive wastage. Looking at pre-natal and post-natal mortality Al Husain and Al Bunyan (1997) could not demonstrate a difference between consanguineous and non-consanguineous offspring in a cross-sectional study of 2,001 women living in Riyadh married to Saudis aged 20 to 45 in 1993. Bundey and Alam (1993) demonstrated in a prospective study of 4,934 children in Pakistan an increased rate of post-neonatal deaths as compared to non-consanguineous couples (1.85% versus 0.34%).

Chitty and Winter (1989) demonstrated in a population identified from four hospitals in the North West Thames region of the UK that Pakistanis had a peri-natal mortality increased odds ratio of 1.39 ($CI_{95\%}$ =1.1-1.8). The increase was due to a significantly higher incidence of autosomal recessive disorders, neural tube defects and renal malformations. In terms of prevalence it was a difference between 16 per 1000 in the Pakistani population versus 11 per 1000 in the European population. However, only one of the 4 hospitals collected data on consanguinity and the method of collection is not discussed.

Basaran et al., (1989) in Turkey reported increased rates of abortion, stillbirths, prenatal losses and neonatal deaths in the consanguineous group compared to the non-consanguineous. They studied 56,664 married couples collected from 1970 to 1988 in three areas. In Iraq, Hamamy and Al-Hakkak (1989) reported on 233 families with severely disturbed reproductive health, 227 families with moderate levels of reproductive wastage and 155 families with no reproductive disturbance and found that the inbreeding coefficients of these three groups were 0.0358, 0.0241 and 0.0208, respectively.

In a case control study in Alexandria, Egypt, Mokhtar and Abdel-Fattah (2001) collected data from 730 couples with a history of reproductive losses and 2,081 controls in the period 1998 to 2000. In the 730 couples with reproductive losses, the proportion of

consanguinity was 69 percent compared to 21 percent in the controls. However, this was a particularly low rate as Basaran admits. Most studies from Egypt found a background prevalence of consanguinity ranging from 29 to 50 percent. In an adjusted analysis, consanguinity between couples increased the relative risk of repeated abortion to odds ratio 4.0 ($CI_{95\%}$ =3.0-5.1); stillbirths to odds ratio 10.6 ($CI_{95\%}$ =6.7-17.0) and neonatal death to odds ratio 17.2 ($CI_{95\%}$ =10.8-27.3).

Under 5 mortality

Hussain, Bittles and Sullivan (2001) performed a cross-sectional analysis from two population surveys. Indian data of 5,447 infants from 1992-93 and Pakistani data of 3,993 infants collected from 1990 to 1991 looking at under 5 mortality. They found that there was an increased risk for infants from consanguineous unions for early mortality. Only first cousin unions were analyzed, only singletons and only offspring from women married but one time were included. The rate for Indian infants was a relative risk of 1.2 ($CI_{95\%}$ =1.0-1.4) and for Pakistani infants it was 1.3 ($CI_{95\%}$ =1.2-1.6). The method of measuring consanguinity was not defined.

Hearing loss

Hearing loss has been suggested to be associated with consanguinity. Despite the limitations of the studies conducted to date, the preponderance of data suggests that some proportion of sensori-neural hearing loss is an autosomal recessive disorder. Its risk therefore will be increased with consanguinity.

Zakzouk, El-Sayed and Bafaqeeh (1993) reported on results from Saudi Arabia. They demonstrated in a random sample of 6,421 Saudis less than 12 years of age a relative risk of 2.0 (no confidence limits presented) for sensori-neural hearing impairment associated with consanguinity. The prevalence was 17 per 1000. However, the data were not independent and multiple deaf children from the same consanguineous union were included. Additionally, the method for collecting data on consanguinity was not provided. In a follow up study covering Saudi Arabia, Zakzouk (2002) tested 9,549 children up to the age of 15 and found a prevalence of 5 per 1000. The second study found a lower percent of children from first cousin marriages (19%). However, the study is again hampered because independence of measurement was not discussed by the author.

Bener, El Hakeem and Abdulhadi conducted a cross-sectional study of 2,277 newborns in Doha, Qatar in 2005 and determined that the overall hearing loss prevalence was 5.2 percent. Sixty-one percent of hearing loss cases were from consanguineous unions versus only 25 percent consanguineous in the non-hearing loss group. However, the population in Qatar is extremely mixed with less than 25 percent of the population being Qatari. The other 75 percent are temporary and more permanent immigrants from across the globe but predominantly from other Arab countries (particularly Palestine) and Asia (particularly the Philippines and India). Additionally, hearing loss was not subdivided into congenital versus environmental and results were not stratified by bilateral versus unilateral hearing loss. Furthermore, this was a particularly low rate of consanguinity in the background population. Bener and Hussain (2006) (and Bener and Alali, 2006) reported a background prevalence of consanguinity of 54 percent ($CI_{95\%}$=52.3-55.7).

Al Khabori (2004) reported on an Omani paediatric population. He collected data retrospectively, from 1986 to 2000, on 1,400 Omani children who were suffering severe to profound deafness. The rate of consanguinity in the parents of the affected children was 70 percent compared to a background prevalence of 53 percent.

Ben Arab et al., (2004) performed a cross-sectional study of 5,020 individuals in Northern Tunisia and found 160 deaf children (3%). The risk associated with consanguinity was 10 times with 62 percent of the children having parents who were first cousins or closer versus 21 percent of the controls.

In the United Arab Emirates, Al-Gazali studied children attending classes for the deaf and found that the level of consanguinity in the study group was 74 percent versus the background rate of 51 percent.

Serious cognitive and mild cognitive disability

In a cross-sectional, national household survey of childhood disability conducted from 1987 to 1988 in Bangladesh, Durkin et al. (2000) reported an odds ratio of 15.1 ($CI_{95\%}$ =3.1-74.3). The method of consanguinity collection was not identified. The authors were not able to distinguish between congenital serious / mild cognitive disability and acquired cognitive disability.

Afzal (1988) measured cognitive behaviour using the Weschler's Intelligence Scale for Children in 566 randomly selected healthy 9 to 12 year old children from Bhagalpur, India. The survey was conducted door to door and they found that consanguinity ($p<0.001$) and locality ($p< 0.001$) independently affected IQ scores and locality interacted with consanguinity ($p< 0.05$). However the IQ of the parents was not tested. In another study conducted in India with 186 males, aged 13 to 15, the Raven matrices IQ test was used (Agawal, Sinha, Jensen, 1984). The authors reported that there was more variance in the first cousin group ($p<0.01$) than in the non-related group. The mean IQ adjusted for age and SES was 28 for first cousins and 34 for not related ($p< 0.001$).

In a cross-sectional study of 3,203 Arab children from grades 4 to 6 in Israel Bashi, (1977) demonstrated that 12 year olds from double first cousin families showed higher variance in general intelligence tests, Arabic, Hebrew and Science. Outbred children performed the best overall and offspring of double first cousins the worst.

Stein, Belmont, Durkin (1987) obtained frequencies of severe mental retardation (IQ less than or equal to 55) (SMR) and mild mental retardation (IQ greater than 55 and less than or equal to 70) from pilot surveys of severe childhood disability in eight under-developed countries. Approximately, 1,000 children aged 3 to 9 were surveyed in each location. The study found that SMR children were more likely to be from consanguineous families and that they had associated impairments. All mentally retarded children were from a lower SES than comparison families.

Down syndrome

In 11,614 singleton births in Kuwait consanguinity was found to be significantly associated with Down syndrome (DS) after controlling for maternal age (Alfi, Chang, Azen, 1980). The relative risk was 4.1 for consanguineous infants whose mothers were less than 40 at birth and 5.0 for those consanguineous infants whose mothers were 40 or older. Confidence intervals were not shown.

Zlotogora (1997) reported that the rate of consanguinity in Palestinian Arabs was 44 percent with 23 percent between first cousins. His study was conducted on 2,000 families who attended a genetic clinic catering to residents of Jerusalem and the West Bank. There was not any significant difference between the rate of consanguinity in the population

with trisomy 21 (46%) versus the general population (44%). (Zlotogora did not collect his own background prevalence but relied on the theoretical data published three years earlier by Jaber et al., (1994)). The rate of consanguinity however in the population with rare autosomal recessive disorders was 93 percent.

Stoll et al., (1998) found a rate of 4.5 percent consanguinity in the cases of DS versus 1.2 percent in the controls ($p < 0.01$) indicating an association. The control population of 238,942 births were ascertained during the period 1979 to 1996 from the registry of congenital malformations of the Strasbourg area of France. The cases were 398 babies delivered in Alsace, North-eastern France.

In a study using data from the Latin-American Collaborative Study of Congenital Malformations registry, a network of 114 reporting maternity hospitals distributed in nine South American countries, Rittler et al., (2001) reported that congenital anomalies were significantly associated with consanguinity. With respect to DS the effect appears to be confounded by maternal age. In Turkey, Basaran et al., looked at 1,598 DS patients from 1,578 families. They found that the rate of consanguinity was lower among the parents of the 21 trisomics than in the parents of the offspring without DS. In Egypt, Mokhtar and Abdel-Fattah (2001) performed a case control study with 514 infants with DS collected been 1995 and 2000. They found that in DS infants consanguinity greatly increased the risk of CHD with an adjusted odds ratio of 7.5 ($CI_{95\%}$=4.3-15.1).

Apnea of prematurity

In a cross-sectional study of 597 newborns less than 37 weeks of gestation admitted to the ICU with apnea of pre-maturity Tamim et al., (2003) demonstrated that there was an increased risk of 2.9 ($CI_{95\%}$ =1.3-6.4) for offspring from first degree consanguineous relationships. Furthermore, they demonstrated that in multiple gestations in first degree consanguinity the odds ratio was further increased to 4.4 ($CI_{95\%}$ =1.4-14.1). They restricted their analysis to cases with no congenital malformations, sepsis or neurological disorders. The data were collected from 1998 to 2001 in the Greater Beirut area of Lebanon. The controls were not taken from the general population and the method of pedigree collection was not described.

All major malformations

Queisser-Luft et al. (2002) demonstrated with a population based birth cohort of 30,940 from Mainz, German that the risk of all major malformations, including chromosomal was greater for those from consanguineous unions. They reported an odds ratio of 2.6 ($CI_{95\%}$ =1.7-4.0). The study considered all conceptions greater than the fifteenth week of gestation, all induced abortions and all newborn infants. The study was thorough and the data gathered from active surveillance however the method for collecting consanguinity was not reported.

Shafi, Khan, Atiq (2003) reported that 29 percent of 123 Pakistani children with cleft lip and/or palate (CL/CP) had a second major anomaly. In this population, 74 percent of the children were from a consanguineous union. By contrast, in the population of CL/CP children without a second major anomaly only 40 percent were from a consanguineous union.

Sheiner et al., (1999) studied a population of 295 Bedouin Arabs mothers diagnosed with a malformed foetus from the Negev Desert of Israel from 1990 to 1996. Of these, 188 had foetuses with severe defects and 107 had infants with mild defects. There was no significant relationship between consanguinity and the severity of defects found in this population. The method for pedigree collection however is not discussed and the authors only used the "None", "First cousins" "Other" categories.

Narchi and Kulaylat (1997) collected data on 18,146 live births occurring in one institution in Al-Hasa, Saudi Arabia from 1987 to 1992. Of these, 607 infants had congenital malformations for a live birth prevalence of 33 per 1000. The prevalence of consanguinity was 40 percent first cousins. Despite the high prevalence of consanguineous marriages the overall prevalence of congenital anomalies was not higher than in other parts of the world.

In a cross-sectional survey of 2,033 married, parous residents of Dubai and Al Ain in the United Arab Emirates, over 15 years of age, collected from October 1994 to March 1995 Abdulrazzaq et al., (1997) presented results on several outcomes including congenital abnormalities. The authors did not state that the data were independent and the data collection method for consanguinity was not defined. They found that congenital abnormalities were more likely among the consanguineous with an odds ratio of 1.7

($CI_{95\%}$ =1.5-1.9). They also presented odds ratios for mental retardation 1.5 ($CI_{95\%}$ =1.2-1.9), other neoplasms 1.5 ($CI_{95\%}$ =1.1-2.1) and chronic liver disease 1.7 ($CI_{95\%}$ =1.3-2.1). Consanguinity was protective for eye disease with an odds ratio of 0.6 ($CI_{95\%}$ =0.4-0.9).

Al-Gazali et al., (1995) presented data on 16,219 consecutive live and stillbirths from three hospitals in Al Ain, UAE with the outcome of multiple congenital abnormalities suspected or diagnosed up to 1 week. They found an elevated odds ratio of 1.7 ($CI_{95\%}$ =1.3-2.2) however again the data collection method was not defined and the data were not stated to be independent.

Abu-Rezq et al. (1995) in Kuwait, reported in a letter his comparison of 212 cases of multiple congenital handicaps recruited from one tertiary care hospital with 212 controls recruited from six general hospitals. They found that consanguinity was associated with an increased risk of having multiple congenital handicaps ($p<0.01$).

Sawardekar (2005) presented the profile of major congenital malformations in Oman. There were 541 infants with major congenital malformations or single–system abnormalities identified in the 10 year period from 1993 to 2002. The overall rate of consanguinity was 53 percent but the consanguinity rate in those with major malformations was 75 percent.

Pre-reproductive death

In another study of the Amish in the USA Khoury et al. (1987) conducted a case control study of 211 cases of pre-reproductive death ascertained between 1969 and 1980. These early life deaths were compared with 213 live controls for differences in inbreeding coefficients, congenital malformations, and other factors. Data was obtained by linkage to foetal death certifications obtained from the Health Department. Adjusted results showed that offspring closer than second cousin were 2.4 times more likely to have a birth defect recorded. Inbred offspring were 1.5 times likely to have a positive family history of a sibling dying in the pre-reproductive period and inbred offspring were more at risk of inter-uterine growth retardation. Of course, the results could be influenced by the Hawthorne effect whereby cases of pre-reproductive death are investigated more closely for defects.

Govinda Reddy (1983) studied three socioeconomic levels in Andhra Pradesh, South India. Members of the wealthier group married consanguineously more frequently than did the members of the poorer group. The consanguineous unions were found to be more fertile than were non-consanguineous unions. However, the child mortality was higher among the offspring of consanguineous unions.

One consequence of survival of inbred offspring to reproductive age is that more recessive alleles could be released into the gene pool. Ober, Hyslop and Hauck (1999) studied a population of Hutterites in the state of South Dakota, USA and found that there was reduced fecundity in the more-inbred Hutterite women indicating the presence of recessive alleles that adversely affected either conception or peri-implantation loss rates in the population. However, completed family sizes were the same between the less inbred and the more inbred women in the most recent cohort suggesting that there was reproductive compensation among the more inbred women (probably due to cultural expectations of family size). This reproductive pattern, the authors suggest, results in the maintenance of the recessive alleles in the population.

Breast cancer

Denic et al., (2005) looked for an association between breast cancer and consanguinity but were not able to find one. Over a 36 month period, consecutive female breast cancer patients were recruited from the main cancer hospital in the UAE. These women were compared to locally born Arab women without breast cancer matched by sex, age and residence. The rate of consanguinity in both cases and controls was 29 percent. An earlier study conducted in Pakistan (Shami, Qaisar, Bittles, 1991) reported that of a population of 20 patients with breast cancer, 15 of them were children of first cousins. However, there was no control group, the sample was small and the data were collected opportunistically.

Schizophrenia

In a group of schizophrenic patients at KFSH&RC, Chaleby and Tuma (1987) did not show that consanguinity was a risk factor however the study was underpowered and the control group was not tested to be free from disease. Also, the controls were chosen because they accompanied the patients to the hospital and were therefore assumed to be of the same socio-economic status. Theoretically, it is possible that in fact the "companions" were household help and possibly not even Saudi Arabians.

1.5.3 Prevalence of consanguinity

Table 1.6 presents a review of the literature of consanguinity prevalence in Saudi Arabia. In Appendix 1D are further consanguinity studies that were reviewed to assess worldwide prevalence. Bittles et al., (1998, 1994, 1993, 1991) have produced several comprehensive reviews on the subject of consanguinity prevalence. There have been only 9 studies in Saudi Arabia with the earliest one in 1987 and the most recent being this one. Estimates of the prevalence in Saudi Arabia vary from 29 percent in a study of the companions or visitors of people referred to KFSH&RC for schizophrenia (Chaleby and Tuma) to 52 percent identified in the Family Health Survey (Khoja and Farid, 2000).

Table 1.6 Review of the consanguinity literature in Saudi Arabia with prevalence indicators

	Authors (Year)	Region	DC %	FC %	FC_1 %	SC %	DR %	NC %
1	This study	Riyadh: Cases	5	23	12	7	5	48
		Controls	5	21	12	8	4	51
2	Khoja, Farid (2000) 8,894 women	Riyadh	41			11		48
		North	43			19		37
		South	38			10		52
		East	48			9		51
		West	40			10		50
		Total	41			11		48
3	Al-Abdulkareem, Ballal, (1998)	Dammam	13	20	8	3	9	48
4	Al Husain, Al Bunyan (1997)	Riyadh	1	27	11	2	10	49
5	El-Hazmi, Al-Swailem, Warsy, Al-Swailem, Sulaimani, Al-Meshari, (1995)	Saudi Arabia	26			15	16	57
		Riyadh	30			13	18	61
		Northern	18			17	17	52
		North western	27			21	20	68
		South western	26			12	12	54
		Eastern	41			9	9	59
6	Zazouk, (2002) 9540 children < 15	Saudi Arabia	22			23		55
	Zakzouk, El-Sayed, Bafaqeeh (1993) 6421 children < 12 from Riyadh	Riyadh	19			28		53
7	Saedi-Wong, Al-Frayh, Wong (1989) 4,498 obstetric inpatients	Riyadh	31			23		46
8	Serenius, Edressee, Swailem. (1988) N=1,149 obstetric inpatients	Riyadh	52			3	11	34
9	Chaleby and Tuma (1987) 143 schizophrenic patients	All Saudi Arabia	16			09	22	52
	their companions		12			07	10	71

DC=Double first cousin, FC=First cousin, FC_1=First cousin once removed, SC=Second cousin, DR=Distant Relation, NC=Non-Consanguineous.

CHAPTER 2 Aims and Objectives

The two primary aims of this thesis are to describe, and to investigate risk factors for congenital heart defects in a population of Saudi Arabian infants. Consanguinity is of particular interest as a risk factor in this population.

To achieve these overall aims, my objectives are:

1. To use three of the six meta-nosologies to describe and analyze cases from the case-control study and compare the results obtained in order to demonstrate that this Riyadh population of infants with CHD is comparable to other populations.
    a. Using the isolated versus parallel meta-nosology to describe Riyadh Registry data June 2002 to December 2004
    b. Using the embryological meta-nosology the Riyadh Registry data June 2002 to December 2004 will be compared to data published by the BWIS group.
    c. Using the lesion analysis meta-nosology the Riyadh Registry data June 2002 to December 2004 will be compared to data published by EUROCAT.
    d. Using the lesion analysis meta-nosology the Saudi Arabian Registry data 2001-2002 will be compared to data published by EUROCAT.
2. To estimate the rate of consanguinity in the control population by use of the phylogram method.
3. To conduct a well powered case control study to a high standard in Saudi Arabia.
4. To thoroughly document the results of the investigation.

CHAPTER 3 Methods

3.1 Study design

The study was an interview-based unmatched case-control study of risk factors for all structural congenital heart defects in Saudi Arabian children resident in Riyadh. The primary exposure of interest was consanguinity (up to and including third cousin).

3.2 Study setting

The study was conducted in Riyadh, the capital and largest city in Saudi Arabia.

3.3 Source of cases

Cases were recruited from a registry of CHD housed within the King Faisal Specialist Hospital and Research Centre (KFSH&RC), a tertiary care 600 bed facility with, as of 2004, 9000 staff. Established in 1975, the mission of KFSH&RC is to provide specialized medical care for Saudi Arabian citizens, reducing the need for treatment abroad.

3.3.1 CHD Registry

In 1998, the first step towards a national registry for congenital heart defects was established at KFSH&RC and it was this registry which provided the cases for the study. From 1999 until 2002 ALS was the registry's epidemiologist and was responsible for design and analysis of the data. When more than one member of an immediate family was registered (two siblings or parent and sibling) a family number was assigned so that independence of measurement could be guaranteed in research studies.

It was estimated that approximately half of all CHD cases in Riyadh were registered by the CHD registry. Cases were registered actively by in-house trained native Arabic speaking CHD registrars who visited the specific areas of the hospital to register cases and interview families.

The registration process had five components: case finding, case interviewing, diagnosis, subsequent treatment and follow-up.

Case finding

Registrars found cases through visits to the following areas of the hospital:

- Poly clinic - an outpatient clinic available freely to every Saudi Arabian.

- Paediatric Section of the Cardiology Department – an outpatient clinic to which one gains access either by referral from one of the PHCC in the country or by direct admission.
- Wards – CHD cases were directly admitted to two wards (A1 and C2). Admissions occurred in the case of extremely sick infants, particularly newborns, via the Social Services Department which has established links with Obstetric Departments throughout the country or the Emergency Room.
- General Paediatric Department - some cases with minor defects were identified in this way or cases with Down syndrome.
- Neo-Intensive Care Unit - some infants were sent directly after birth prior to surgery or after surgery.
- Cardiac Surgery Ward - those cases immediately sent to surgery from admission.

On a monthly basis registrars additionally reviewed the hospital's death file for potential registrations. If a case was referred to the registry with a confirmed diagnosis of CHD and died before contact then the case was registered.

Case interviewing for the registry

After registration, the registrar would interview a parent of the case. Optimally, the interview occurred at the same time as registration but sometimes a case was missed. This interview consisted of approximately 20 questions relating to name, contact information, nationality, sex, date of maternal birth, date of paternal birth, prematurity, diabetes, family history of CHD (including inclusion of family number where applicable) presence of maternal rubella during pregnancy, prenatal diagnosis, assisted conception and parental consanguinity with *phylogram*.

Diagnosis

Diagnosis was recorded directly from medical records abstraction with the assistance of the registry's paediatric cardiologist, as required. Case records were not abstracted until 3 months following registration in order to allow definitive CHD diagnosis to be made.

Treatment

Registrars collected treatment data as the case returned to the hospital for surgery et cetera, and then for follow-up on a 3, 6 or 12 monthly schedule.

Follow-up

For patients who did not return to clinic for three years a system of telephone follow-up was instituted to document outcome (especially survival) from CHD.

Timing of interviews for the Case Control Study

The interview conducted by the CHD Registry was not detailed enough for this case control study. Therefore the CHD registrar was responsible for reporting to the research assistant the medical record number of all cases who met the study criteria (new registration, age, nationality, and residency in Riyadh). Ideally case control interviews were conducted at registration, or at least between the case finding and diagnosis phases. To minimize missed cases due to death interviews were conducted presupposing that the initial diagnosis of a structural CHD was correct.

Some cases were not interviewed within the first three months following registration due to logistical problems. The primary logistical problem was that if the research assistant was not available to conduct an interview it was difficult to convince mothers to return to clinic if they did not have a scheduled appointment with the physician. Therefore, we had to wait for their natural return which increased the risk of loss due to the infant's death. The second reason for a missed interview was that the research assistant was not available to conduct interviews due to her already interviewing a patient when the new registration was made or she was sick or the CHD registrar failed to notify her.

For the study, in order to confirm that no eligible cases were missed the research assistant and ALS kept a log of potential cases (Appendix 3A). On a monthly basis the registration forms, kept in a central location in the registry, were reviewed and compared to the log of cases reported by the registrars. On a tri-monthly basis the data from the registry were downloaded by ALS and the eligible cases were compared to the log. Any missing cases were added to our list of active CHD cases to be recruited.

3.4 Definition of cases

The criteria for defining cases were:

Inclusions

1. A newly registered case (*de novo*) from the Saudi Arabian CHD registry registered between 1 June 2002 and 31 December 2004.

2. Only Saudi Arabian infants with an Arabic speaking mother available for interview.
3. Structural congenital heart defect confirmed by echocardiogram, cardiac catheterization or surgery (ICD 9 codes 745.0 to 747.9).
4. Interview completed for this study prior to the child's 4th birthday (*Gregorian* reckoning).
5. The father reporting current residence in Riyadh region or the father reporting that he was originally from Riyadh region.
6. All cases will have had to survive from birth to registration.
7. Interviews were conducted only for those cases alive at the time of interview.

The following were excluded:

1. The interview interrupted prior to the consanguinity question, (Question 71).
2. A second infant from the same mother. (I.e., if a second child with CHD had been born prior to the study or during the study we interviewed the earliest registration within the June 2002 to December 2004 timeframe.)
3. Isolated types of non-structural CHD where there was no structural defect:
   isolated patent or persistent foramen ovale (PFO) (ICD-9 745.5)
   isolated dilated or hypertrophic cardiomyopathy (DCM/HCM) (ICD-9 746.84)
   isolated patent ductus arteriosus (PDA) (ICD-9 747.0)
   isolated Wolff-Parkinson-White syndrome (WPW) (ICD-9 426.7)
   isolated supraventicular tachycardia (SVT) (ICD-9 427.89).

3.5 Source of controls

The source of controls was the Riyadh Al Kharj Armed Forces Hospital (RAFH) Department of Family and Community Medicine's Well Baby Clinic which operated as a drop-in clinic Saturday to Wednesday from 4pm until 7pm (8pm to 11pm in the Holy month of Ramadan). The population who visit the RAFH for Well Baby Services are all connected to the Saudi Arabian military service in some way. Because the military is the single largest employer of individuals in Saudi Arabia and the notion of the "military" is broader in a country like Saudi Arabia than it would be in the UK for example this was taken to be a random selection of controls. Unlike the PHCC which are specific to particular neighbourhoods it gave access to a broad spectrum of the Riyadh population similar to the case population.

Five days a week mothers with their infants presented to registration for the Well Baby Clinic. Visits were at 3 months, 6 months, 1 year, 18 months and 2 years. A few infants presented at greater than 2 years. The registration receptionist would take the small booklet for the infant brought in by the mother and place it in a holder in the nurse's work room. Following the order of registration nurses would triage the infants (weight, length and head circumference measurements). After triage the nurse returned the infant's booklet to the holder in the nurse's work room. The research assistant was instructed to take the bottom booklet from the stack in the holder (in order to reduce waiting time for the mothers). After the study interview the infant (with the mother) was then seen by the physician or the health visitor (for the hearing check). A formal randomization schedule could not be put into place although three were attempted. The number of patients (and physicians) per day who attended the clinic was erratic and ranged from 3 to over 80.

3.6 Definition of controls

Controls could be any child attending the clinic for a Well Baby appointment. Exclusion criteria for controls were:

1. Non-Saudi Arabian citizens.
2. Mother not available for interview.
3. Residence outside of Riyadh defined in the same manner as the cases.
4. The interview interrupted prior to the consanguinity question, (Question 71).
5. A second sibling from a previously interviewed family.
6. Known or suspected CHD.

3.7 Questionnaire

The instrument was a 23 page questionnaire with a separate booklet for pregnancies (6, 12 or 18) and 5 possible supplemental sheets: consanguinity, diabetes, other major illnesses, cardiac diseases (in self or family), non-cardiac diseases (in self or family). Not all variables were to be analyzed in this thesis. The questionnaire covered demographics, exposures and confounders and comprised approximately 200 questions (depending on the number of pregnancies and associated conditions). It was completely designed and drafted by ALS with the exception that the separate pregnancy booklet's design was suggested by her supervisor Pat Doyle, LSHTM and the idea of the cards was adapted from the BWIS (Ferencz et al., 1993).

The questionnaire was translated from English to Arabic and reverse translated by an official translation service recommended by the KFSH&RC Translation Department. The development of the questionnaire went through many iterations and was approved by the LSHTM Upgrading Committee. It was administered in a face to face interview with the mother by a trained bilingual, native speaking Arabic interviewer or research assistant. Questions were taken in large part directly from the published literature in order to ensure comparability in the analysis phase. Sources included the BWIS initiative (Ferencz et al., 1993); Boneva et al., (1999); the Saudi Arabian Family Health Survey (Khoja, Farid, 2000); Strandberg et al., (2001); and Botto, Mulinare, Erickson (2000).

Consanguinity was collected by means of a *phylogram* which the research assistant used to assist the mother in completely identifying the relationship between her and her spouse. The consanguinity question was embedded about halfway through the body of the questionnaire in order to

1. give the research assistant a chance to develop a rapport with the mother
2. give the mother a chance to get into the flow of the interview so that she would not realize that the *phylogram* was the salient question.

Some questions were intentionally duplicated. For example question 3 (In what month and year was this child born?) and question 4 (How old is this child now?) were intended to confirm reliability from the mother during the interview. The CHD registrar would have completed a *phylogram* for the cases at registration but the case control research assistant did not have access to this *phylogram* and completed a second one which was later compared for reliability.

3.8 Interviews

Three research assistants were assigned the responsibility of interviewing the mothers. They underwent thorough training (see Section 3.10). Data were collected on interview quality, place of interview, method of capture of patient and privacy of interview for both cases and controls. In general, case interviews took 35 to 60 minutes (average 43) and control interviews 18 to 45 minutes (average 22). It was expected that control interviews would be shorter as the BWIS group found less cardiac problems and less other abnormalities with them. Over 90 percent of the interviews for both cases and controls

were conducted in a private room. Less than 10 percent were conducted in a semi-private area such as the women's section of the patient waiting room. This occurred when there were no private rooms available.

During the interview the mother was shown samples of skin lightening creams, kohl, saoot, nogd, licorice, nausea medications and heart burn medications available locally to help her remember what she might have used during her pregnancy. There were two samples kits with exactly the same materials: one for the case interviews and one for the control interviews as for approximately 3 months these interviews occurred simultaneously. The kohl was especially important to show to the mother as it was important that she understand that our interest was in the natural, potentially lead-based kohl, available from local beauticians rather than the commercial variety available from Revlon, Clinique or any other trademark.

For the cases, ALS observed the first 20 to 25 interviews of each of the three research assistants in order to supervise the style and content of the interview and to be able to answer any questions posed by the mothers. The most common question was why ALS, an American, was interested in studying Saudi Arabians. It was explained that ALS was a researcher employed by KFSH&RC (a well known institution) and that it was part of her job to do this project. It was explained that it was hoped that this project would in some measure contribute to a better understanding of CHD.

3.9 Pilot study

It was difficult to pilot this study in the hospital because of the rareness of the disease. As only two eligible cases per week were expected it was decided to conduct the pilot in two stages:

First, in September 2001, the lead research assistant and ALS tested the questionnaire on 16 consenting mothers of infants with CHD. The specific objectives of this first pilot were

- to develop a system for working in the three clinics and on the wards to
    - identify patients
    - find a quiet place for the interview
    - to return the patient to normal patient flow
- to practice administering informed consent

- to assess the acceptability of the questionnaire language
- to practice reading *fusha* Arabic (the language in which the questionnaire was written) but speaking Saudi dialect
- to practice using the questionnaire's supplemental forms and samples
- to determine if the questionnaire was too long to complete in a reasonable time.

In May 2002 a second, more formal attempt was made at a pilot however the project's lead research assistant was unexpectedly transferred to another section. It was therefore decided that the effort that would have been spent in a pilot should instead be spent to recruit and train a new lead research assistant.

3.10 Training sessions

From June to September, 2002 interviewing technique training sessions took place. In addition there were two group training sessions in interviewing technique which were facilitated by ALS, the former lead research assistant (AAH), and one of the co-investigators (AAR). The following issues were covered:

- Questions were to be read to the mother from the questionnaire in *fusha* Arabic. If the mother did not understand then the research assistant was allowed to rephrase into the dialect which seemed most appropriate for the mother.
- The art of "probing" was distinguished from "bullying" for an answer. If the mother responded that she "didn't know" how old her infant's father was, for example, the research assistant was allowed to ask "Would you say that he is older than you, or younger than you? Much older? Could you give me an approximate age or can you estimate how many years older than you he is?" If the mother however repeated that she "Didn't know" the answer to a question then the research assistant moved onto the next question.
- The concept of the 6 month window was explained. For several exposures, the three months prior to conception and the three months post conception were the time of interest. The research assistant was to ask the mother to think back to those 6 months. To help the mother identify this period of time, the research assistant asked her for the date of conception (which was usually provided as a *Hejira* date) and then the research assistant calculated the window based on the number of weeks of gestation. The mother was involved in the calculations to

increase her understanding of the window concept. From this calculation the research assistant knew whether or not the mother had had a Ramadan within her window period. This was useful because as that is the first question (question 65) after the window determination the mother's correct answer confirmed that she understood the concept of the window.

> Question 65: Thinking back to the 3 months before you got pregnant and the three months after you got pregnant, did the holy month of Ramadan fall during this period? Yes or No

For those instances where the mother could not remember the conception month – or if the mother reported a *Gregorian* month, a calendar (Appendix 3B) with *Hejira* months was provided to help the research assistant help the mother figure out what her conception month for a delivery month would be, given her weeks of gestation. Throughout the questionnaire administration, the research assistant reminded the mother as necessary of the window period.

- All possible sensitive areas (such as ethnicity, smoking behaviour, divorce, mother's age, congenital and familial defects, income, skin lightening cream, mother's opinion of possible causes of CHD) were explored with the research assistants in a round table format so that if any of them were uncomfortable with the question they could discuss their feelings. Also, ALS wanted to confirm that the research assistants understood the relevance of these questions.
    - The concept of "Bedouin" was described. The research assistants were told to ask the question and then allow the mother to answer it as best she could, but that if asked, to say that we were not restricting the answer of "Bedouin" to include people who were currently nomadic.
    - Skin Lightening Creams – Research assistants were told that it was possible that some skin lightening creams had mercury or other heavy metals in them.
    - The use of saoot and nogd was described by the lead research assistant and a sample was shown to them. Traditional medicines were discussed. A speaker, Hassan El Bushra, consultant to the World Health Organization,

described, in Arabic, traditional medicines and practices common in the Gulf Region.

- One of the co-investigators, Mansour Al Jufan described the language a mother might use for cardiac abnormalities and supplied his pager number in case questions arose during the interview.
- One of the co-investigators, Wesam Al Kurdi described the language a mother might use for obstetric problems and congenital abnormalities and supplied her pager number in case questions arose during the interview.
- Research assistants were taught the *phylogram* method by the lead research assistant (AH). AH had 3 years of experience in *phylogram* collection. One of the co-investigators, (AAR) who had experience with collecting this information in the 1992 Saudi census, also participated in this training. Firstly ALS explained in English how to use the *phylogram* chart prior to conducting an interview, with several simple and more complex examples. Secondly AH explained in Arabic prior to conducting an interview. Thirdly, after 3 to 5 interviews with patients the research assistants were given an opportunity to discuss with AAR, in Arabic, their experiences with collecting data on consanguinity. Research assistants were reminded regularly to ask if the relationship was the only blood relationship and if the initial relationship was between half or full siblings.

3.11 Recruitment and accrual of cases

Patients were identified by registrars of the KFSH&RC CHD registry (Mitri et al., 2002, Appendix 3C) in one of the 5 hospital clinics or wards (Section 3.3.1) regularly monitored by the registrars for new patients. The registrar would complete a simple one page registry form (example found in Appendix 3C[1], page 80). If the patient met the study criteria of *de novo*, residency, age and nationality (and the mother was present) the registrar would contact the research assistant via pager. The registrar would briefly describe the study to the prospective participant and tell her that a research assistant would like to interview her. When the research assistant arrived from the study office (approximately 3 to 5 minutes away by foot) she would receive the completed registry form from the registrar and approach the mother for informed consent. If the patient were identified in one of the clinics (Outpatient or Polyclinic) given the logistics of the clinic the mother would be interviewed immediately or between visits to the various stations of

the hospital where the infant had to present (i.e., x-ray, laboratory for blood work, echocardiogram or afternoon appointment with the physician). However, if the patient was identified by the registrar in the inpatient ward (A1 or C2) then the research assistant might interview the mother immediately in the patient's room or make an appointment to come back at a time convenient for her. Some patients were admitted directly to the cardiac surgery ward or the neo-natal intensive cardiac care unit prior to or following surgery. In the case of an infant immediately proceeding to surgery following registration the mother was only gently approached if at all. The progress of that infant would be monitored by the research assistant on the hospital's patient appointment system until such time that the patient's mother could be approached in the step-down unit.

In some cases, the research assistant was unavailable when the infant was identified by the registrar. In this case the research assistant would be given the registry form as soon as possible and then she would be responsible for contacting the mother at home and inviting her to come to the hospital for interview or she, using the hospital's appointment system, would identify when the infant (or sometimes the mother herself) was next scheduled to come into the hospital. The research assistant would then approach the mother at the time of the appointment.

Data collection began 16 September 2002. By the end of December 2002 only 10 cases had been collected. By this time, there were over 60 eligible cases on the log (the target population was all those registered from June, 2002). By January 2003, after identifying the problems with the reporting of cases by registry staff to the research assistant patients began to be accrued at the expected rate.
Interviews were performed for 28 months of registrations plus an additional initial three month head start for a total of 31 months. As described (Section 3.3) a log of cases was kept from the beginning of study (Appendix 3A). This log helped to identify which patients would be expected to come for interview, which patients had been interviewed, who had refused, who were deceased and who were otherwise non-eligible.

During the study period there were 337 infants reported by registry staff based on the established criteria (*de novo* registration, structural defect, interview completed before 4 years of age, resident in Riyadh, Saudi Arabian and mother available for interview) (table

[1] Family number written in by hand. Boxes added to a later version of the registry form.

3.1). Of the 337 reported infants, 40 were subsequently found to have only a non-structural defect such as PDA, PFO, SVT or WPW and an additional 6 were excluded for

Table 3.1: Description of inclusions and exclusions for all case interviews		N	%
Inclusions	Case	233	69
	Incomplete - after consanguinity question	2	1
Exclusions	Erroneously interviewed – 1 family from Dammam, 1 aunt interviewed rather than mother	2	1
	Siblings interviewed (excluded for independence of measurement)	2	1
	Refused mid-interview	1	0
	Incomplete - before consanguinity question	1	0
	Interviewed and excluded CHD - Type not included	33	10
	Excluded prior to interview because they did not have a structural defect	7	2
Eligible and missed interviews	Missed/LTFU	44	13
	Known to have died prior to interview	12	4
	Total	337	100.0

other reasons. From the eligible population of 293 (table 3.2), a total of 58 infants were not interviewed (n=56) or did not have complete interviews (n=2) for a capture rate of 80%. Of the 56, twelve died before the interview could be performed and another 44 were lost to follow up. There were 235 interviews available for analysis.

Table 3.2: Overall Accrual of Cases for CHD Case Control Study

	Year	Number Reported	Number eligible	Known death prior to interview	Completed Eligible Interviews	Interview Completion Rate (%)
Jan-Dec	2004	123	100	2	83	83
Jan-Dec	2003	131	128	6	109	85
Jun-Dec	2002	83	65	4	43	66
	Total	337	293	12	235	80

Table 3.2 presents overall accrual of cases by year. The overall completion rate (completed eligible interviews/number of eligible) varied from 66 percent in the first year of study to 85 percent in the second year and dropping to 83 percent in the third year.

3.12 Recruitment and accrual of controls

The recruitment of controls was performed in two stages (September 20, 2003 to March 29, 2004 and May 1 to June 1, 2004). That year Ramadan fell from October 26 to November 24. During this period interviewing moved from 4 to 7pm until 8 to 11pm. The Haj holidays[2] fell in February, 2004 and only five interviews were collected in that

[2] During the middle of the 12th month of the *Hejira* year, Dhu Al Hijjah, the Haj to Mecca is undertaken by many Muslims. There are 10 days of official holidays at this time throughout Saudi Arabia.

entire month. The research assistant resigned at the end of March and therefore no interviews were collected in April, 2004 while a new research assistant was trained.

In November the control data were reviewed and stratum comparability between cases and controls regarding age of child at interview was compared and found to appear different. Therefore, from December 1 there was a special effort to include children over 1 year of age. It was difficult to monitor any other stratum (e.g., mother's age, sex of the child, parity of the mother and birth year of the child).

For the actual interview, the mother was approached by the research assistant and given a brief introduction to the study. All communication between the research assistant and the mothers was conducted in Arabic. The mother was assured that she would not lose her place in the queue if she agreed to participate. If the mother initially agreed to participate she and usually her infant (and possibly other children and occasionally a nanny or female relative or husband) were then led to a private office where the full details of the informed consent were explained (see pocket). After the 6 page informed consent was explained and the mother given the opportunity to ask questions she was given a choice as to her participation. If the mother indicated at any time that the control infant had a heart defect or if s/he was suspected to have a heart defect that infant was excluded.

There were 272 mothers approached as controls (table 3.3). Of these, three were not eligible according to inclusion and exclusion criteria. One infant was not Saudi Arabian (Eritrean); one mother was not present – her sister had brought the infant in for the visit; one infant was not resident in Riyadh – they were visiting from Dammam. Six infants were known or suspected to have CHD. There were 15 mothers who were approached and who refused to participate. There was one family who refused mid-interview. This left a population of 247 control interviews (94%).

Table 3.3 Accrual of controls for CHD case control study		N	%
Eligible	Controls	247	93.9
	Refused prior to interview	15	5.7
	Refused mid-interview	1	0.4
		263	100.0
Not-eligible	Excluded due to study criteria	9	
	Total Approached	272	

3.13 Sample size

Sample size for the primary research objective of assessing consanguinity as a risk factor was calculated prior to the commencement of the study, using the estimated proportion of first cousin consanguinity in the background population (table 3.4). It was estimated that the level of first cousin marriages would be 28 percent in the general population. With a 5 percent level of significance and power of 92 percent, 220 cases and 220 controls were required in order to detect a doubling. There was 100 percent power to detect an OR = 3.0. Given estimates of case accrual based on previous experience with the CHD registry it was expected that two years would be required to collect sufficient data.

Table 3.4: Power Table for alpha = 0.05 showing number of cases required

Prevalence of exposure in the background population	ODDS RATIO				
	OR = 1.5 β = 57%	OR=1.75 β = 78%	OR=2.0 β = 92%	OR=2.5 β = 99%	OR=3.0 β = 100%
All sampled					
Consanguinity 28%	278	230	220	196	230
Consanguinity 25%	295	243	232	205	239
Diabetes 0.04%	12 462	9 843	9 050	7 535	8 384
Ramadan Fasting 97.3%	2 802	2 571	2 691	2 785	3 701
Exposure to pesticides 13.6%	448	362	339	292	333
Use of skin creams 16.4%	853	316	297	153	295
Use of hair dyes 13.0 %	464	375	351	302	344
Khol 5.6%	961	766	710	599	673
Nogd or Saoot 1.0%	5 028	3 976	3 659	3 051	3 398

There was little data on which to estimate power for other exposures *a priori* however, based on the data collected in the controls the following estimates on some of the additional exposures studied can be made. The sample sizes required to identify a risk increase of 1.5 to 3.0 for various risk factors are presented in table 3.4.

In table 3.5 is presented the actual power achieved given the sample sizes in the four analyses in Chapter 5 (n=235 for all sampled; n=151 for cardiac cases only, n=44 for embryologically earliest (EE) and n=89 for embryologically latest (EL)). Each risk factor is discussed separately following the table. The first risk factor, consanguinity is described in some detail while the others follow the same model.

Table 3.5: Actual Power achieved given number of cases = 235, 151, 44 and 89

Factor with prevalence in background population	All Sampled n=235				Isolated and Parallel n=151				EE n=44	EL n=89
	OR	β	OR	β	OR	β	OR	β	OR (β)	OR (β)
Consanguinity 25%	1.7	78	1.9	88	2.0	76	2.1	82	4.0 (83)	2.9 (90)
Diabetes 0.04%	2.7	5	13.0	80	3.5	5	75	17.5	80 (90)	40 (90)
Ramadan Fasting 97.3%	25.0	50	55.0	55	50	31	50	31	50 (4)	50 (14)
Exposure to pesticides 13.6%	2.0	78	2.4	90	2.3	78	2.6	90	4 (70)	2.8 (72)
Use of skin creams 16.4%	1.9	78	2.0	84	2.2	78	2.3	83	3.8 (70)	2.8 (78)
Use of hair dyes 13.0 %	2.0	78	2.1	84	2.4	80	2.5	85	4.7 (80)	3.1 (81)
Khol 5.6%	2.8	85	3.0	90	3.3	80	3.7	90	6 (65)	4.5 (81)
Nogd or Saoot 1.0%	6.5	78	7.2	85	9.0	79	10.0	85	16 (50)	12 (70)

EE: Embryologically earliest; EL: Embryologically latest. To be defined in Chapter 5.

Consanguinity

Power was adequate to detect an association for the sample sizes of 235 and 151. The two additional analyses had inadequate power for a doubling of effect. For the sample size of 235 if the true odds ratio had been 1.7 there was 78 percent power to detect it. If the true odds ratio had been higher, say 1.9 then there was 88 percent power to detect it. Of the smaller group of cardiac only defects (isolated and parallel) we had 75 percent power to detect a true odds ratio of 2.0 and 82% power to detect an odds ratio of 2.1. Unfortunately, with the sample sizes for EE and EL quite strong true odds ratios were necessary. For example, the study only had sufficient power (83%) to detect a true odds ratio of 4.0 or more with a background prevalence of 25 percent.

Diabetes

Given that the prevalence of diabetes was so low in the background population (0.40 %) the power to detect a difference of magnitude of OR 2.7 with 235 cases would have been only 5 percent (table 3.4). There was even less power for the sub-analyses.

Ramadan fasting

As can be seen in table 3.5, given that the prevalence of Ramadan fasting was so high there was inadequate power to detect odds ratios below 25.0 even for the all case group. It would be nearly impossible to do a conclusive study with 235 people as the association would have to be of a magnitude greater than 50. A false result would be hard to support with a power of 55 percent. The power to look at Ramadan fasting for the sub-analyses was extremely low.

Exposure to pesticides, skin creams, hair dyes

There was adequate power to study this type of risk factor with a background prevalence of 13 to 16 percent for the samples sizes of 235 and 151. Power became weak for the smaller sub-analyses.

Nogd/Saoot

If a risk factor such as nogd or saoot had a very strong association in excess of an OR of 6 this study might have been able to detect it with a sample size of 235. However the smaller sub-analyses of 151, 89 and 44 were inadequately powered to detect even this elevated measure of effect.

3.14 Data management and processing

All data management and processing, if not done by her, was closely supervised by ALS.

3.14.1 Classifying and coding diagnosis data

The specific congenital heart defect diagnosis or diagnoses were obtained for the most part directly from the registry. Cases registered in 2002 and 2003 were abstracted by trained registrars and diagnoses available in mid-2004. However, the cases for 2004 would not be abstracted before mid-2005 which would have held up analysis. Therefore ALS abstracted, according to the registry criteria, the 83 cases from 2004 as well as any cases reported in 2004 which had not been interviewed so that all cases with non-structural defects could be excluded from the log. ALS also selected a random sample of 15 percent of cases from 2002 and 2003 and abstracted them. In the 15 percent, 4 cases were found from 2002 that had been inaccurately diagnosed[3]. These 4 were reported to the registrar and it was explained by her that there had been one coder who worked for the registry for several months in 2003 when the coding for 2002 was being done. It was later found she was not consistent in her coding. This affected a possible additional 39 cases which were re-coded by the registrar. No other errors were found.

Two systems of classification were used to define diagnosis of the cases for the analysis. As will be shown in Chapter 4, there were 855 unique combinations of disease and therefore as described in Chapter 1 the cases were coded into groups. The first method

[3] Patient 1: TOF but the registry had recorded her as only having VSD; Patient 2: AVSD but coded as ASD and VSD; Patient 3: TGV but coded as AVSD; Patient 4: TGV coded as Aortic stenosis, common truncus and VSD .

was inclusion of all cases according to the criteria outlined in section 3.12.5 where the data were converted from ICD-9 parallel defect data to single lesion data as used by EUROCAT (Chapter 4) and the second where the data were converted from ICD-9 to embryologically coded data (Chapter 5).

3.14.2 Coding other components of the questionnaire

Consanguinity

The 47 categories identified by the *phylogram* were collapsed in two different ways. Firstly, a dichotomous type: "yes /no" was coded from the detailed data. "Yes, Consanguinity" was defined as up to and including all third cousin marriages. "No, not-related" was any participant less closely related than third cousin or those who stated that they were not related to a relative. *Juma'a* were counted as non-consanguineous. Secondly, *phylograms* were also categorized as follows:

- first cousin or closer (includes double first cousins, multiple relationships where at least one is a first cousin and full first cousins)
- all other (lesser) First Cousins (First cousins once removed, First half-cousins)
- all other cousin relationships less close than above
- non-consanguineous.

Pregnancy form data

Using a pregnancy form (see pocket), data were collected on the complete pregnancy history of the mother. The number of pregnancies varied from 1 to 17. It was impossible to distinguish between miscarriage and stillbirth in this population except at the far edges (e.g., 3 months versus 8 months). All pregnancies were collected on the pregnancy form to enhance the capture of all pregnancy losses. At the beginning of the pregnancy form section the research assistant said, "Now, I want you to tell me about all your pregnancies." At the end of the pregnancy form section she said, "I want to confirm that you've told me about every time that you have been pregnant, including all miscarriages, stillbirths and other pregnancy losses." The third validation was counting. The mother had been asked how many times she had been pregnant prior to the pregnancy section. The research assistant would then count the number of pregnancies she had recorded and compare that to the number previously stated by the mother.

These pregnancy data were entered into a separate record than that of the main questionnaire. At the beginning of the preliminary analysis phase the data elements from the index pregnancy were merged with the main questionnaire dataset to maintain a rectangular dataset. These data elements were: infant's sex, use of artificial reproductive technologies, birth weight, gestational age, mother's age, father's age and problems during index pregnancy. In a separate step an aggregated number was created for the following variables per infant:

- total number of pregnancy losses
- total number of neo-natal deaths
- total number of infant deaths
- total number of deceased children
- total number of pregnancies with bleeding lasting more than 1 day
- total number of pregnancies with a maternal health problem and
- total number of pregnancies while mother suffered from a major illness.

These 7 aggregated numbers per infant (reflecting the mother's obstetric experience) were then merged to the main questionnaire dataset again maintaining the rectangular nature of the dataset.

A FORTRAN program, written by my colleague, William Greer, PhD, created aggregate pregnancy data. This program was tested on 50 randomly selected cases. Errors were found with the program. It was then re-written and checked again (Appendix 3D). The third iteration showed 100% accuracy in aggregating the pregnancies for total numbers.

Paternal age

Many mothers did not know the current age of the father of the infant at first asking. However, if the research assistant could estimate his current age with the mother from probing then this was accepted. As the results (Chapter 5) show however there was a high number of missing data for this variable.

Extra cardiac malformations (ECM)

There were two ways to capture information on ECM from cases: the first was by asking the mother herself, and the second was via the registry which routinely abstracted all

medical records of patients registered. The registry procedure includes coding congenital anomalies to ICD-9. However, to validate this information all the volumes of the 84 infants with reported congenital anomalies (either by registry or by mother) were reviewed by ALS.

With respect to the controls, being a CHD registry, and given that there is no Saudi Arabian birth defects registry, registry staff did not collect ECM for the control infants. This information was collected only by the research assistant from the mother herself (shading in table 5.1e). Ideally ALS would have gained permission from the control hospital and would have reviewed those medical records but there was no time to arrange the permission for this exercise. However, as will be described in Section 3.14.3 some control data were validated.

Maternal weight and height

The research assistant collected the case mothers weight and height at the completion of the interview on a standard hospital scale located near the interview room or in the wards where the interviews occurred. Body mass index (BMI) was calculated using the formula: BMI = (weight in kilograms) / (height in meters)^2. The mother took off her shoes for weight and height measurement but not her *abaya* and *hijab* (the outer garments usually worn by Saudi Arabian women in public). Different scales were used and it was not possible to calibrate them. For controls there was one scale which was used.

Pre-pregnancy weight (the weight of true interest as a potential risk factor) was introduced four weeks after data collection had begun. It was estimated by asking the mother how much weight she had lost or gained since prior to her conception with the index pregnancy. This number was subtracted from or added to her current weight and used in the BMI formula.

Major maternal health problems (index pregnancy)

While the best way to control for a variety of different problems simultaneously is to use a multi-variate method of analysis, there was an interest to obtain a flavour of the data at a more preliminary stage. During data collection it was observed that every mother had something that stood out as an "explanation" for the CHD in the infant. Therefore, during

preliminary analysis a variable was created to capture the aggregation of major health problems associated with the index pregnancy. This variable tabulated the occurrences of

- having a serious disease in pregnancy (details of diseases are included in table 5.9)
- previous child with CHD or with Down syndrome or with any other serious birth defect (e.g., congenital lung disease, hydrocephalus, shortened forearm, brain atrophy, cleft-lip with or without cleft palate, or a neural tube defect)
- previous miscarriages greater than 3
- any index pregnancy using IVF
- severe bleeding requiring intervention (pills or injections) to maintain the pregnancy.

Maternal health problem (previous pregnancy)

This variable is reported in table 5.1f. It was aggregated to create *total number of pregnancies with a maternal health problem.*

Pregnancies while mother suffered from a major illness

This variable is reported in table 5.1f. It was aggregated to create *total number of pregnancies while mother suffered from a major illness.*

Fasting variables

If Ramadan fell within the critical window for the mother then her fasting was relevant. On the questionnaire there were questions about Ramadan fasting and other religious, non Ramadan, fasting. The total number of days fasted in the window was summed from those days fasted during Ramadan plus the other religious, non Ramadan fasting days.

Household income per capita excluding servants per month

In order to estimate socio-economic status several variables were collected. These included household income, number of household members and number of servants. Other variables including family land ownership, number of cars and number of livestock were also collected but were not found to be useful for creation of the SES composite score as there was not enough variation (data not shown). A created variable was calculated which computed the household income per capita excluding servants per month.

3.14.3 Validation of the data

Much of the data for cases was able to be validated while less of the control data could be validated because of the nature of the clinic and the question of access to the data.

Case validation

The medical charts for all cases were available at KFSH&RC and any missing information was collected where possible from them. Information which was not missing but which could be validated from the medical record was validated and preferred. For example, mothers were asked the birth weight of the infant however, if the birth weight was recorded in the medical chart that information was used in the dataset in preference to the mother's memory. While not all case infants were born at KFSH&RC, most referral notes included birth weight. Twenty-eight case mothers were not able to recall the index infant's birth weight and the information was not recorded in the chart.

Gestational age was collected as continuous data although many women with 'normal' gestations could only report that it was "normal" which was assumed to be 37-40 weeks. Even the medical record and the referral note were not always more precise. Women with premature deliveries (defined as less than 37 weeks) were able to remember the number of weeks but there was obvious confusion over the difference between weeks from last menstrual period and weeks of gestation proper.

A second source of validation was the registry itself which collected data on sex, father's region of birth, current residence, father's age, mother's age, nationality, consanguinity (with *phylogram*), prematurity, use of assisted reproductive technologies (ART), diabetes, date of diagnosis, date of birth. There was a high correspondence between mothers who did not know the infant's father's age in the registry interview and then again did not know it when the research assistants conducted the in-depth case control interview. However, the registry would also accept the data from the Saudi National ID for age of father as well as region of father's birth which this case control study did not accept because of reliability.

Control validation

As mentioned above in Section 3.5 each control infant had a booklet associated with it. This small booklet was brought in by the mother each visit and recorded vaccination dates

as well as some basic data on the infant: date of birth, mother's type of delivery and complications, birth weight, gestational age at birth, general health of infant, maternal age, maternal parity and gravidity.

At the Well-Baby visit a blue form was completed and this was sent to medical records where it was filed in the complete medical record.

3.14.4 Data processing

Case control data

All interviews were reviewed for completeness by ALS. This included being entered into an SPSS dataset so that data could be tabulated as necessary. Where information was found to be missing the research assistant was immediately contacted and asked to clarify. Generally, missing data was limited (table 5.12). Consanguinity data was coded by ALS. Other coding, such as problems with the pregnancy (type and quantity of bleeding), maternal health problems, and major maternal illnesses, was done using the method of a running list. Many questions were pre-coded. From time to time it was necessary to have meetings of the research assistant(s) and myself with the co-investigators (the paediatric cardiologist, the paediatrician and the obstetrician) to clarify the description of the condition affecting the mother or infant as documented in the open ended questions.

Using the SIR (Scientific Information Retrieval, Pty, Ltd), version 4.0, database package a relational database was built. The data from the main form were *double-data entered* (entered twice and then the two entries are compared by the software itself to identify data-entry errors) by a member of the Research Data Management Group (RDM) of the Biostatistics, Epidemiology and Scientific Computing Department. The main form was in a separate record from the pregnancy form and the MRN was the key. The data from the pregnancy form was entered only once by a member of RDM. The supplemental pages, with the exception of the consanguinity form, were kept separately and were entered into EXCEL spreadsheets all at the same time by a recently graduated high school student in the months of September to December, 2004. The supplemental data were *double-data entered* by ALS.

The first entry into SIR was done within the week of data collection and the second entry was started in September, 2004. This was completed December 31, 2004. The data were

transferred to SPSS where univariate frequencies were produced for all continuous and categorical data by case or control status to look for outliers and data entry errors. From January 2005 until May 2005 the data were cleaned and checked. All inconsistencies in the pregnancy form (which had only been single entered) were validated. Additionally, these pregnancy data were processed as follows:

1. Where the date of birth of a non-index child was not remembered in its entirety (month, day and year) it was estimated at the time of the interview in either *Hejira* or *Gregorian* – whichever calendar the mother proposed.
2. *Hejira* given dates were converted to Gregorian dates using the KFSH&RC in-house designed software for that purpose.
3. Calculations were implemented to confirm that all pregnancy dates were reasonable within a woman.
4. Pregnancy dates corresponded to the age of the mother at the time of the pregnancy and the current age.

As mentioned in Section 13.14.2 all pregnancies were documented. However, the analysis was only interested in those pregnancies *prior to* the index pregnancy. Therefore, during processing all subsequent pregnancies after the index pregnancy (unless it was a twin) were excluded. There were 60 of these pregnancies.

Lesion data

Using the CHD registry data the 7,714 Saudi Arabian patients registered from 1998 to 2003 were selected. For these, using the stacking command in JMP, the dataset was transformed from a dataset with irregular row lengths where the parallel diagnoses were all on one row to a rectangular dataset where every row represents one lesion (one row per individual versus possible multiple rows per individual) (table 3.6 and 3.7). The lesion is made unique by the combination of the medical record number with the lesion number. The 7,714 ***patients*** had 12,554 ***lesions***.

The Riyadh registry data had to be handled with care as not all cases had been diagnosed by the registry in time for analysis. Diagnoses for 83 of the cases had to be added to the file (Section 3.12.1). These diagnoses were obtained from the case control data and were entered into the lesion dataset and validated.

Table 3.6: Example of a dataset with irregular row lengths with parallel diagnoses on single row

Medical Record Number	Sex	Diagnosis 1	Diagnosis 2	Diagnosis 3	Diagnosis 4
1234	Female	Dextrocardia	AVSD		
2345	Male	TOF			
3456	Female	VSD	TAPVR	PDA	
4567	Female	Truncus	IAA	COA	PDA

Table 3.7: Example of a rectangular dataset where every row represents one lesion

Medical Record Number	Sex	Lesion Number	Diagnosis
1234	Female	1	Dextrocardia
1234	Female	2	AVSD
2345	Male	1	TOF
3456	Female	1	VSD
3456	Female	2	TAPVR
3456	Female	3	PDA
4567	Female	1	Truncus
4567	Female	2	IAA
4567	Female	3	COA
4567	Female	4	PDA

After removing duplicate defects, according to EUROCAT procedures, the Riyadh data for 2001 to 2002 were compared to the Saudi data for 2001 to 2002 (Chapter 4).

3.15 Analysis

3.15.1 Analysis of case control data

Data were analyzed for associations between exposures and congenital heart defects. Confounders were ultimately controlled for using logistic regression for unmatched case control studies. SPSS was used for the creation of variables and for initial univariate presentations which are available upon request. Continuous variables were grouped using percentile cut points where possible or natural categories.

The endpoint of this analysis was an unconditional logistic regression model developed with the dependent variable of *Yes CHD/No CHD* (Bagley, White, Golumb, 2001). Logistic regression establishes the strength of an association between exposure variables and disease while controlling for confounding. This multivariate technique uses the log odds ratios and associations can be represented as an odds ratio with corresponding confidence intervals (usually 95%). Odds ratios that are greater than the number '1' with a confidence limit that does not include the number '1' represent an increased risk of, in this case, CHD compared to the baseline category. The significance of an association between an exposure factor and CHD was assessed using the likelihood ratio test

(Hosmer, Lemeshow, 1989). The baseline level is usually what is considered the category with the least natural risk. In maternal age we expect that both older and younger mothers have an increased risk of having an infant with a congenital anomaly therefore, with maternal age the middle category is accepted as *baseline.* In this case 21-28 years was the middle category for mother's age. Multiple logistic regression takes into account a number of variables simultaneously, describing most efficiently the association between the exposures of interest and the disease (Kirkwood, Sterne 2003). The logistic regression method has limitations however. The most significant one is that for a given analysis missing data is not allowable.

One main analysis and three sub-analyses were decided upon:

- All Sampled: 235 cases and 247 controls
- Cardiac only: isolated or parallel cardiac only cases (n=151) and 242 healthy controls.
- Embryologically earliest (EE): Hierarchical groups 1 and 2 (n=44) and 242 healthy controls.
- Embryologically latest (EL): Hierarchical group 6 (n=89) and 242 healthy controls.

Statistical significance was set at $p < 0.05$.

From the stratified analyses, using STATA, estimates of odds ratios with 95% confidence intervals were calculated. Stratum specific chi-square statistics were used to examine the statistical significance which was set at $p<0.25$. The likelihood ratio chi-square was used to examine the overall effect of the variable on the dependent variable *Yes CHD/No CHD.*

After variables were identified by the criteria of statistical significance (set at $p < 0.25$ (or biologically plausible)) correlations were generated and examined. Variables that are highly correlated should not be introduced into the logistic model (Hosmer, Lemeshow, 1989). Correlations were assessed using the p-values associated with the Pearson product-moment correlation procedure for continuous data, the Spearman's *rho* for non-parametric data or Kendal's *tau* for non-parametric ordinal data as appropriate. Please note that Spearman's approximates Pearson. P values associated with correlations less than 0.05 were considered. Given a significant p value, data with a correlation result greater than 0.2 were considered as correlated.

Therefore, two criteria were set for possible inclusion into the model and four for exclusion:

Possible inclusion:

1. p value in univariate analysis of 0.25
2. biological plausibility.

Possible exclusion:

1. correlation
2. grouping into categories
3. substantial missing data
4. biological non-plausibility.

All potentially influential variables were entered into the full model. This was followed by a second analysis using the forward stepwise procedure.

Once the relevant model had been identified by the forward stepwise procedure then variables were entered and removed using the log likelihood ratio test. These variables were chosen for testing on three criteria:

1. they were found to be significant in the model
2. they are of specific interest but could not be included for they had failed an exclusion criterion.
3. they were of specific interest despite the fact that they had not been found significant in the univariate analysis.

As defined by the logistic regression procedure the dataset was required to be complete with no missing relevant variables. A master dataset was produced with no missing values on the variables included in the model. Because these datasets excluded cases that had been present in the univariate analyses the frequencies and percents were re-run using SPSS. This explains why the numbers (and percents) in tables 5.1, 5.18 and 5.22 differ from those in the adjusted tables 5.17, 5.22, 5.25 and 5.27.

3.15.2 Analysis of lesion data

Prevalence can only be estimated using the CHD registry data because no census data has been released since 1996 (of the status in 1992) thus the denominator data is severely out of date given the huge changes in the Saudi Arabian population pyramid in the last 10

years. Therefore, the comparison to the EUROCAT data was limited. Data were grouped as described on the EUROCAT website and then relative percentages were compared.

3.16 Software

Patients were tracked on the KFSH&RC in-house patient information system. The data were entered in SIR, (version 2000). Correlations were investigated using JMP (version 5.1., SAS, Inc.) Preliminary analysis was run in SPSS (version 10.0) and confirmed in STATA (version 14.0). The data were converted from SPSS to STATA 2.0 (or JMP version 5.1) using DBMSCOPY version 8. Gregorian to Hejira (and vice versa) conversions were made using the KFSH&RC in-house software designed for that purpose.

3.17 Ethics committee approval and informed consent

For this project ethical approval was obtained from the four ethics committees responsible for the work:

- King Abdulaziz City for Science and Technology, Ethics Committee
- Research Advisory Committee, King Faisal Specialist Hospital and Research Centre
- Riyadh Al Kharj Armed Forces Military Hospital, Ethics Committee
- London School of Hygiene and Tropical Medicine, Ethics Committee

An informed consent form was prepared in English and translated into Arabic using the back translations methodology as described for the questionnaire. According to Good Clinical Practice the consent included the following points:

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

2. A description of any reasonably foreseeable risks or discomforts to the subject;

3. A description of any benefits to the subject or to others which may reasonably be expected from the research;

4. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

5. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

6. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

As requested by the Research Advisory Committee of KFSH&RC, the study was documented in the case infant's chart and a copy of the informed consent was placed in the chart. A second copy of the informed consent was handed to both the control and the case mothers. ALS observed the explanation of informed consent, as well as the interview, for 15% of the cases and the controls. A copy of the informed consent may be found in the pocket of this thesis.

CHAPTER 4 Results I – Description of cases and their lesions

In this first set of results, the cases are described using three of the available meta-nosologies: isolated versus parallel, the embryological system and lesion analysis. The first two meta-nosologies are case (person) based and the third is lesion based.

Chapter 5 presents an analysis of the total number of cases (n=235) and three sub-analyses: (1) those with isolated and parallel defects (n=151); (2) the embryologically earliest cases (n=44) and (3) the embryologically latest cases (n=83).

4.1 Introduction to the data

Despite differences in case definition, ascertainment and follow up the Saudi Arabian Congenital Heart Defects Registry is successfully compared to two other large datasets: the one collected by the Baltimore Washington Infant Survey group and the one collected through the auspices of EUROCAT.

4.1.1 BWIS case definition and ascertainment

As described in Section 1.4.2 the case definition for the BWIS allowed for a more comprehensive range of CHD and a more exact description of CHD. All live born cases of CHD obtained from the population of one large region in the USA and diagnosed by 1 year were included. Diagnoses for both cardiac defects and ECM were initially coded by one paediatric cardiologist and then reviewed by another. Additionally, all infants enrolled could be followed and not only the survivors. All data that were compared to Saudi Arabian CHD data were obtained from Ferencz et al., (1993) and Ferencz et al., (1997).

4.1.2 EUROCAT case definition and ascertainment

The EUROCAT population which was compared to the Saudi Arabian CHD population was obtained from publicly available data (http://www.eurocat.ulster.ac.uk/). While EUROCAT collects a wide range of data including live births, stillbirths and foetal deaths only data from live births were used in this analysis. Data from six of the 31 EUROCAT

full members were compared to the Riyadh data. These were the six UK registries that reported data on CHD in the period 2001-2002.and all reporting full members (table 4.1).

Table 4.1: All Full Member and UK registries that reported CHD data for the period 2001-2002

Country	City/Region/Area	Maximum age at diagnosis
Austria	Styria	1 year
Belgium	Antwerp	1 year
	Hainaut	1 year
Croatia	Zagreb	1 year
Denmark	Odense	7 years
France	Paris	1 week
	Auvergne/Strasbourg	2 to 5 years
Germany	Mainz	1 week
	Saxony-Anhalt	1 week
Ireland	Cork and Kerry	Not reported
	Dublin	5 years
	Southeast	Not reported
Italy	Campania	No limit
	Emilia Romagna	No limit
	South East Sicily	1 year
	North East	3 years
	Tuscany	1 year
Malta	Entire coverage	1 year
Netherlands	North	No limit
Poland	Wielkopolska	Not reported
Portugal	South	1 month
Spain	Asturias	1 year
	Barcelona	Not reported
	Basque Country	1 year
Switzerland	Vaud	No limit
United Kingdom	Newcastle-upon-Tyne	Not reported
	North Thames	1 year
	Oxford	Not reported
	Trent	Not reported
	Wales	1 year
	Wessex	Not reported

Source: Appendix 7, EUROCAT Registries: Population Definition, Geographical Area, Stillbirth Definition, Maximum Age at Diagnosis: http://www.eurocat.ulster.ac.uk/pdf/Report%208%20Appendix%207.pdf

The registries which participate in EUROCAT define the populations from which they accrue their cases in various ways. Registries are either hospital-based or population-based. Hospital-based registries include pregnancies from all mothers delivering in selected hospitals irrespective of place of residence. Population-based registries include pregnancies from: (1) all mothers resident in a defined geographic area, (2) all mothers delivering within a defined geographic area irrespective of place of residence, or (3) all mothers delivering in a defined geographic area excluding non-residents of that area.

The observed upper age of diagnosis for the Saudi Arabian CHD data included in this study was two years of age although over 60 percent of the cases were registered by one year (table 4.2). Thus, the EUROCAT and BWIS populations differ from that of the Saudi Arabian Registry. Nevertheless, it could be argued that because of problems in infrastructure in a developing nation that including infants who are diagnosed up to two will not introduce a difference of case mixture. Additionally, the maximum upper age limit was not reported for eight EUROCAT registries. It varied from 1 week to no limit in the other 23 registries although the most common maximum age at diagnosis was 1 year (11 registries) (table 4.1).

4.2 Description of cases

After exclusions, detailed in the methods, there were 235 cases and 247 controls for analysis. Table 4.2 shows the ages of the infants at the time of initial CHD diagnosis as well as the BWIS category into which they are classified. (The BWIS categories will be discussed in Section 6.5 under Severity.)

Table 4.2 Age at CHD diagnosis by BWIS Category with N (% only for those diagnosed at birth and for age category totals)	Prenatal	Birth N (%)	1-2 months	2-3 months	3-6 months	6 months to 2 years	Total
Laterality and Looping	1	8 (73)	0	0	2	0	11
Defects of Ventricular Outlets and Arterial Trunks (DVOAT)							
Mesenchymal cell	1	13(59)	3	2	2	1	22
Complete Transposition	0	18 (72)	4	1	2	0	25
Extracellular Matrix Defects	0	14 (70)	1	1	3	1	20
Targeted Growth Defects	0	4 (50)	3	0	0	1	8
Cell Death Defects	0	13 (76)	1	1	0	2	17
Hemodynamic defects (HD)							
Right-sided flow lesions	0	12 (63)	3	1	1	2	19
Left-sided flow lesions	3	17 (61)	3	1	3	1	28
Septal defects	2	47 (55)	10	6	5	15	85
Total N	7	146	28	13	18	23	235
(%)	(3)	(62)	(12)	(6)	(8)	(10)	(100)

The number and proportion of the four different types of disease status is presented in table 4.3: (1) those with only 1 isolated defect and no other problems (29%); (2) those with several congenital heart defects in parallel (35%); (3) those with an isolated CHD and some other extra-cardiac malformation (ECM) (20%); and (4) those with parallel CHD and ECM (15%). The severity of the ECM ranges from Down or William syndrome

to dysmorphic features and minor defects such as polydactaly. Most commonly in the Riyadh population parallel defects were found in an infant free from any ECM.

Table 4.3 CHD with or without an ECM, in isolation or in parallel	CHD Alone N (%)	CHD with ECM N (%)	Total
Isolated defect	68 (29)	48 (20)	119
Parallel defect	83 (35)	36 (15)	116
Total	151	84	235

Table 4.4 summarises the congenital defects of the 84 cases with ECM. A complete description of the ECM in this population can be found in Chapter 5, tables 5.7 and 5.8. Table 4.4 shows that by far the highest proportion of the ECM was for Down syndrome infants (52%), although, anomalies of other organs were present in 33% of the cases. This was most commonly a problem with the kidney (10%).

Table 4.4 Extra-cardiac malformations found in the case population		N	%	N (%) of 84	(%) of 235
Chromosomal abnormalities				45 (54)	(19)
	Down syndrome*	44	52.4		
	Partial trisomy 11	1	1.2		
Heritable syndromes				11 (13)	(5)
	Alagille syndrome	1	1.2		
	Noonan syndrome	1	1.2		
	William syndrome	2	2.4		
	DiGeorge syndrome	2	2.4		
	Rubenstein Taybi syndrome	1	1.2		
	Other syndromes	4	4.8		
Anomalies of organs				28 (33)	(12)
	Cleft lip, cleft palate	2	2.4		
	Dysmorphic features	7	8.3		
	Congenital malformation of kidney	8	9.5		
	Other organ anomalies	11	13.1		
			Total	84 (100)	
			No ECM (N=151)		(64)
			Total		(100)

*1 also had cleft lip/cleft palate

4.3 Description of cases according to the BWIS classification system and comparison with BWIS results

The frequency and proportion of cases classified according to the meta-nosology of the Baltimore Washington Infant Survey (BWIS) group is shown in Table 4.5 along with the number of unique combinations and the ratio of number of patients to type. The table presents the sub-categories within categories 2 (DVOAT) and 6 (HD). Also, a direct comparison is made to the BWIS results. The BWIS methodology is described in Section 1.3.2. The details of the lesions within each group are shown in Appendix 4A. In short, the earliest lesion manifested embryologically determines the category.

Table 4.5 shows that the *laterality and looping* categories and the DVOAT *mesenchymal cell* categories have the lowest ratio of unique types to the number of cases found in the Riyadh registry. The most common defect category was the *septal defects* where 7 types

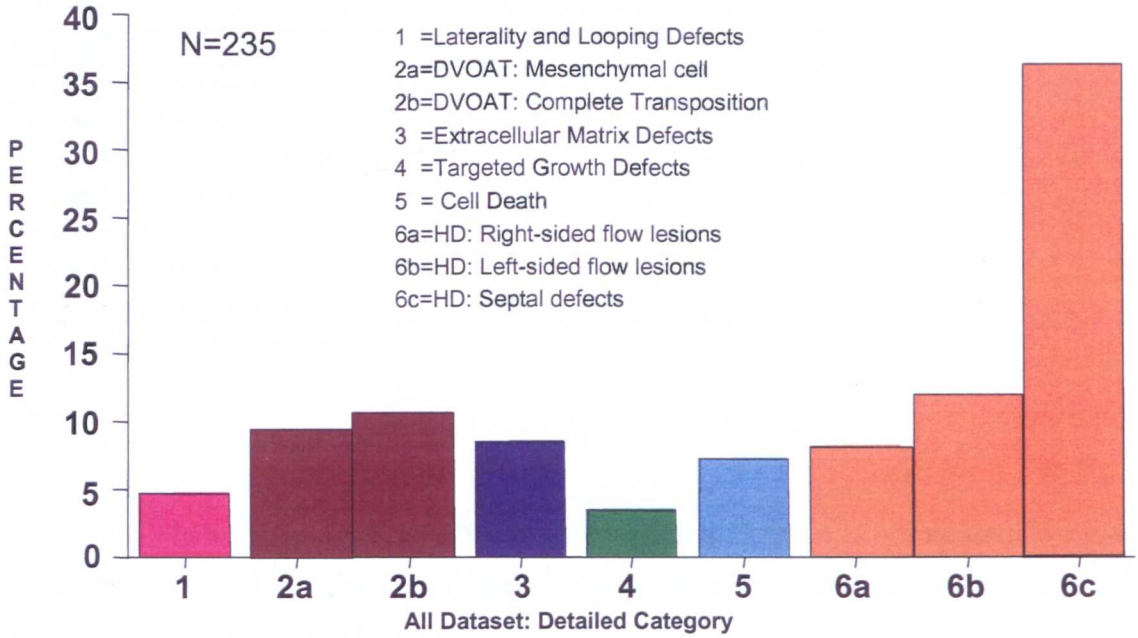
Table 4.5 Using BWIS Categories* to classify and compare Riyadh data with BWIS data		Riyadh data N (%)	Unique Types	Ratio	BWIS N**(%)
1	Laterality and Looping	11 (4.7)	9	1.2	231 (5.5)
2	Defects of Ventricular Outlets and Arterial Trunks (DVOAT)				
a	Mesenchymal cell	22 (9.4)	17	1.3	423 (10.1)
b	Complete Transposition	25 (10.6)	10	2.5	206 (4.9)
3	Extracellular Matrix Defects	20 (8.5)	8	2.5	321 (7.6)
4	Targeted Growth Defects	8 (3.4)	7	1.1	59 (1.4)
5	Cell Death Defects	17 (7.2)	8	2.1	474 (11.3)
6	Hemodynamic defects (HD)				
a	Right-sided flow lesions	19 (8.1)	12	1.6	505 (12.0)
b	Left-sided flow lesions	28 (11.9)	16	1.8	595 (14.2)
c	Septal defects	85 (36.2)	7	12.1	1383 (33.0)
	Total	235 (100.0)			4197

*from table 3.2, Ferencz et al., 1993
**from tables 3.2 and 3.3, Ferencz et al., 1993

accounted for 85 infants, for a ratio of 12 infants for each type of defect combination. The comparison to the BWIS data shows that the data appear comparable for all categories except *complete transposition* where there were 10.6 percent found in the Riyadh data versus 4.9 percent found in the BWIS data. The BWIS had a smaller proportion of *targeted growth defects* than the Riyadh data (1.4% versus 3.4%) but as with the Riyadh data it was the least frequently found. The BWIS data have a higher proportion of *cell death defects* (11.3% versus 7.2%). This was also true for the *right-sided flow lesions* (11.9% versus 8.1%) and the *left sided flow lesions* (14.2% versus 12.0%).

Figure 4.1 presents the data from table 4.5 graphically. The majority of cases were *hemodynamic defects* (56%) of which septal defects makes up the largest part.

Figure 4.1: Bar chart comparing proportion of cases within each of the 6 major categories (by colour) and by the 9 sub-categories



DVOAT: Defects of Ventricular Outlets and Arterial Trunks
HD: Hemodynamic defects

Table 4.6 and figure 4.2 also present the cases classified according to the BWIS system. Table 4.6 is subdivided for cases with cardiac defects only (n=151), and cases with an ECM (n=84).[1] While the proportion of DVOAT: *mesenchymal cell* patients in the Cardiac only and ECM categories is the same, the proportion of DVOAT: *complete transposition* is much lower for the ECM category (10.6% versus 3.6%). When the data are combined in the All CHD dataset the difference between the two categories of DVOAT is not apparent.

In the *right-sided flow lesions* we see a higher proportion of the cardiac only cases compared to the ECM cases. With the *left-sided flow lesions* this is not the case and with *septal defects* it is reversed with a higher proportion being present in the ECM category. In figure 4.2 only six categories are presented; the two sub-categories of DVOAT and the three sub-categories of HD have been merged. Because of the predominance of the AVSD lesion, this figure shows the influence of the Down syndrome infants in the

[1] The All CHD data is shaded as it is already presented in table 4.5. It is presented again in table 4.6 for ease of comparison.

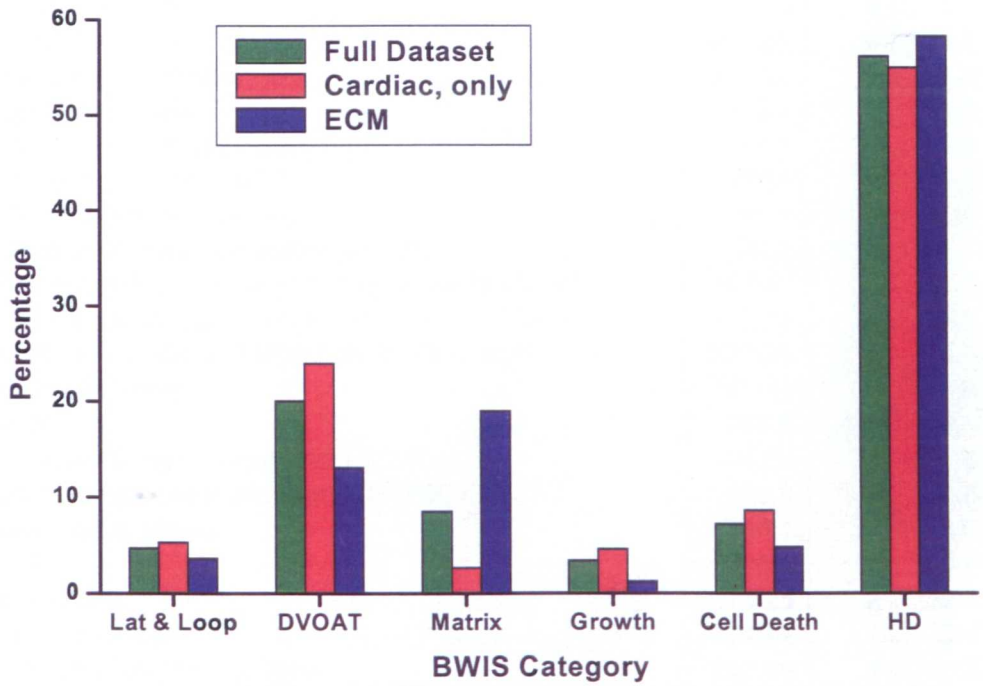
extracellular matrix defects category. The cardiac-only group has only a few in this category whereas the ECM group has substantially more.

Table 4.6 Presentation of cases by BWIS Category stratified by Cardiac only and those with an ECM

	All CHD		Cardiac only		ECM	
	N	(%)	N	%	N	%
1 Laterality and Looping	11	4.7	8	5.3	3	3.6
2 DVOAT: Mesenchymal cell	22	9.4	14	9.3	8	9.5
2 DVOAT: Complete Transposition	25	10.6	22	14.6	3	3.6
3 Extracellular Matrix Defects	20	8.5	4	2.6	16	19.0
4 Targeted Growth Defects	8	3.4	7	4.6	1	1.2
5 Cell Death Defects	17	7.2	13	8.6	4	4.8
6 HD: Right-sided flow lesions	19	8.1	17	11.3	2	2.4
6 HD: Left-sided flow lesions	28	11.9	19	12.6	9	10.7
6 HD: Septal defects	85	36.2	47	31.1	38	45.2
Total	235	100.0	151	100.0	84	100.0

However, when the data are collapsed into one this difference is obfuscated. We also see from this graph that there is a dearth of ECM infants in category 4 (targeted growth defects) (1.2%) compared to the Cardiac only (4.6%).

Figure 4.2: Comparison of percentages of cases in the All, Cardiac only and ECM datasets by embryological category



4.4 Description of lesions and comparison of Saudi Arabian registry data with EUROCAT data

There were 29 types of lesions coded to ICD-9 that were counted using the lesion analysis method. 531 lesions were identified for the 235 cases. Table 4.7 presents the relative frequency of these lesions. ASD II was the most common (23%) followed by VSD (20%) and PDA (18%). The number of isolated cases of ASD II was 36 and coincidentally the number of isolated cases of VSD was 36 (data not shown). VSD was not separated into the two categories of muscular and membranous. Due to the exclusion criteria, there were no isolated PDAs and PDA to premature infants was excluded. The fourth most common lesion was TGV, (corrected or complete) followed by AVSD, COA, PV *stenosis*, DORV and TOF.

Table 4.7 Relative frequency of CHD lesions found in a population of 235 Saudi infants

Defect or lesion	ICD 9 Code	N	%
Atrial septal defect, secundum (ASD II)	745.5	122	23.0
Ventricular septal defect (VSD) membranous and muscular	745.4	105	19.8
Patent ductus arteriosus (PDA)	747.0	93	17.5
Transposition of great vessels (d-TGV and l-TGV)	745.10	28	5.3
Atrioventricular septal defect (AVSD)	745.69	20	3.8
Coarctation of the aorta (COA)	747.1	19	3.6
Pulmonary valve stenosis	746.02	17	3.2
Double outlet right ventricle (DORV)	745.11	13	2.4
Tetralogy of Fallot (TOF)	745.2	13	2.4
Aortic valve stenosis	746.3	9	1.7
Dextrocardia	746.87	9	1.7
Pulmonary valve atresia	746.01	9	1.7
Bicuspid aortic valve	746.4	8	1.5
Pulmonary artery hypoplasia/stenosis	747.3	8	1.5
Ostium primum defect (ASD I)	745.61	7	1.3
Double inlet left ventricle (DILV)	745.3	6	1.1
Hypoplastic left heart syndrome (HLHS)	746.7	6	1.1
Total anomalous pulmonary venous return (TAPVR)	747.41	6	1.1
Partial anomalous pulmonary venous return (PAPVR)	747.42	5	0.9
Interruption of aortic arch/Anomaly of aortic arch	747.21	5	0.9
Sub-aortic stenosis	746.81	5	0.9
Truncus	745.0	3	0.6
Double chambered right ventricle (DCRV)	746.83	3	0.6
Hypoplastic right heart syndrome (HRHS)	746.9	3	0.6
Tricuspid valve atresia	746.1	3	0.6
Sinus ASD	745.8	2	0.6
MItral stenosis	746.5	2	0.4
Ebstein's anomaly	746.2	1	0.4
Other anomalies of great veins	747.49	1	0.2
Total defects		531	100

Table 4.8 Comparison of selected CHD numbers (percent) between Saudi Arabian Registry data, Riyadh Registry data and EUROCAT Registry data (All Full members and all reporting UK registries)

	CHD Registry		Live Births as reported by EUROCAT						
Defect	Saudi Arabia 2001-2002	Riyadh N=235	All Full Members	CARIS Wales UK	NORCAS	North Thames	Oxford	Trent	Wessex
Malformations of cardiac septa (ICD-9 745.01, 745.2, 745.4-745.9)	**1111 (44)**	**200 (52)**	5239 (64)	469 (58)	396 (65)	100 (49)	14 (40)	284(57)	95 (51)
Malformations of great arteries and veins (ICD-9 747.0-747.4)	**710 (28)**	**88 (23)**	1285 (16)	190 (23)	78 (13)	41 (20)	10 (29)	101(20)	44 (23)
Malformations of valves (ICD-9 746.0-746.7)	**466 (19)**	**56 (14)**	1046 (13)	123 (15)	104 (17)	34 (17)	5 (14)	59 (12)	22 (12)
Anomalies of cardiac chambers and connections (ICD-9 745.00, 745.1, 745.3, 745.7)*	**227 (9)**	**43 (11)**	587 (7)	32 (4)	29 (5)	31 (15)	6 (17)	52 (10)	27 (14)
Total	**2514 (100)**	**387 (100)**	8157 (100)	814 (100)	607 (100)	206 (100)	35 (100)	496	188 (100)
Transposition of great vessels (complete) (ICD-9 745.1)*	79 (16)	28 (31)	321 (20)	19 (20)	19 (17)	11 (14)	2 (22)	31 (20)	15 (19)
AVSD (ICD-9 745.6)	153 (30)	25 (27)	336 (21)	21 (23)	25 (23)	14 (18)	0	29 (19)	14 (18)
Coarctation of aorta (747.1)	131 (26)	18 (20)	390 (24)	32 (34)	31 (28)	20 (26)	2 (22)	43 (28)	17 (22)
Tetralogy of Fallot (745.2)	121 (24)	11 (12)	334 (20)	9 (10)	26 (24)	17 (22)	1 (11)	40 (26)	16 (21)
Hypoplastic left heart syndrome (ICD-9 746.7)	6 (1)	6 (7)	163 (10)	9 (10)	5 (5)	12 (16)	3 (33)	6 (4)	14 (18)
Truncus (745.0)	14 (3)	3 (3)	95 (6)	3(3)	4 (4)	2 (3)	1 (11)	4 (3)	2 (3)
Total	504 (100)	91 (100)	1639 (100)	93 (100)	110 (100)	76 (100)	9 (100)	153(100)	78 (100)
Not presented by EUROCAT:									
Dextrocardia (ICD-9 746.87)	45 (25)	9 (45)							
Sub-aortic stenosis (ICD-9 746.81)	65 (36)	5 (25)							
Double chambered right ventricle (ICD-9 746.83)	18 (10)	3 (15)							
Hypoplastic right heart (ICD-9 746.9)	40 (22)	3 (15)							
Mitral atresia (746.89)	11 (6)	0 (0)	-	-	-	-	-	-	-
Total	179 (100)	20 (100)							

EUROCAT 2001-2002 data downloaded from http://eurocat.ulster.ac.uk/pubdata/tables.html 31 May 2006. Red indicates order different than the Saudi Arabian data. CARIS: Congenital anomaly registry and information system. NORCAS: Northern Region, Newcastle-upon-Tyne.

* The category *Anomalies of cardiac chambers and connections* includes DORV however the Transposition of great vessels category does not include DORV.

Table 4.8 compares the distribution of lesions between the cases and EUROCAT registered live births for 2001-2002 in two ways. Firstly, the 531 lesions described in table 4.7 were grouped according to the method used by EUROCAT (Appendix 4B). Data from the Saudi Arabian CHD registry from 1998 to 2003 were also analyzed in this way (Appendix 4C). Data for 2001 and 2002 (Appendix 4C) from the Saudi CHD Registry were summed for a comparison which is presented in table 4.8

The lesions from the EUROCAT data can be divided into four categories:

1. Malformations of cardiac septa (*septa*)
2. Malformations of great arteries and veins (*arteries and veins*)
3. Malformations of valves (*valves*)
4. Anomalies of cardiac chambers and connections (*chambers*)

Secondly, EUROCAT presents six individual defects: TGV, AVSD, COA, TOF, HLHS and common *truncus*. An individual may be counted in more than one group (i.e., *septa* and *valves*) but not twice with the same group. Similarly, the category AVSD (as defined by EUROCAT) includes all patients with ICD-9 745.6. This includes both AVSD (745.69) and ASD I (745.61). Because of the detailed coding of the Saudi Arabian CHD registry there were patients with both 745.69 and 745.61 however in the category of "AVSD (745.6)" in table 4.8 they were only included once.

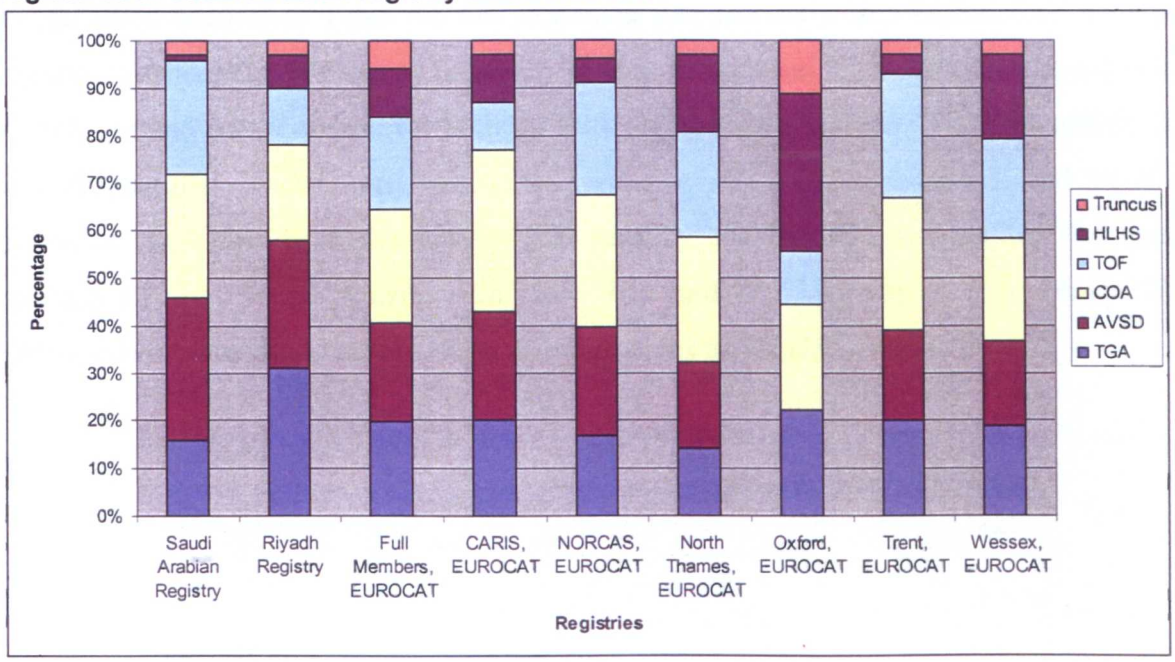
The topmost (orange) section of table 4.8 shows that within the cases there were 200 malformations of *septa* (52%), 88 of *arteries and veins* (23%), 56 of *valves* (14%) and 43 of *chambers* (11%). In comparison with the data from the entire Saudi Arabian registry we see that a smaller proportion of 44 percent were registered with lesions of *septa*, 28 percent were registered with lesions of *arteries and veins*, 19 percent were registered with lesions of *valves* and 9 percent were registered with lesions of the *chambers*. While the proportions are different in magnitude we see that the order is the same with *septa* being more common than *arteries and veins*, being more common than *valves* and *chambers* being the least prevalent.

The data were compared with data from the 6 UK registries which report cardiac anomalies to EUROCAT and with all full EUROCAT members.[2] Three of the six UK registries follow the same pattern of *septa*, *arteries and veins*, *valves* and *chambers*. NORCAS[3], Oxford and Wessex do not although in each registry there is only one deviation which is marked in red.

Considering only the 6 registry groups which follow the same order of *septa*, *arteries*, *valves* and *chambers* we see that the data range from 40 percent to 65 percent for the *septa* category; 13 percent to 29 percent for the arteries category; 12 percent to 19 percent for the valves category and 4 to 15 percent for the *chambers*. For all nine registries *septa* lesions are most common, proportionally followed by *arteries*.

In the blue section of table 4.8 the individual defects which EUROCAT reports are compared. At this individual lesion level there is more variability between the Saudi Arabian registry data, the registry data of Riyadh only, the full member data and the 6 UK registries. In fact, no pattern could be discerned.

Figure 4.3 Visual presentation and comparison of relative frequency data of lesions registered in Saudi Arabian registry and EUROCAT



[2] Full Members to EUROCAT must meet specific criteria. See the EUROCAT website: http://www.eurocat.ulster.ac.uk/index.html. There are 31 Full Member registries which report on the majority of cardiac defects.

[3] Northern Region, Newcastle-upon-Tyne (NORCAS)

Figure 4.3 shows four of the six UK registries (CARIS, Oxford, Trent, Wessex) have approximately 20 percent of their individually identified lesions being TGV. The Saudi Arabian CHD Registry reported 16 percent and the Riyadh region reported 31 percent (the highest number of TGV in this analysis).

There is comparability between Riyadh and Saudi Arabia with regard to AVSD, but the other registries reported a smaller proportion of AVSD lesions. The range for registered AVSD cases was zero[4] to 30 percent reported by the Saudi Arabian registry.

The range of COA was 20 percent to 34 percent with *All Full Members* reporting 24 percent compared to the Saudi Arabian Registry which reported 26 percent. The Riyadh registry only reported 12 percent TOF whereas the Saudi Arabian registry reported 24 percent which was more similar to the findings of the *All Full Members* (20%).

Only one percent of cases were HLHS in the Saudi Arabian registry and this contrasts with 16 percent of cases from North Thames, 18 percent of cases from Wessex and 33 percent of cases from Oxford.

In the green section of Table 4.8 are presented five lesions which EUROCAT does not report: *dextrocardia, sub-aortic stenosis, double chambered right ventricle, hypoplastic right heart* and *mitral atresia* for both the 2001-2002 Saudi Arabian CHD data and for the Riyadh sample. These were presented because of their seriousness and relative commonness within both the Saudi CHD registry and the Riyadh sample. The Saudi Arabian Registry found *dextrocardia* more than half as frequently as they found *TGV. Mitral atresia* was found nearly twice as many times as HLHS.

[4] Oxford reported only 35 cases in all for 2001-2002. Zero cases of these were AVSD.

Summary of results Chapter 4

1. In the Riyadh registry population 62 percent of the defects were discovered at birth which may indicate a high degree of severity of illness. 100% of these cases had been diagnosed by 2 years of age.
2. Most commonly CHD was found in parallel without an ECM (35% of cases).
3. In the Riyadh registry population the highest proportion of ECM were found to be Down syndrome. Nineteen percent of the 235 cases (n=44) had Down syndrome.
4. Using the BWIS system of grouping defects the EMBRYOLOGICALLY EARLIEST defects (laterality and looping and DVOAT mesenchymal cell) have the lowest ratio of unique types to the number of individuals found in the Riyadh registry. The most common defect characterization was septal defects which also had the highest ratio of 12 infants for each type of defect combination. The smallest proportion of cases are those with targeted growth defects (3.4%). The majority of cases were hemodynamic effects (56%) of which septal defects make up the largest part.
5. Using the BWIS system of grouping defects, we see 2.6 percent extracellular matrix defects in CARDIAC ONLY versus 19 percent in the ECM group. This is driven by the large number of Down syndrome infants with AVSD (Figure 4.2). Also, there are few infants within the ECM group with targeted growth defects (1%) and many with septal defects (45%). The proportion of mesenchymal cell (DVOAT) infants is nearly the same in both the CARDIAC ONLY and ECM datasets.
6. Using the lesion analysis method, we see that the Riyadh registry data is comparable to the Saudi Arabian registry data. ASD II was the most commonly found defect (23%) followed by VSD (20%) and non-isolated PDA (18%). Although the relative frequency in combination with other defects was greater for ASD II than VSD, there were equal numbers of patients (n=36) with either isolated ASD II or isolated VSD.
7. Using the lesion analysis method as defined by EUROCAT, in the Riyadh registry *septa* defects were relatively most common (52%) followed by *arteries and veins* (23%), *valves* (14%) and *chambers* (11%). The data follow the same order of frequency as the group of All Full EUROCAT members and three of six UK registries. However, the proportions for the individual defects does not appear to be the same for Riyadh compared to All Full members nor does it appear to be the same for the UK registries as a group. These differences may stem from the differing case definitions and ascertainment procedures used by EUROCAT versus the Saudi Arabian Registry.

CHAPTER 5 Results II – Case control study

In this chapter the results from four analyses conducted on the case control data are presented:

- ALL CASES (all CHD cases)
- CARDIAC ONLY (isolated and parallel combined)
- EMBRYOLOGICALLY EARLIEST cases
- EMBRYOLOGICALLY LATEST cases

Each analysis comprised a descriptive comparison of the characteristics of cases and controls, followed by multivariate analysis using logistic regression. There are summary tables of the models at the end of the relevant section.

5.1 Analysis of all cases

There were 235 cases and 247 controls after exclusions detailed in the Methods.

5.1.1 Univariate results: description of cases and controls

The questionnaire included 238 data elements. In the preliminary analysis stage the data set was increased to 278 variables as new variables were created (e.g., grouping continuous data into categories). The final analysis is restricted to 83 variables of interest. Univariate statistics are presented on these in table 5.1 (a-j). Table 5.13 shows a summary of the number of missing values associated with each variable.

Consanguinity (table 5.1a)

The phylogram chart identified forty-six categories of consanguinity (Appendix 5B). These forty-six were collapsed into "yes/no" and four levels (table 5.1a). Although there were a higher proportion of cases then controls who were from consanguineous unions (52% versus 49%) this difference was not statistically significant. When broken down by category we see that the proportions of both the "First cousin or closer" and the "All other cousin relationships less close than above" categories were virtually the same (25% versus 25% and 12% versus 12% in cases and controls respectively). It was in the "All other (lesser) First Cousins" where there was a higher proportion in cases than in controls (16% versus 13%). However no statistically significant difference was found in the crude odds ratio for being the product of a consanguineous relationship.

Table 5.1 (a-j) Characteristics for all sampled n=482

5.1a Consanguinity

Characteristic	Stratum	Cases		Controls		Crude odds ratio		p value
Consanguinity	Yes	123	52.3	122	49.4	1.2	(0.8-1.7)	0.90
	No	112	47.7	125	40.6	1.0		
	Total	235	100.0	247	100.0			
First Cousin or closer		58	24.7	62	25.1	1.0	(0.7-1.6)	0.78
All other (lesser) First Cousins		37	15.7	31	12.6	1.3	(0.8-2.3)	
All Second and Third Cousins		28	11.9	29	11.7	1.0	(0.6-1.9)	
Non-Consanguineous		112	47.7	125	50.6	1.0		
Total		235	100.0	247	100.0			

Cuzick Test for trend across ordered groups 0.6

Infant characteristics (table 5.1b)

Cases and controls had a similar sex ratio (table 5.1b). There was a significant difference in the age of the case and control infants at the time the interview took place, the cases

5.1b Infant characteristics

Characteristic	Stratum	Cases N (%)		Controls N (%)		Crude odds ratio (95% CI)		Chi^2 (LR) p value
Infant's Sex	Male	121	(51.5)	122	(49.4)	1.1	(0.8-1.6)	0.65
	Female	114	(48.5)	125	(50.6)	1.0		
	Total	235	(100.0)	247	(100.0)			
Infant's Age at Interview	15 days to 3 months	52	22.1	29	11.7	1.0		< 0.001
	3 to 6 months	41	17.4	73	29.6	0.3	(0.2-0.6)	
	6 months to 1 year	54	23.0	92	37.2	0.3	(0.2-0.6)	
	1 to 1.5 years	44	18.7	31	12.6	0.8	(0.4-1.5)	
	1.5 to 2 years	18	7.7	19	7.7	0.5	(0.2-1.2)	
	More than 2 years	26	11.1	3	1.2	4.8	(1.3-18.2)	
	Total	235	100.0	247	100.0			
Infant's Birth weight	< 1500 grams	9	4.3	0	0.0	-		< 0.001
	1500-2499 grams	53	25.6	22	9.2	3.7	(2.1-6.4)	
	2500-3499 grams	108	52.2	165	68.8	1.0		
	3500-3999 grams	28	13.5	44	18.3	1.0	(0.6-1.7)	
	> 4000 grams	9	4.3	9	3.8	1.5	(0.6-4.0)	
	Total*	207	100.0	240	100.0			
Gestational Age	31 or less weeks	8	3.5	1	0.4	10.1	(1.2-83.0)	< 0.001
	32 to 36 weeks	37	16.2	12	4.9	3.9	(1.9-7.8)	
	37 or more weeks	184	80.3	232	94.7	1.0		
	Total	229	100.0	245	100.0			
Multiplicity	Singleton	224	95.3	245	99.2	1.0		< 0.001
	Twins or higher	11	4.7	2	.8	6.1	(1.3-27.8)	
	Total	235	100.0	247	100.0			

* For details on missing see table 5.13.

being younger than controls. The mean age of cases was 11.3 months (s.d. 10.2 months) and the mean age of controls was 8.3 months (s.d. 5.9 months) at interview ($p< 0.001$). Both sex and age of infant at interview were monitored during data collection with the aim of achieving a stratum matched sample of controls. However, the control hospital's immunization plan did not have many infants appearing naturally at more than two years.

There was a statistically significant difference between the mean birth weight of cases and controls. For cases it was 2.7 kg (s.d. 687 gms) and for controls 3.1 kgs (s.d. 619 gms) ($p < 0.001$). Descriptive statistics for cases and controls for age at interview and birth weight are presented in table 5.2

Table 5.2: Descriptive statistics for age at interview and birth weight

	Age at Interview		Birth weight	
	Cases N (%)	Controls N (%)	Cases N (%)	Controls N (%)
N	235	247	207	240
Missing	0	0	28	7
Mean	11.3 months	8.3 months	2738 gms	3129 gms
Median	8.4 months	6.8 months	2900 gms	3128 gms
Std. Deviation	10.2 months	5.9 months	687 gms	488 gms
Minimum	15 days	29 days	600 gms	1500 gms
Maximum	1528 days	1634 days	4500 gms	4500 gms

The highest gestational age for cases and for controls was 42 weeks except for two controls with gestational ages of 43 weeks. A significantly higher proportion of cases were born prematurely (20%) than controls (5%) ($p < 0.001$). There was a higher proportion of multiple births among the cases (4.7%) than the controls (0.8%). For cases, there were ten twin infants and one triplet infant. Among the controls there were two twin infants.

Maternal characteristics (table 5.1c)

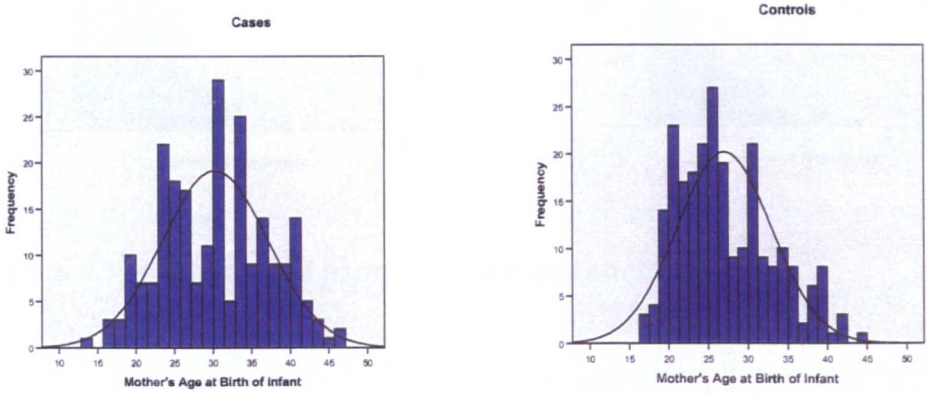
Nearly all (99.6%) case and control mothers were Saudi by birth and nationality (table 5.1c). There was one case mother who was a Saudi national although she and her husband were originally from the Yemen. One case mother was Qatari and one control mother was Syrian. With regards to ethnicity, a higher proportion of case mothers than control mothers classified themselves as Bedouin (37% versus 21%) ($p< 0.001$). Case mothers were significantly older than control mothers with the point estimate of the odds ratio for greater than 38 years of age being 4.0 ($CI_{95\%}$ = 1.9-8.3). The mean age for case mothers was 30 years (s.d. 6.9) and for controls it was 27 years (s.d. 5.9). Figure 5.1 presents histograms of maternal age in years at the birth of the infant. The case mothers had a broader range of ages although both case and control curves approximate a normal distribution.

5.1c Maternal characteristics

Characteristic	Stratum	Cases N (%)		Controls N (%)		Crude odds ratio (95% CI)		Chi^2 (LR) p value
Mother's Nationality	Saudi	234	99.6	246	99.6			
	Other Arab	1	0.4	1	0.4	-		
	Total	235	100.0	247	100.0			
Mother's Ethnicity	Bedouin Ethnicity	87	37.2	52	21.1	2.2	(1.5-3.3)	< 0.001
	Urban Ethnicity	147	62.8	194	78.9	1.0		
	Total*	234	100.0	246	100.0			
Mother's age at infant's birth (years)	14-20	17	7.4	35	14.5	0.7	(0.4-1.4)	
	21-28	78	33.8	120	49.6	1.0		
	29-38	102	44.2	74	30.6	2.1	(1.4-3.2)	< 0.001
	39+	34	14.7	13	5.4	4.0	(1.9-8.3)	
	Total*	231	100.0	242	100.0			
Mother's age at first birth	14-19	75	32.5	91	37.8	0.8	(0.6-1.2)	
	20-29	142	61.5	145	60.2	1.0		0.05
	30+	14	6.1	5	2.1	2.9	(1.0-8.2)	
	Total*	231	100.0	241	100.0			
Marital Status	Married to baby's father	233	100.0	245	99.2			
	Separated/divorced	0	0	2	.8	-		
	Total*	233	100.0	247	100.0			
Gravida	1 pregnancy	34	14.5	72	29.1	1.0		< 0.001
	2-5 pregnancies	128	54.5	126	51.0	2.2	(1.3-3.5)	
	6-8 pregnancies	58	24.7	36	14.6	3.4	(1.9-6.3)	
	9 or more pregnancies	15	6.4	13	5.3	2.4	(1.0-5.8)	
	Total	235	100.0	247	100.0			
Parity	1 birth	44	19.0	82	33.2	1.0		< 0.001
	2-5 births	139	59.9	127	51.4	2.0	(1.3-3.2)	
	6 or more births	49	21.1	38	15.4	2.4	(1.4-4.3)	
	Total*	232	100.0	247	100.0			

*For details on missing see table 5.13.

Figure 5.1 Histograms of maternal age at birth of infant (years) for cases and controls



We stratified maternal ethnicity by consanguinity and found that the Bedouin cases do have a higher proportion of first cousin or closer and all other (lesser) first cousin than the urban cases (p, 0.003) (table 5.3). In the controls, there is a difference between the proportion of all second and third cousins in the Bedouin cases versus the urban cases.

Table 5.3 Ethnicity stratified by consanguinity

Characteristic	Bedouin N (%)		Urban N (%)	
	Cases	Controls	Cases	Controls
First Cousin or closer	28 (32)	12 (23)	30 (20)	50 (26)
All other (lesser) First Cousins	17 (20)	6 (12)	20 (14)	25 (13)
All Second and Third Cousins	12 (14)	9 (17)	15 (10)	20 (10)
Non-Consanguineous	30 (35)	25 (48)	82 (56)	99 (51)
Total	87 (100)	52 (100)	147 (100)	194 (100)

The variable *maternal age at first birth* was also investigated but did not appear superior to *maternal age at infant's birth*. Nearly all of the case mothers and the control mothers were currently married to the father of the baby. Two control mothers were divorced. Marital information was unknown for two cases who discontinued the interview halfway through. Increased gravida and increased parity were significantly associated with increased odds of CHD in univariate analysis. Histograms for gravida and parity and univariate statistics are presented in figures 5.2 and 5.3 and table 5.4, respectively. The average gravidity for cases was 4 with a range of 1 to 17 whereas for cases it was 3 with a range of 1 to 13. Parity shows similar if less remarkable differences.

Figure 5.2 Histograms for number of pregnancies (gravidity) for cases and controls

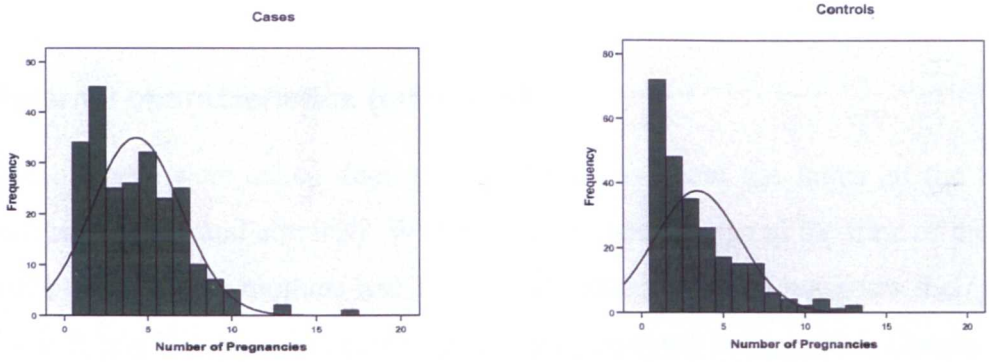


Figure 5.3 Histograms of parity for cases and controls

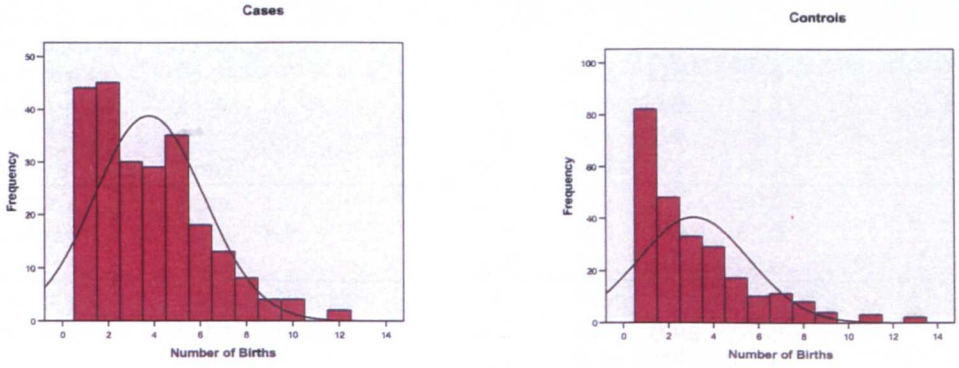


Table 5.4 Univariate statistics for gravida and parity

Number of pregnancies or births	Gravida				Parity			
	Cases N (%)		Controls N (%)		Cases N (%)		Controls N (%)	
1	34	14.5	72	29.1	44	19.0	82	33.2
2	45	19.1	48	19.4	45	19.4	48	19.4
3	25	10.6	35	14.2	30	12.9	33	13.4
4	26	11.1	26	10.5	29	12.5	29	11.7
5	32	13.6	17	6.9	35	15.1	17	6.9
6	23	9.8	15	6.1	18	7.8	10	4.0
7	25	10.6	15	6.1	13	5.6	11	4.5
8	10	4.3	6	2.4	8	3.4	8	3.2
9	7	3.0	4	1.6	4	1.7	4	1.6
10	5	2.1	2	.8	4	1.7		
11			4	1.6			3	1.2
12			1	.4	2	0.9		
13	2	0.9	2	.8			2	0.8
14								
15								
16								
17	1	0.4						
	235	100.0	247	100.0	232	100.0	247	100.0
	Cases		Controls		Cases		Controls	
Missing	0		0		3		0	
Mean	4.31		3.41		3.78		3.13	
Median	4.00		3.00		3.00		2.00	
Std. Deviation	2.68		2.62		2.40		2.44	
Range	1-17		1-13		1-12		1-13	

Paternal characteristics (table 5.1d)

The mothers were asked demographic questions about the father of the baby: paternal age, nationality and ethnicity. With respect to paternal age at the time of the infant's birth there were 16 case mothers and 28 control mothers who did not know their husband's age (table 5.1d). Histograms for paternal age are presented in figure 5.4. Despite the missing

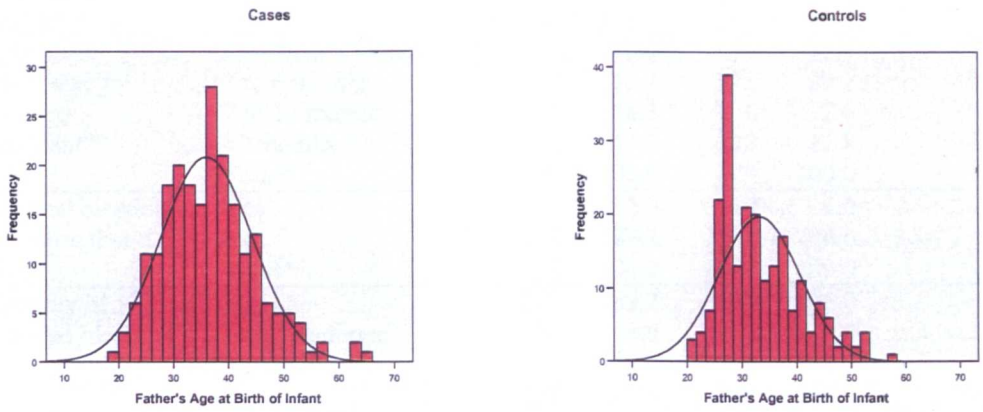
5.1d Paternal characteristics

Characteristic	Stratum	Cases N (%)		Controls N (%)		Crude odds ratio (95% CI)		Chi^2 (LR) p value
Father's age at infant's birth (years)	19-24	16	7.3	14	6.4	1.9	(0.9-4.2)	< 0.001
	25-34	81	37.0	126	57.5	1.0		
	35-44	90	41.1	60	27.4	2.3	(1.5-3.6)	
	45+	32	14.6	19	8.7	2.6	(1.4-5.0)	
	Total*	219	100.0	219	100.0			
Father's Nationality	Saudi	235	100.0	247	100.0			
	Other Arab	0	0.0	0	0.00	-		
	Total*	235	100.0	247	100.0			
Father's Ethnicity	Bedouin Ethnicity	92	39.3	57	23.1	2.2	(1.4-3.2)	< 0.001
	Urban Ethnicity	142	60.7	190	76.9	1.0		
	Total*	234	100.0	247	100.0			

*For details on missing see table 5.13.

data, older paternal age was clearly associated with a greater risk of having an infant with CHD. Fifteen percent of case fathers were aged 45 or more compared to only 9 percent of control fathers. All fathers were Saudi Arabian although one had originally been Yemani as described above. Approximately, the same proportion of fathers as mothers were Bedouin. These data were highly correlated r=0.8853; correlations are discussed more fully in section 5.1.2.

Figure 5.4 Histograms of paternal age at birth of the infant for cases and controls



Both maternal ethnicity and paternal ethnicity were significantly associated with outcome in univariate analyses and the two variables were highly correlated. Excluding those cases and controls whose parents did not share the same ethnicity was considered (table 5.5 marked in red). However, despite the high correlation this would have excluded 23 infants (7% of the cases and 3% of the controls). Therefore, maternal ethnicity was chosen for further analysis as it was considered to be more reliable. It was obtained from the mother herself rather than the mother's opinion of the father.

Table 5.5 Comparison of maternal and paternal ethnicity

Characteristic	Stratum	Bedouin Father N (%)		Urban Father N (%)		Total N (%)	
Cases	Bedouin Mother	82	89	5	4	87	37
	Urban Mother	10	11	137	96	147	63
	Total	92	100	142	100	234	100
Controls	Bedouin Mother	50	89	2	1	52	21
	Urban Mother	6	11	188	99	194	79
	Total	56	100	190	100	246	100

Index pregnancy characteristics (table 5.1e)

Nine of the case mothers and three of the controls reported use artificial reproductive technology (ART) in the conception of the index child (table 5.1e). Four of the cases used

5.1e Index pregnancy characteristics

Characteristic	Stratum	Cases N (%)		Controls N (%)		Crude odds ratio (95% CI)		Chi^2 (LR) p value
Did this pregnancy use ART?	Yes	9	3.8	3	1.2	3.3	(0.9-12.3)	0.06
	No	223	94.9	243	98.4	1.0		
	Total*	232	98.7	246	99.6			
Was this pregnancy planned?	Yes	102	44.0	82	33.3	1.0		
	No	130	56.0	164	66.7	0.6	(0.4-0.9)	0.02
	Total*	232	100.0	246	100.0			
How many weeks did it take to become pregnant?*	Less than 3 months	25	26.0	28	35.4	1.0		< 0.001
	3 to 6 months	10	10.4	23	29.1	0.5	(0.2-1.2)	
	7 to 12 months	8	8.3	6	7.6	1.5	(0.4-5.0)	
	12 months +	53	55.2	22	27.8	2.7	(1.3-5.8)	
	Total*	96	100.0	79	100.0			
Vaginal bleeding for more than 1 day	Yes	25	10.8	10	4.0	2.9	(1.3-6.1)	< 0.001
	No	207	89.2	237	96.0	1.0		
	Total*	232	100.0	247	100.0			
Severity of Vaginal bleeding	None	207	89.2	237	96.0	1.0		0.01
	Mild/Moderate	20	8.6	7	2.8	3.3	(1.3-8.0)	
	Severe	5	2.2	3	1.2	1.9	(0.4-8.1)	
	Total*	232	100.0	247	100.0			
Extra-cardiac anomaly (ECM) (Mother)	None	183	79.0	242	98.0	1.0		< 0.001
	ECM	49	21.0	5	2.0	12.9	(4.8-34.8)	
	Total	232	100.0	247	100.0			
Any ECM (Registry)	None	163	69.4	242	98.0	1.0		
	ECM	72	30.6	5	2.0	21.4	(7.8-58.6)	< 0.001
	Total	235	100.0	247	100.0			
All ECM (Registry or Mother)	None	151	64.3	242	98.0	1.0		< 0.001
	ECM	84	35.7	5	2.0	26.9	(10.7-67.9)	
	Total	235	100.0	247	100.0			
Mother's BMI at interview	Underweight (<18.5)	1	.5	2	.8	0.6	(0.1-6.5)	
	Normal (18.5 – 24.9)	62	28.6	71	29.2	1.0	-	0.96
	Overweight (25.0-29)	80	36.9	87	35.8	1.1	(0.7-1.7)	
	Obese (30+)	74	34.1	83	34.2	1.0	(0.6-1.6)	
	Total*	217	100.0	243	100.0			
Estimate of Mother's BMI pre-pregnancy	Underweight (<18.5)	3	2.3	5	3.2	0.6	(0.1-2.9)	
	Normal (18.5 – 24.9)	45	34.1	48	30.6	1.0	-	0.60
	Overweight (25.0-29)	49	37.1	52	33.1	1.0	(0.6-1.8)	
	Obese (30+)	35	26.5	52	33.1	0.7	(0.4-1.3)	
	Total*	132	100.0	157	100.0			
Diabetes during index pregnancy	Yes	42	17.9	33	13.4	1.4	(0.9-2.3)	0.20
	No	193	82.1	214	86.6	1.0		
	Total	235	100.0	247	100.0			
Diabetes	No Diabetes	193	82.5	214	87.3	1.0		
	Gestational Diabetes	31	13.2	30	12.2	1.1	(0.6-2.0)	0.01
	Overt	10	4.3	1	0.4	11.1	(1.4-89.4)	
	Total*	234	100.0	245	100.0			
Major maternal health problem with index pregnancy	Yes	63	27.2	34	13.8	2.3	(1.5-3.7)	< 0.001
	No	169	72.8	213	86.2	1.0		
	Total*	232	100.0	247	100.0			

*For details on missing see table 5.13.

Clomid with hormonal injections alone, four cases reported *gamete intra-fallopian transfer* (GIFT) or *intra-cellular sperm insemination* (ICSI) and one used a traditional remedy. The three controls availing themselves of ART used Clomid with hormonal injections alone. Multiplicity does not appear to be associated with ART as shown in table 5.6 although this could not be tested statistically (the expected count was less than 5). Eight of the thirteen multiple gestations (62%) did not report use of ART.

Table 5.6 Comparison of multiple births with artificial reproductive technologies by case and control status

Characteristic	Stratum	ART Yes N	(%)	ART No N	(%)	Total N	(%)
Cases	Singletons	5	56	216	97	221	95
	Twins	3	33	7	3	10	4
	Triplets	1	11	0	0	1	0
	Total	9	100	223	100	232	100
Controls	Singleton	2	67	243	99	245	99
	Twins	1	33	1	1	2	1
	Total	3	100	244	100	247	100

Forty-four percent of the case mothers reported that the pregnancy was planned versus 33 percent of the control mothers ($p<0.02$). Of those who planned to become pregnant, 55 percent of case mothers versus 28 percent of control mothers found that they had to wait more than one year to conceive. Vaginal bleeding for more than one day was significantly more prevalent in the case pregnancies than the control pregnancies (OR=2.9, $CI_{95\%}$ =1.3-6.1). Severe vaginal bleeding however was not found to be significantly different.

As described in the methods (Section 3.14.2) there were two ways to capture information on extra-cardiac malformations (ECM) from cases. The reliability of these two sources differed. Only 49 case mothers reported a problem at the time of the interview whereas 72 of the infants were registered with an associated diagnosis by the registry. In total there were 84 infants with an associated diagnosis using both the mother's report and the registry (table 5.7).

Table 5.7 Comparison of source for identification of extra-cardiac malformation

	N	%
No defect reported	151	64.3
Mother reported, only	12	5.1
Registry reported, only	35	14.9
Mother and registry	37	15.7
Total	235	100.0

The 35 examples (15% of all cases) where the ECM was reported only by the registry includes 11 of the chromosomal cases, 6 of the heritable cases, 6 of the dysmorphic

features and 12 of the other organ anomalies. The 12 examples where the ECM was only reported by the mother includes 11 cases of Down syndrome and 4 cases of anomalies of organs. The detailed description of the ECM anomalies is found in tables 5.8 (cases) and 5.9 (controls). Please note the ECM reported in the case infants have been categorized into the groups described by the BWIS (Ferencz et al., 1993).

The only source of ECM information for control infants was from the mother although theoretically this information should have been included on the Well Baby booklet. It was not noted on any of the ones seen by the author although the author did not see them all. This information is shaded in table 5.1e.

As can be seen from table 5.1e, ECM were highly associated with being a case with an odds ratio of 27 and a 95% confidence limit of 11 to 68. It was decided therefore to examine separately those cases without an ECM (Section 5.2).

In the all case analysis, no association was found between mother's estimated pre-pregnancy body mass index (BMI) and risk of CHD in the infant, or her BMI at interview and risk of CHD. Thirty-four percent of cases and controls were obese at interview and another 36 percent of cases and controls were overweight at interview. Only 56 percent of cases and 64 percent of controls were able to estimate their pre-pregnancy weight. Therefore, due to the paucity of data (and despite the fact that obesity has been shown to be a risk factor for anomalies) this variable will not be considered in further analysis.

There were approximately the same proportion of gestational diabetics in each group, but significantly more overt diabetics in the case group (OR 11.1, $CI_{95\%}$ =1.4-89.4).

As described in the methods section (Section 3.14.2) a variable was created to count the major health problems affecting the index pregnancy. It was found to be significantly associated with outcome (OR = 2.3, $CI_{95\%}$ =1.5-3.7). There were 63 cases and 34 controls with a major maternal health problem in the index pregnancy or in a previous pregnancy that may have affected this index pregnancy. A listing of these major maternal health problems is found in table 5.10 as well as the data for the 35 (of 151) CARDIAC ONLY cases to be analyzed in Section 5.2.

Previous pregnancy characteristics (table 5.1f)

There was increased risk associated with two previous pregnancy losses (OR = 2.5, $CI_{95\%}$ =1.3-5.0), with the increased risk for three or more previous losses being even higher (OR= 6.1, $CI_{95\%}$ =1.3-28.1) (table 5.1f). Vaginal bleeding lasting more than one day in two previous pregnancies was associated with increased risk (OR=7.2, $CI_{95\%}$ =2.1-24.9). Three or more previous pregnancies while the mother suffered from a maternal

Table 5.8 Extra-cardiac malformations found in cases categorized according to system used in the BWIS

Abnormalities	N	%
No Non-CHD associated anomalies	151	
Chromosomal abnormalities		
Down syndrome	40	47.6
Down syndrome and duodenal atresia	1	1.2
Down syndrome and congenital hypothyroidism	2	2.4
Partial trisomy 11, sub glottic stenosis, inguinal hernia	1	1.2
Down syndrome and bilateral cleft lip, cleft palate	1	1.2
Heritable syndromes		
Alagille syndrome	1	1.2
DiGeorge syndrome	2	2.4
Lactic Acidosis and micrognathia	1	1.2
Noonan syndrome	1	1.2
Polydactyly	1	1.2
Polydactyly and dysmorphic featrues	1	1.2
Rubenstein Taybi syndrome	1	1.2
Tuberous sclerosis (Rhabdemyoma)	1	1.2
Williams syndrome	2	2.4
Anomalies of organs		
Cleft lip, cleft palate	1	1.2
Incomplete cleft lip, unilateral	1	1.2
Dysmorphic features	2	2.4
Dysmorphic features and undescended testes	1	1.2
Dysmorphic features: micrognathia, web neck, hemangioma, depressed nasal bridge	1	1.2
Dysmorphic features: low set ears, hirsute, short neck, mild clubbing	1	1.2
Dysmorphic features: Facial asymmetry, micrognathia, widely spaced nipples	1	1.2
Congenital malformation of kidney	3	3.6
Congenital hydronephresis	4	4.8
Hyperplasia of kidney	1	1.2
Cloacal exstrophy, perforated anus, other serious defects	1	1.2
Omphalocele	2	2.4
Lumbosacral spine agenesis	1	1.2
Short bowel syndrome "twisted intestine"	1	1.2
Ectopic testes	1	1.2
Subglottic stenosis	2	2.4
Unidentified congenital abnormalities	1	1.2
Duodenal atresia	1	1.2
Craniosynthesis	1	1.2
Problem with endocrine gland	1	1.2
Total	84	100.0

Table 5.9 Extra-cardiac malformations found in controls

Abnormalities	N	%
Mental retardation	1	20.0
Kidney problem	2	40.0
Sickle cell trait	1	20.0
Small head for weight and length	1	20.0
Total	5	100.0

health problem was also indicated (OR=3.9, $CI_{95\%}$ =1.4-10.8). The total number of neonatal deaths, infant deaths, deceased children and total number of pregnancies while the mother suffered from a major illness were not found to be significantly associated with risk of CHD in the index pregnancy.

5.1f Previous pregnancy characteristics

Characteristic	Stratum	Cases N (%)		Controls N (%)		Crude odds ratio (95% CI)		Chi^2 (LR) p value
Total pregnancy losses[+]	No losses	160	69.0	194	78.5	1.0		< 0.001
	1 loss	35	15.1	38	15.4	1.1	(0.7-1.8)	
	2 losses	27	11.6	13	5.3	2.5	(1.3-5.0)	
	3 or more losses	10	4.3	2	.8	6.1	(1.3-28.1)	
	Total	232	100.0	247	100.0			
Total neonatal deaths (<30 days)	No neonatal deaths	225	97.0	244	98.8	1.0		
	1+ neonatal deaths	7	3.0	3	1.2	2.5	(0.6-9.9)	0.16
	Total	232	100.0	247	100.0			
Total infant deaths (31 to 365 days)	No infant deaths	226	97.4	243	98.4	1.0		
	1 or more deaths	6	2.6	4	1.6	1.6	(0.4-5.8)	0.55
	Total	232	100.0	247	100.0			
Total lost children	No deaths	216	93.1	236	95.5	1.0		
	1 or more deaths	16	6.8	11	4.5	1.6	(0.7-3.5)	0.25
	Total	232	100.0	247	100.0			
Pregnancies with vaginal bleeding > 1 day[++]	No bleeding	177	76.3	213	86.2	1.0		< 0.001
	1 pregnancy	29	12.5	28	11.3	1.2	(0.7-2.2)	
	2 pregnancies	18	7.8	3	1.2	7.2	(2.1-24.9)	
	3+ pregnancies	8	3.4	3	1.2	3.2	(0.8-12.3)	
	Total	232	100.0	247	100.0			
Maternal health problem	None	151	65.1	182	73.7	1.0		0.01
	1 pregnancy	56	24.1	46	18.6	1.5	(0.9-2.3)	
	2 pregnancies	9	3.9	14	5.7	0.7	(0.3-1.8)	
	3 pregnancies	16	6.9	5	2.0	3.9	(1.4-10.8)	
	Total	232	100.0	247	100.0			
Pregnancies while mother suffered from a major illness	None	224	96.6	232	93.9	1.0		0.39
	1 pregnancy	3	1.3	9	3.6	0.3	(0.1-1.3)	
	2 pregnancies	2	.9	2	.8	1.0	(0.1-7.4)	
	3 pregnancies	3	1.3	4	1.6	0.7	(0.2-3.5)	
	Total	232	100.0	247	100.0			

[+] Cuzick Test for Trend across ordered groups 0.01

*For details on missing see Table 5.13.

Table 5.11 presents the detailed results for diabetes by type and treatment. Of those with diabetes a higher proportion of case mothers had type I diabetes than control mothers (17% versus 3%). No control mothers had type II diabetes while 7 percent of cases had it. Of the total sample (table 5.1e) thirteen percent of cases had gestational diabetes versus

12 percent of controls. The treatment of the gestational diabetes for the majority was diet although a proportion of these mothers reported that they received insulin injections: 4 of 31 case mothers and 3 of 30 control mothers.

Table 5.10 Condition, illness or previous history affecting this pregnancy

Health Problem	All Cases N (%)		Controls N (%)		Cardiac Only N (%)	
Index pregnancy using Assisted Reproductive Therapy (ART)						
ART, drugs only this pregnancy	2	3.2	1	2.9	1	2.9
ART, this pregnancy	3	4.8				
ART, drugs only, this pregnancy and previous CHD child	1	1.6				
ART, this pregnancy and previous CHD child	1	1.6			1	2.9
Having a serious disease in index pregnancy						
Thalessemia in mother			1	2.9		
Thalessemia in mother and previous CHD child	1	1.6			1	2.9
Thyroid disease in mother	2	3.2	6	17.6	1	2.9
Thyroid disease and more than 3 previous pregnancy losses			1	2.9		
Thyroid disease and ART, drugs only, this pregnancy			2	5.9		
Thyroid disease and severe vaginal bleeding requiring medications to prevent labour	1	1.6			1	2.9
Thyroid disease in mother and previous CHD child	1	1.6			1	2.9
Thyroid disease, severe bleeding requiring medications to prevent labour and other major birth defect previous child			1	2.9		
Appendectomy, week 4 gestation, in mother	1	1.6				
Epilepsy in mother	1	1.6	1	2.9	1	2.9
Hepatitis B virus in mother while pregnant	1	1.6	2	5.9	1	2.9
Insulin diabetes type 1/2 in mother	9	14.3			5	14.3
Insulin diabetes type 1/2 in mother and previous CHD child			1	2.9		
Insulin diabetes type 1/2 in mother and more than 3 previous pregnancy losses	1	1.6				
More than 3 previous pregnancy losses						
More than 3 previous pregnancy losses	6	9.5	1	2.9	3	8.6
More than 3 previous pregnancy losses and ART, drugs only, this pregnancy	1	1.6			1	2.9
More than 3 previous pregnancy losses and unknown traditional remedy for infertility	1	1.6				
More than 3 previous pregnancy losses, other major birth defect previous child and previous CHD child	1	1.6				
Severe vaginal bleeding requiring medications to prevent labour	4	6.3	2	5.9	3	8.6
Previous child with CHD, Down syndrome or any serious birth defect						
Previous CHD child	12	19.0	10	29.4	9	25.7
Two previous CHD children	1	1.6	1	2.9	1	2.9
Previous CHD and Down syndrome child			1	2.9		
Previous Down syndrome child with other major birth defect	1	1.6			1	2.9
Previous CHD and Down syndrome child with an other major birth defect	1	1.6				
Previous child with major birth defect	10	15.9	3	8.8	4	11.4
Total	63	100	34	100	35	100

If overt diabetes is excluded there was double the proportion of *serious* illness among control mothers than case mothers (8 (3%) cases versus 14 (6%) controls). Ten control mothers had thyroid disease compared with only four case mothers (table 5.12).

Table 5.11 Comparison of cases and controls on diabetes type and diabetes treatment

	Stratum	Cases N (%)		Controls N (%)	
Diabetes Type	Type I	7	17.1	1	3.2
	Type II	3	7.3	0	0.0
	Gestational	31	75.6	30	96.8
	Total	41	100.0	31	100.0
Diabetes treatment	Diet	25	67.6	26	86.7
	Tablets	1	2.7	0	0.0
	Insulin injections	11	19.7	4	13.3
	Total	37	100.0	30	100.0

Table 5.12 Comparison of significant illness in control and case mothers any previous pregnancy

Stratum	Cases N (%)		Controls N (%)	
Epilepsy	1	5.6	1	6.7
Hepatitis virus B	1	5.6	2	13.3
Thyroid disease	4	22.2	10	66.7
Thalessemia	1	5.6	1	6.7
Insulin Diabetes Type 1/2	10	55.6	1	6.7
Appendectomy week 4 gestation	1	5.6	0	0.0
Total	18	100.0	15	100.0

Fasting (table 5.1g)

Because of the unique opportunity to look at fasting and its relationship to pregnancy events, a number of questions were asked on this nearly universal Saudi Arabian practice (table 5.1g). Ramadan occurred within the three months prior to pregnancy and the three months post pregnancy for approximately 60 percent of mothers. However Ramadan fasting and other days of religious, non-Ramadan, fasting were not found to be associated with increased risk in the population of 235.

5.1g Fasting

Characteristic	Stratum	Cases N (%)		Controls N (%)		Crude odds ratio (95% CI)		Chi^2 (LR) p value
Ramadan fell within 3+/- window?	Occurred	151	64.3	149	60.3	1.8	0.8-1.7	0.40
	Did not occur	84	35.7	98	39.7	1.0		
	Total	235	100.0	247	100.0			
Ramadan fasting in window?	Yes	143	94.7	145	97.3	0.5	0.1-1.7	0.30
	No	8	5.3	4	2.7	1.0		
	Total	151	100.0	149	100.0			
Other fasting** days within 3+/- window?	Yes	146	62.1	146	59.3	1.2	0.8-1.7	0.40
	No	86	36.6	100	40.7	1.0		
	Total*	232	100.0	246	100.0			
Days fasting in window	Less than 1 week	77	32.8	85	34.4	1.0		0.50
	1 to 3 weeks	17	7.2	21	8.5	0.9	(0.4-1.8)	
	3 to 5 weeks	77	32.8	88	35.6	1.0	(0.6-1.5)	
	More than 5 weeks	64	27.2	53	21.5	1.3	(0.8-2.2)	
	Total	235	100.0	247	100.0			

*For details on missing see Table 5.13.
** Other religious, non-Ramadan, fasting

Environmental factors (table 5.1h)

Skin lightening creams (which may contain mercury), khol (traditional eyeliner which contains lead), nogd and saoot (traditional medicines which are inhaled) were not found to be associated with increased risk although hair colouring (chemical dyes, peroxide and henna) were (table 5.1h). Chemical hair dye use in the window was associated with a doubling of effect (OR=2.0, $CI_{95\%}$=1.2-3.3) as was peroxide use in the window (OR=2.1, $CI_{95\%}$=1.1-3.8) and henna use (OR=2.2, $CI_{95\%}$=1.4-3.3).

With respect to nogd, fifty-seven of the case mothers and 106 of the control mothers did not know what nogd was and therefore were not sure if they had been exposed or not. This was despite having a sample and having its use explained by the interviewer.

Maternal nausea was not found to be protective but mothers who suffered heartburn had increased risk. Being ill with influenza or having a cold during the six month window, or an illness that included a fever or medications in general were not found to be associated with CHD risk. Neither was being exposed to cigarettes within the six month window nor the consumption of caffeinated beverages. If the house was sprayed with pesticides or rodenticides within the window there was an increased risk. For pesticides sprayed in the house, an odds ratio of 3.3, ($CI_{95\%}$=2.1-5.3) was found. For rodenticides, the risk increased 8 fold (OR=8.4, $CI_{95\%}$=1.9-38.0). However, only two control families were exposed to rodenticides. Exposure to an extremely high ambient temperature at least once during the window period was not found to be associated with increased risk of CHD.

Socio-economic status characteristics (table 5.1i)

Variables were collected concerning various aspects of socioeconomic status characteristics as described in Section 3.14.2. Location of house was not found to be significant although income greater than 2500 SR monthly was significantly associated with CHD (table 5.1i). Income was calculated on the basis of reported income divided by the number of household members excluding servants. A higher proportion of the case mothers (31%) had bachelor's degrees or more versus 26 percent of the control mothers. Conversely, a higher proportion of the case mothers were illiterate (OR=3.0, $CI_{95\%}$=1.4-6.8). Paid employment was found more frequently in the case mothers (OR=2.2, $CI_{95\%}$=1.4-6.8). If someone besides her father was financially responsible for the mother when she was a child this provided a protective effect (OR = 0.5, $CI_{95\%}$=0.3-1.0, $p<0.03$).

5.1h Environmental risk factors

Characteristic	Stratum	Cases N (%)		Controls N (%)		Crude odds ratio (95% CI)		Chi^2 (LR) p value
Skin lightening creams?	Yes	32	13.9	40	16.4	0.8	(0.5-1.4)	0.50
	No	198	86.1	204	83.6	1.0		
	Total*	230	100.0	244	100.0			
Chemical hair dye use in window	Yes	54	23.1	32	13.0	2.0	(1.2-3.3)	< 0.001
	No	180	76.9	215	87.0	1.0		
	Total*	234	100.0	247	100.0			
Peroxide use in window	Yes	35	15.0	19	7.7	2.1	(1.1-3.8)	0.01
	No	199	85.0	228	92.3	1.0		
	Total*	234	100.0	247	100.0			
Henna use in window	Yes	79	33.8	47	19.0	2.2	(1.4-3.3)	< 0.001
	No	155	66.2	200	81.0	1.0		
	Total*	234	100.0	247	100.0			
Khol Bought from herbalist		11	4.6	14	5.6	1.3	(0.58-3.2)	0.50
Didn't use or commercially obtained		224	95.3	233	94.3	1.0		
Total		235	100.0	247	100.0			
Nogd	Yes	4	2.2	0	0	-		
	No	174	97.8	139	100.0			
	Total*	178	100.0	139	100.0			
Saoot	Yes	4	1.7	2	.8	2.2	(0.4-11.7)	0.78
	No	230	98.3	244	99.2	1.0		
	Total*	234	100.0	246	100.0			
Vitamin use in window	Yes	167	71.7	200	81.3	1.0		
	No	66	28.3	46	18.7	1.7	(1.1-2.6)	0.01
	Total*	233	100.0	246	100.0			
Folic acid use in window	Yes	135	57.9	135	56.3	1.0		0.71
	No	98	42.1	105	43.8	0.9	(0.6-1.3)	
	Total*	233	100.0	240	100.0			
Nausea	Yes	171	73.4	188	76.4	0.9	(0.6-1.3)	0.44
	No	62	26.6	58	23.6	1.0		
	Total*	233	100.0	246	100.0			
Heartburn	Yes	157	68.0	143	57.9	1.5	(1.1-2.2)	0.02
	No	74	32.0	104	42.1	1.0		
	Total*	231	100.0	247	100.0			
Illness during pregnancy with a influenza or cold?	Yes	97	42.4	96	39.7	1.1	(0.8-1.6)	0.60
	No	132	57.6	146	60.3	1.0		
	Total*	229	100.0	242	100.0			
Illness with fever	Yes	72	75.0	63	65.6	1.6	(0.8-2.9)	0.20
	No	24	25.0	33	34.4	1.0		
	Total*	96	100.0	96	100.0			
Medications	Yes	99	43.2	107	43.5	1.0	(0.7-1.4)	0.95
	No	130	56.8	139	56.5	1.0		
	Total*	229	100.0	246	100.0			
Passive cigarette smoke exposure	Yes	92	39.7	82	33.2	1.3	(0.9-1.9)	0.10
	No	140	60.3	165	66.8	1.0		
	Total*	232	100.0	247	100.0			
Consumption of caffeinated beverages in window	Yes	219	94.0	222	89.9	1.8	(0.9-3.5)	0.10
	No	14	6.0	25	10.1	1.0		
	Total*	233	100.0	247	100.0			
House sprayed with pesticide in window	Yes	78	34.3	33	13.6	3.3	(2.1-5.3)	< 0.001
	No	149	65.6	210	86.4	1.0		
	Total*	227	100.0	243	100.0			
House treated with rodenticides in window	Yes	15	6.4	2	.8	8.4	(1.9-38)	< 0.001
	No	218	93.6	245	99.2	1.0		
	Total*	233	100.0	247	100.0			
Hyperthermia in window	Yes	38	13.3	34	14.1	1.2	(0.8-2.0)	0.43
	No	190	83.3	208	85.9	1.0		
	Total*	228	100.0	242	100.0			

*For details on missing see table 5.13.

Mothers who lived in a city or a town for the first 12 years of their lives were not found to be significantly more at risk of having a baby with CHD than mothers who lived in the

5.1i Socioeconomic status characteristics

Characteristic	Stratum	Cases N (%)		Controls N (%)		Crude odds ratio (95% CI)		Chi^2 (LR) p value
Location of House	On a busy street	35	14.9	27	11.0	1.5	(0.9-2.5)	
	Near an industry	5	2.1	1	.4	5.7	(0.7-50.0)	
	In a residential area	186	79.1	213	86.9	1.0		0.06
	Rural **	9	3.8	4	1.6	2.6	(0.8-8.5)	
	Total*	235	100.0	245	100.0			
Household income/capita excluding servants /month	500 or less	32	15.4	28	12.6	1.8	(0.9-3.4)	
	501 to 1000 riyals	63	30.3	63	28.3	1.5	(0.1-0.9)	
	1001 to 1500 riyals	35	16.8	54	24.2	1.0		0.04
	1501 to 2499 riyals	44	21.2	59	26.5	1.2	(0.6-2.1)	
	2500 riyals or more	34	16.3	19	8.5	2.8	(1.3-5.7)	
	Total*	208	100.0	223	100.0			
Household (Collapsed) income/capita excl. servants /month	Poor	32	15.4	28	12.6	1.4	(0.8-2.5)	
	Middle	142	68.3	176	78.9	1.0		0.02
	Well off	34	16.3	19	8.5	2.2	(1.2-4.1)	
	Total*	208	100.0	223	100.0			
Mother's Education	No schooling at all	24	10.3	9	3.7	2.4	(1.0-5.5)	
	Literate, no schooling	6	2.6	7	2.8	0.8	(0.2-2.4)	
	Adult Literacy class	2	.9	3	1.2	0.6	(0.1-3.7)	
	Primary School	23	9.9	33	13.4	0.6	(0.3-1.2)	0.03
	Preparatory School	39	16.7	51	20.7	0.7	(0.4-1.2)	
	Secondary School	48	20.6	67	27.2	0.6	(0.4-1.1)	
	Diploma	20	8.6	13	5.3	1.4	(0.6-3.0)	
	University or more	71	30.5	63	25.6	1.0		
	Total*	233	100.0	246	100.0			
Mother's Education	None	24	10.3	9	3.7	3.0	(1.4-6.8)	< 0.001
	Some (includes adult)	209	89.7	237	96.3	1.0		
	Total*	233	100.0	246	100.0			
Has mother ever had paid employment?	Yes	63	27.0	35	14.2	2.2	(1.4-3.6)	< 0.001
	No	170	73.0	212	85.8	1.0		
	Total*	233	100.0	247	100.0			
Mother's Occupational Field	Education	56	88.9	31	88.6	1.0	(0.1-4.2)	0.78
	Business	2	3.2	2	5.7	0.6	(0.3-7.6)	
	Medical	5	7.9	2	5.7	1.4		
	Total	63	100.0	35	100.0			
Mother's early SES	Her father	218	93.6	217	87.9	1.0		
	Someone else	15	6.4	30	12.1	0.5	(0.3-1.0)	0.03
	Total*	233	100.0	247	100.0			
Mother's residence birth to 12	City/Town	165	70.2	190	77.2	1.4	(1.0-2.2)	0.08
	Village/Desert	70	29.8	56	22.8	1.0		
	Total*	235	100.0	246	100.0			
Mother's Father's Education (detailed)	No schooling at all	51	22.6	74	30.2	0.4	(0.2-0.9)	< 0.001
	No school, but literate	47	20.8	15	6.1	1.7	(0.6-4.5)	
	Literacy class	3	1.3	4	1.6	0.4	(0.1-2.2)	
	Primary	55	24.3	68	27.8	0.4	(0.2-1.0)	
	Preparatory	30	13.3	45	18.4	0.4	(0.1-0.9)	
	Secondary	18	8.0	24	9.8	0.4	(0.1-1.1)	
	Diploma	5	2.2	6	2.4	0.4	(0.1-1.9)	
	University	17	7.5	9	3.7	1.0		
	Total*	226	100.0	245	100.0			
Mother's Father's Education	None	90	38.6	83	33.6	1.2	(0.9-1.8)	0.30
	Some (includes adult)	143	61.4	164	66.4	1.0		
	Total*	233	100.0	247	100.0			

Characteristic	Stratum	Cases N	Cases %	Controls N	Controls %	Crude odds ratio	(95% CI)	Chi^2 (LR) p value
Mother's Father Employed	Yes	208	89.7	222	90.25	1.0		
	No	24	10.3	24	9.75	1.1	(0.6-1.9)	0.80
	Total*	232	100.0	246	100.0			
Mother's Father's Occupation	Military	41	20.8	107	48.9	0.3	(0.1-0.5)	< 0.001
	Education	9	4.6	8	3.7	0.8	(0.3-2.2)	
	Professional	40	20.3	27	12.3	1.0		
	Police/Security	5	2.5	2	.9	1.7	(0.3-9.5)	
	Manual Labour	29	14.7	25	11.4	0.8	(0.4-1.6)	
	Office Work	43	21.8	33	15.1	0.9	(0.5-1.7)	
	Tradesman	24	12.2	14	6.4	1.2	(0.3-2.6)	
	Semi-professional	6	3.0	3	1.4	1.3	(0.3-5.9)	
	Total*	197	100.0	219	100.0			
Mother's Father's Occupational Field	Military	46	23.4	109	49.8	0.3	(0.2-0.5)	< 0.001
	White Collar	98	49.7	71	32.4	1.0		
	Trade and Manual	53	26.9	39	17.8	0.9	(0.6-1.6)	
	Total*	197	100.0	219	100.0			
Father's Education (detailed)	No schooling at all	4	1.7	4	1.6	0.5	(0.1-2.3)	< 0.001
	No school, but literate	6	2.6	1	.4	3.2	(0.4-28.1)	
	Literacy class			1	.4	-		
	Primary	21	9.0	31	12.6	0.4	(0.2-0.7)	
	Preparatory	49	21.0	57	23.2	0.5	(0.3-0.8)	
	Secondary	61	26.2	102	41.5	0.3	(0.2-0.5)	
	Diploma	17	7.3	10	4.1	0.9	(0.4-2.2)	
	University	75	32.2	40	16.3	1.0		
	Total*	233	100.0	246	100.0			
Father's Education	None	9	3.9	4	1.6	2.4	(0.7-8.1)	0.13
	Some (includes adult)	224	96.1	243	98.4	1.0		
	Total	233	100.0	247	100.0			
Has father ever had paid employment?	Yes	229	98.7	247	100.0			
	No	3	1.3	0	0.0		-	
	Total*	232	100.0	247	100.0			
Father's Occupation (detailed)	Military	77	33.8	220	89.1	1.0		< 0.001
	Education	17	7.5	5	2.0	9.7	(3.3-28.5)	
	Professional	37	16.2	3	1.2	35.2	(9.1-136.6)	
	Police/Security	15	6.6	0	0.00	-		
	Manual Labour	10	4.4	0	0.00	-		
	Office Work	54	23.7	10	4.0	15.4	(6.8-34.9)	
	Tradesman	8	3.5	4	1.6	5.7	(1.6-19.9)	
	Semi-professional	10	4.4	5	2.0	5.7	(1.9-17.6)	
	Total*	228	100.0	247	100.0			
Father's Occupational Field	Military	77	33.8	220	89.1	1.0		
	White Collar	118	51.8	23	9.3	14.7	(7.9-27.1)	
	Manual	33	14.5	4	1.6	23.6	(7.2-76.9)	< 0.001
	Total*	228	100.0	247	100.0			

*For details on missing see table 5.13.
** Rural = in a village, in the desert or on a farm

village or desert. There was no difference between the cases and controls for mother's paternal education or mother's father's employment. Father's education was not significantly different for cases and controls, although an association with father's occupational field was found ($p<0.001$). A lower proportion of case fathers (34%) worked in the military compared to control fathers (89%). A higher proportion of case fathers

(52%) than control fathers (9%) held white collar positions (OR=14.7, CI $_{95\%}$=7.9-27.1). Those who were manual labours had increased odds (OR=23.6, CI $_{95\%}$=7.2-76.9).

Maternal beliefs of causes of CHD (table 5.1j)

At the completion of the interview session mothers were asked for their own beliefs of the causes of CHD. Case mothers were less likely to believe that consanguinity was a risk factor for CHD (OR = 0.3, CI $_{95\%}$=0.2-0.5). Case mothers were also less likely to think that exposure to environmental toxins was responsible for CHD (OR = 0.4, CI $_{95\%}$=0.3-0.7). However, feeling that exposure to video display terminals or feeling especially angry within the six month window of exposure was neither protective nor harmful.

5.1j Maternal beliefs of causes of CHD

Characteristic	Stratum	Cases N (%)		Controls N (%)		Crude odds ratio (95% CI)		Chi^2 (LR) p value
Exposure to video display terminals	Yes	71	34.6	66	41.5	0.7	(0.5-1.14)	0.18
	No	134	65.4	93	58.5	1.0		
	Total	205	100.0	159	100.0			
Consanguinity is risky?	Yes	86	36.9	104	65.8	0.3	(0.2-0.5)	< 0.001
	No	147	63.1	54	34.2	1.0		
	Total	233	100.0	158	100.0			
Feeling angry during the 6 month window?	Yes	76	36.9	51	20.6	1.2	(0.8-1.9)	0.36
	No	130	63.1	107	43.3	1.0		
	Total	206	100.0	158	64.0			
Exposure to environmental toxins?	Yes	104	44.8	103	64.8	0.4	(0.3-0.7)	< 0.001
	No	128	55.2	56	35.2	1.0		
	Total	232	100.0	159	100.0			

*For details on missing see table 5.13.
Notes: Where more than 1 stratum are present stratum specific Chi square have been presented (i.e., not the Wald statistics). The overall p value is a Chi square.

5.1.2 Multivariate analysis

Table 5.13 presents a summary of univariate results for all 83 characteristics studied in the preliminary analysis and the number of missing values. This table will be useful in discussing the selection of variables for the logistic regression.

Correlations

The data were first assessed for correlations between variables. These correlations were compared within the entire data set and not examined for differences between cases and controls. In Appendix 5C you will find selected variables which were found to be correlated to the level of $p< 0.05$ ($r > 0.2$). Also, you will find some variables which were assessed for correlation and were found not to be correlated. The results of the correlation examination were used in the next step of the analysis, where the 83 variables were reduced to a smaller number for use in the multivariate analysis.

Table 5.13 Summary table presenting 83 variables considered in preliminary analysis with All Sampled (n=235 cases and 247 controls) baseline p value, number of missing by case and control status and justification for multivariate decision selection of those 21 selected

	Variable	Baseline	Missing	Criteria(on) for selection
Consanguinity				
1	Consanguinity	NS	None	S1, S5
2	Detailed consanguinity	NS	None	N1, N2, N4
Infant Characteristics				
3	Infant's Sex	NS	None	N9
4	Infant's Age at Interview (days)	< 0.001	None	N1, N2, N3, N4
5	Infant's Birth weight (grams)	< 0.001	CASES = 28. CONTROLS = 7.	N3, N6
6	Infant's Gestational Age (weeks)	< 0.001	CASES =6. CONTROLS=2.	N3
7	Multiple gestations	< 0.001	None	S2, S3, S4, S5
Maternal Characteristics				
8	Maternal Nationality	NS	None	N9
9	Maternal Ethnicity	< 0.001	CASES = 1. CONTROLS = 1	S2
10	Maternal Age at Infant's Birth	< 0.001	CASES = 4. CONTROLS = 3.	S2, S4, S5
11	Maternal Age at First Birth	0.05	CASES = 4. CONTROLS = 3.	N2
12	Marital Status	NV	CASES = 2. CONTROLS = 0.	N9
13	Gravida	< 0.001	None	N1, N2
14	Parity	< 0.001	CASES = 3 (Pregnancy form not completed).	N1, N2
Paternal Characteristics				
15	Paternal Age at Infant's Birth	< 0.001	CASES =16. CONTROLS= 28.	S2, S4, S5*
16	Paternal Nationality	NS	CASES = 1. CONTROLS = 0.	N9
17	Paternal Ethnicity	< 0.001	CASES = 1. CONTROLS = 0.	N1
Index Pregnancy Characteristics				
18	ART	0.06	CASES s = 3. CONTROLS = 1.	S2, S5
19	Planned	0.02	CASES = 3. CONTROLS = 1.	S2, S5
20	Planning time	< 0.001	CASES = 6. CONTROLS = 3.	N1, N2, N4
21	Vaginal bleeding > 1 day	< 0.001	CASES = 3. CONTROLS = 0.	N2
22	Vaginal bleeding severity	0.01	CASES = 3. CONTROLS = 0.	N2
23	Non-CHD anomaly (mother)	< 0.001	CASES = 3. CONTROLS = 0.	N1, N5
24	Non-CHD anomaly (registry)	< 0.001	None	N1, N5
25	All non-CHD reported anomalies	< 0.001	None	S2
26	BMI at interview	NS	CASES = 18. CONTROLS = 4.	N9
27	BMI pre-pregnancy (estimated)	NS	CASES = 103.CONTROLS = 90.	N9
28	All Diabetes	0.20	None	N1
29	None, vs Gestational, vs Overt diabetes	0.01	CASES = 1. CONTROLS = 2.	S2, S4, S5
30	Major maternal health prob (index preg)	< 0.001	CASES = 3. CONTROLS = 0.	S2, S3, S4, S5
Previous Pregnancy				
31	Total pregnancy losses	< 0.001	CASES = 3. CONTROLS = 0.	S2, S3, S4, S5
32	Total neonatal losses	0.16	CASES = 3. CONTROLS = 0.	S2, S3, S4, S5
33	Total infant losses	NS	CASES = 3. CONTROLS = 0.	N9
34	Deceased children	0.25	CASES = 3. CONTROLS = 0.	N1, N2
35	Vaginal bleeding (previous preg)	< 0.001	CASES = 3. CONTROLS = 0.	N1, N2
36	Maternal health problem (previous)	0.01	CASES = 3. CONTROLS = 0.	N1, N2
37	Major illness	NS	CASES = 3. CONTROLS = 0.	N1, N2

	Variable	Baseline	Missing	Criteria(on) for selection
Fasting				
38	Holy month of Ramadan fell in +/- 6 month window	NS	None	N9
39	Ramadan fasting	NS	None	N9
40	Other religious, non-Ramadan, fasting	NS	CASES = 3. CONTROLS = 1.	N9
41	Total days fasting	NS	None	N9
Environmental				
42	Skin lightening cream	NS	CASES = 5. CONTROLS = 3.	N9
43	Chemical hair dyes	< 0.001	CASES = 1. CONTROLS = 0.	S2, S5
44	Peroxide	0.01	CASES = 1. CONTROLS = 0.	N1
45	Henna	< 0.001	CASES = 1. CONTROLS = 0.	N1
46	Khol	NS	None	N9
47	Nogd	NV	CASES 57, not sure. CONTROLS, 108, not sure,	N6, N7, N9
48	Saoot	NS	CASES = 1. CONTROLS = 1.	N9
49	Vitamin use	0.01	CASES = 2. CONTROLS = 1.	S2, S4, S5**
50	Folic acid use	NS	CASES = 2. CONTROLS = 7.	N9
51	Nausea	NS	CASES = 2. CONTROLS = 1.	N9
52	Heartburn	0.02	CASES = 4. CONTROLS = 0.	N3
53	Illness	NS	CASES = 6. CONTROLS = 3.	N9
54	Illness with fever	0.20	CASES = 1. CONTROLS = 0.	S2, S4
55	Medications	NS	CASES = 6. CONTROLS = 1.	N9
56	Passive cigarette smoke exposure	0.10	CASES = 3. CONTROLS = 0.	S2, S4, S5
57	Caffeine use	0.10	CASES = 2. CONTROLS = 0.	N1, N2
58	House sprayed with pesticides	< 0.001	CASES = 8. CONTROLS = 4.	S2, S4, S5
59	Rodenticide use	< 0.001	CASES = 2. CONTROLS = 0.	N7
60	Hyperthermia	NS	CASES = 7. CONTROLS = 3.	N9
Socio Economic Status Characteristics				
61	Location of House	0.06	CASES = 0. CONTROLS = 2.	N3
62	Income/capita excl servants /month	0.04	CASES: REFUSED=15; UNKNOWN=10. CONTROLS: 6 REFUSED=6; UNKNOWN=18.	N4, N6
63	Income/capita excl servants /month (collapsed)	0.02	Same as Q62	S3***
64	Mother's Education (detailed)	0.03	CASES = 2. CONTROLS = 1.	N2
65	Mother's Education	< 0.001	CASES = 2. CONTROLS = 1.	N1, N2
66	Has mother ever had paid employment?	< 0.001	CASES = 2. CONTROLS = 0.	N2
67	Mother's Occupational Field	NS	None	N2
68	Mother's Early SES	0.03	CASES = 2. CONTROLS = 0.	S2
69	Mother's residence birth to 12	0.08	CASES = 0. CONTROLS = 1.	N2
70	Mother's Father's Education (detailed)	< 0.001	CASES: 4, UNKNOWN; 5 NOT ASKED. CONTROLS: 2UNKNOWN.	N2
71	Mother's Father's Education	NS	CASES = 2. CONTROLS = 0.	N2
72	Mother's Father Employed	NS	CASES = 3. CONTROLS = 1.	N2
73	Mother's Father's Occupation (detailed)	< 0.001	Cases 11 UNKNOWN. Controls 3 UNKNOWN.	N2

	Variable	Baseline	Missing	Criteria(on) for selection
74	Mother's Father's Occupational Field	< 0.001	Cases 11 UNKNOWN. Controls 3 UNKNOWN.	S2, S3
75	Father's Education (detailed)	< 0.001	CASES = 2. CONTROLS = 1.	N2
76	Father's Education	0.13	CASES = 2. CONTROLS = 0.	N2
77	Has father ever had paid employment?	NV	CASES = 3. CONTROLS = 0.	N2
78	Father's Occupation (detailed)	< 0.001	CASES = 1. CONTROLS = 0.	N2
79	Father's Occupation Field	< 0.001	CASES = 1. CONTROLS = 0.	N2
Maternal beliefs of causes of CHD				
80	Exposure to video display terminals	0.18	CASES = 30.CONTROLS = 88.	N2
81	Consanguinity (Belief)	< 0.001	CASES = 2. CONTROLS = 89.	S2, S3
82	Feeling angry within the 6 month window	NS	CASES = 29.CONTROLS 89.	N9
83	Exposure to environmental toxins	< 0.001	CASES = 3. CONTROLS = 88.	N2, N3

* Also N1, N6 (Maternal age)
** Also N1 (Maternal Ethnicity)
*** Also N6
NS=Not significant (p > 0.25 see Table 5.1 a-j)
NV=No variation (one cell is 0)
NB Variables selected are highlighted in orange

Decisions for Selection	**Decisions for Non-Selection**
S1=Primary end-point as defined in Upgrading S2=Significant at < 0.25 S3=Best of category S4=Biologically plausible S5=Identified in the literature as associated	N1=Correlated with another variable to be used N2=Already chose one from group (the "best") N3=Descriptive, not causative N4=Too many categories, chose simplest N5=Chose more complete version N6=Great quantities of missing data N7=Small numbers N9=Not significant

Selection of variables for multiple logistic regression

Eighty-three variables were considered in the univariate analyses (table 5.1 a-j). These variables naturally fell into 10 categories: consanguinity, infant, maternal, paternal, index pregnancy, previous pregnancy, fasting, environmental, socio-economic status (SES) and maternal beliefs as presented above. Of the 83, 55 were significant at the level of 0.25. However, some of the variables were derived in the same manner or measured the same risk. Examples of these variables (from table 5.13) are summarized in table 5.14.

Other variables of the 83 were correlated, some had a large amount of missing data, others were related to one another (being in the same category). Table 5.13 lists the decision criteria(on) for selection or non-selection for each variable.

Table 5.14 Summary of those variables collected descriptively but which were derived from a principal variable or which estimated the same risk

Variable names	Number in table 5.13	Derived or Estimates same risk
Consanguinity	1	Derived
Consanguinity (detailed)	2	
Maternal age at infant's birth	10	Derived
Maternal age at first birth	11	
Parity and Gravida	13, 14	Estimates same risk
Planned and Planning time	19, 20	Derived
Vaginal bleeding (index)	21	Derived
Vaginal bleeding severity (index)	22	
Vaginal bleeding severity (dichtomous)	23	
Non-CHD anomaly	24, 25, 26	Estimates same risk
All Diabetes	29	Derived
None, versus Gestational, versus Overt diabetes	30	
Income / capital excl servants/month detailed	63	Derived
and collapsed	64	
Mother's education detailed and collapsed	65, 66	Derived
Mother's father's occupation detailed and	74	Derived
collapsed	75	
Father's education detailed and collapsed	76, 77	Derived
Father's occupation detailed and collapsed	79, 80	Derived

This process of variable selection reduced the variables under consideration from 83 to 22. These 21 variables (plus consanguinity) shaded in orange in table 5.13 were then considered for further analysis – the full model of the logistic regression.

5.1.3 Multivariate results

Full model

Following the technique of Hosmer and Lemeshow (1989) and Kirkwood and Stone (2003) all 22 variables as specified in table 5.13 were considered. One of the limitations of logistic regression is that the dataset must not contain any missing values. Therefore, the first model which included variables such as *paternal age at infant's birth* and *income per capita* only used 260 observations. With the exclusion of 5 variables (table 5.15) the dataset increased to 455 observations. These remaining 17 variables were tested as the

Table 5.15 Justification for exclusion of five variables from model

Variable name	Justification for exclusion
Father's age at infant's birth*	Missing data, correlated with Mother's age
Mother's father's occupational field	Missing data
Income per capita excluding servants per month	Missing data
Maternal belief that consanguinity causes CHD	Missing data, perhaps unreliable, what does it mean?
Maternal belief that exposure to environmental toxins causes CHD	

* Descriptive statistics for cases and controls were paternal age is missing are presented in Appendix 5D.

full model. The results (table 5.16, Full Model) showed that 6 of the 17 variables were statistically significantly associated with risk of CHD: *multiplicity*, *maternal ethnicity*, *ECM*, *total pregnancy losses*, *hair dyes* and *house sprayed with pesticides*.

Table 5.16 Summary table for adjusted odds ratio with 95% confidence intervals for all sampled

	Crude n=482	pvalue	Full Model n=455	pvalue	Forward Stepwise n=455	pvalue
Consanguinity : Yes	1.2 (0.8-1.7)	0.90	1.0 (0.7-1.7)	0.84		
Multipicity: **Twins +**	6.1 (1.3-27.8)	< 0.001	8.3 (1.3-54.4)	0.03	5.7 (1.1-29.6)	0.04
Maternal ethnicity: Bedouin	2.2 (1.5-3.3)	< 0.001	2.1 (1.2-3.5)	0.01	2.2 (1.4-3.7)	< 0.001
Maternal age at infant's birth 14-20	0.7 (0.4-1.4)	< 0.001	0.7 (0.3-1.6)	0.41	-	
21-28	-		-	-	-	
29-38	2.1 (1.4-3.2)		1.5 (0.9-2.5)	0.16	1.9 (1.2-3.1)	< 0.001
39+	4.0 (1.9-8.3)		2.4 (0.9-6.0)	0.07	3.1 (1.3-7.2)	< 0.001
IVF: Yes	3.3 (0.9-12.3)	0.06	0.7 (0.07-6.1)	0.73		
Planned: Yes	0.6 (0.4-0.9)	0.02	0.8 (0.5-1.3)	0.33		
ECM: Other problem	12.9 (4.8-34.8)	< 0.001	26.7 (10.1-70.6)	< 0.001	28.0 (10.7-72.9)	< 0.001
None and gestational versus overt diabetes**: Diabetes	9.9 (1.2-80.2)	0.01	5.5 (0.5-57.6)	0.16		
Major health concern during index pregnancy: Yes	2.3 (1.5-3.7)	< 0.001	0.9 (0.5-1.9)	0.83		
Total pregnancy losses** 2 or more	2.8 (1.5-5.4)	< 0.001	2.3 (1.1-5.2)	0.04		
Total neonatal losses 1 or more	1.6 (0.4-5.8)	0.55	0.6 (0.1-4.6)	0.66		
Chemical hair dyes: Yes	2.0 (1.2-3.3)	< 0.001	1.9 (1.1-3.5)	0.03	1.9 (1.1-3.4)	0.03
Vitamin use: Yes	1.7 (1.1-2.6)	0.01	1.1 (0.6-1.9)	0.68		
Illness with fever: Yes	1.6 (0.8-2.9)	0.20	1.0 (0.6-1.7)	0.98		
Passive cigarette smoke exposure: Yes	1.3 (0.9-1.9)	0.10	1.3 (0.8-2.1)	0.35		
House sprayed with pesticides: Yes	3.3 (2.1-5.3)	< 0.001	3.6 (2.1-6.3)	< 0.001	3.8 (2.3-6.5)	< 0.001
Mother's Early SES: Someone besides father responsible	0.05 (0.3-1.0)	0.03	0.5 (0.2-1.2)	0.12		

** Crude odds ratio re-calculated based on two categories

Stepwise procedure

Following the full model, a forward stepwise procedure was performed which again indicated 6 significant variables. In this model, *total pregnancy losses* was replaced with *maternal age* (table 5.16, Forward Stepwise).

Adjustment

The six variables identified through the forward stepwise procedure were used to adjust all 17 variables that had been included in the full model using the likelihood ratio test as the measure of improvement to the model (table 5.17). Ten additional variables of specific interest that were significant in the crude analysis were also examined. Once the data were adjusted, parity was no longer a significant risk factor (p=0.41). However, paternal age at infant's birth remained significant (p=0.01). *ART use* lost significance possibly because it was only borderline (p=0.06) in crude analysis and with the reduction

Table 5.17 Comparison of crude and adjusted odds ratios from analysis of all sampled n=455

Characteristic	Stratum	Cases N (%)		Controls N (%)		Crude OR (95% CI)		Adjusted OR (95% CI)	p value
Consanguinity	Yes	112	50.7	117	50.0	1.0 (0.7-1.5)		1.0 (0.7-1.6)	0.87
	No	109	49.3	117	50.0	1.0			
	Total	221	100.0	234	100.0				
First cousin or closer		52	23.5	59	25.2	0.9 (0.6-1.5)		1.1 (0.6-2.4)	0.42
All other (lesser) first cousins		36	16.3	30	12.8	1.3 (0.7-2.2)		0.6 (0.2-1.3)	
All second and third cousins		24	10.9	28	12.0	0.9 (0.5-1.7)		0.9 (0.5-1.6)	
Non-consanguineous		109	49.3	117	50.0	1.0			
Total		221	100.0	234	100.0				
Remaining Infant, Maternal and Paternal Characteristics									
Multiplicity	Singleton	210	95.0	232	99.1	1.0		1.0	0.02
	Twins or higher	11	5.0	2	.9	6.1	(1.3-27.7)	5.8 (1.1-29.9)	
	Total	221	100.0	234	100.0				
Mother's Ethnicity	Bedouin Ethnicity	82	37.1	51	21.8	2.1	(1.4-3.2)	2.2 (1.4-3.6)	< 0.001
	Urban Ethnicity	139	62.9	183	78.2	1.0		1.0	
	Total	221	100.0	234	100.0				
Mother's Age at Infant's Birth (years)	14-20	17	7.7	35	15.0	0.8	(0.4-1.4)	0.8 (0.4-1.7)	0.01
	21-28	75	33.9	116	49.6	1.0			
	29-38	97	43.9	71	30.3	2.1	(1.4-3.2)	1.8 (1.1-3.0)	
	39+	32	14.5	12	5.1	4.1	(2.0-8.6)	3.0 (1.3-6.9)	
	Total	221	100.0	234	100.0				
Parity	1 birth	43	19.5	80	34.2	1.0			0.41
	2-5 births	133	60.2	121	51.7	2.0	(1.3-3.2)	1.3 (0.7-2.4)	
	6 or more births	45	20.4	33	14.1	2.5	(1.4-4.5)	0.9 (0.3-2.3)	
	Total	221	100.0	234	100.0				
Father's Age at Infant's Birth (years)	19-24	15	7.1	14	6.6	1.7	(0.8-3.7)	3.7 (1.4-9.6)	0.01
	25-34	78	37.1	122	57.5	1.0			
	35-44	87	41.4	58	27.4	2.3	(1.5-3.6)	1.5 (0.8-3.0)	
	45+	30	14.3	18	8.5	2.6	(1.4-5.0)	0.7 (0.2-2.0)	
	Total	210	100.0	212	100.0				
Index Pregnancy Characteristics									
Did this pregnancy use ART?	Yes	8	3.6	3	1.3	2.9	(0.8-11.0)	1.0 (0.1-7.4)	0.99
	No	213	96.4	231	98.7	1.0			
	Total	221	100.0	234	100.0				
Was this pregnancy planned?	Yes	100	45.2	79	33.8	1.0			
	No	121	54.8	155	66.2	0.6	(0.4-0.9)	0.7 (0.5-1.2)	0.19
	Total	221	100.0	234	100.0				
Vaginal bleeding more than 1 day	Yes	24	10.9	9	3.8	3.0	(1.4-6.7)	2.5 (1.0-6.3)	0.06
	No	197	89.1	225	96.2	1.0			
	Total	221	100.0	234	100.0				
ECM	None	140	63.3	229	97.9	1.0			
	Other problem	81	36.7	5	2.1	26.5	(10.5-67.0)	28.1 (10.8-73.4)	< 0.001
	Total	221	100.0	234	100.0				
Diabetes	None or gest diabetes	212	95.9	233	99.6				0.12
	Overt	9	4.1	1	.4	9.9	(1.2-80.1)	5.1 (0.1-50.8)	
	Total	221	100.0	234	100.0				
Major maternal health problem (index preg)	Yes	55	24.9	33	14.1	2.0	(1.3-3.3)	1.1 (0.6-2.1)	0.72
	No	166	75.1	201	85.9	1.0			
	Total	221	100.0	234	100.0				
Previous Pregnancy Characteristics									
Pregnancy losses	1 or fewer losses	185	83.7	219	93.6	1.0		1.0	
	2 or more losses	36	16.3	15	6.4	2.8	(1.5-5.4)	2.0 (0.9-4.2)	0.07
	Total	221	100.0	234	100.0				
Total neonatal deaths (<30 days)	None	218	98.6	231	98.7	1.0			0.84
	1+ neonatal deaths	3	1.4	3	1.3	1.1	(0.2-5.3)	0.8 (0.1-4.7)	
	Total	221	100.0	234	100.0				

Characteristic	Stratum	Cases N (%)		Controls N (%)		Crude OR (95% CI)		Adjusted OR (95% CI)	p value
Environmental Risk Factors									
Chemical hair dye use in window	Yes	49	22.2	32	13.7	1.8	(1.1-2.9)	1.9 (1.1-3.5)	0.03
	No	172	77.8	202	86.3	1.0			
	Total	221	100.0	234	100.0				
Peroxide use in window	Yes	33	14.9	19	8.1	2.0	(1.1-3.6)	1.4 (0.7-3.0)	0.26
	No	188	85.1	215	91.9	1.0			
	Total	221	100.0	234	100.0				
Henna use in window	Yes	76	34.4	47	20.1	2.1	(1.4-3.2)	1.4 (0.8-2.4)	0.19
	No	145	65.6	187	79.9	1.0			
	Total	221	100.0	234	100.0				
Vitamin use in window	Yes	157	71.0	188	80.3	1.0			
	No	64	29.0	46	19.7	1.7	(1.1-2.6)	1.1 (0.7-2.0)	0.63
	Total	221	100.0	234	100.0				
Heartburn	Yes	149	68.0	134	57.3	1.6	(1.1-2.3)	1.7 (1.1-2.8)	0.02
	No	70	32.0	100	42.7	1.0			
	Total	219	100.0	234	100.0				
Illness with fever	Yes	70	31.7	61	26.1	1.3	(0.9-2.0)	1.1 (0.6-1.8)	0.80
	No	151	68.3	173	73.9	1.0			
	Total	221	100.0	234	100.0				
Passive cigarette exposure	Yes	88	39.8	76	32.5	1.4	(0.9-2.0)	1.3 (0.8-2.1)	0.28
	No	133	60.2	158	67.5	1.0			
	Total*	221	100.0	234	100.0				
Consumption of caffeinated beverages in window	Yes	207	93.7	212	90.6	1.5	(0.8-3.1)	1.9 (0.8-4.6)	0.16
	No	14	6.3	22	9.4	1.0			
	Total*	221	100.0	234	100.0				
House sprayed with pesticide in window	Yes	77	34.8	33	14.1	3.3	(2.1-5.2)	3.8 (2.3-6.5)	< 0.001
	No	144	65.2	201	85.9				
	Total*	221	100.0	234	100.0				
Socioeconomic Status Characteristics									
Household income/capita excl. servants /month	Poor	30	15.0	23	10.9	1.6	(0.9-2.9)	0.9 (0.4-2.0)	0.10
	Middle	136	68.0	169	80.1	1.0		1.0	
	Well off	34	17.0	19	9.0	2.2	(1.2-4.1)	2.2 (1.1-4.5)	
	Total	200	100.0	211	100.0				
Mother's education	None	29	13.1	13	5.6	2.6	(1.3-5.1)	3.0 (1.3-6.7)	0.01
	Some	192	86.9	221	94.4	1.0			
	Total	221	100.0	234	100.0				
Has mother ever had paid employment?	Yes	60	27.1	33	14.1	2.3	(1.4-3.6)	0.7 (0.4-1.2)	0.17
	No	161	72.9	201	85.9	1.0			
	Total	221	100.0	234	100.0				
Mother's early SES	Her father	206	93.2	206	88.0	1.0			
	Someone else	15	6.8	28	12.0	0.5	(0.3-1.0)	0.5 (0.2-1.1)	0.07
	Total	221	100.0	234	100.0				
Mother's father's occupational field	Military	44	23.7	106	51.2	0.3	(0.2-0.5)	0.4 (0.2-0.7)	< 0.001
	White Collar	93	50.0	66	31.9	1.0			
	Trade and Manual	49	26.3	35	16.9	1.0	(0.6-1.7)	0.7 (0.4-1.4)	
	Total	186	100.0	207	100.0				

- Adjusted for multiplicity, maternal ethnicity, ECM, maternal age, maternal use of hair dye and house sprayed with pesticides. Where one of the 6 adjusting variables is being tested then that variable is NOT included in the model.
- p-value is from likelihood ratio test comparing the fit of the reduced model (as described above) plus v_t (7 variables) with the fit of the reduced model alone (6 variables). Or, in the case where one of the variables is an adjusting variable then it is comparing 6 variables to 5 variables.
- v_t = Variable to be tested (or confirmed) as not being relevant to model.

of the dataset from 482 to 455 there was a loss of power. Similarly, *planned pregnancy* was no long significant. *Vaginal bleeding for more than one day* did not add to the model although it had borderline significance (p=0.06). The result for *ECM* after adjustment is strong albeit with a wide 95 percent confidence interval (adj. OR = 28.1, $CI_{95\%}$=10.8-73.4).

Diabetes was not shown as a significant risk factor nor was a *major maternal health problem with the index pregnancy*. After adjustment, *pregnancy losses* did not contribute to the model nor did *total neonatal deaths*. *Chemical hair dye use* in the window contributed and this probably explains the reduced influence of *peroxide* and *henna*. *Vitamin use* in the window was no longer significant. *Heartburn* continued to be significant. *Illness with fever, passive cigarette smoke exposure* and *consumption of caffeinated beverages* no longer contributed to the model. However, the *house being sprayed with pesticides* was a significant adjustor. The last category of interest were SES variables. *Mother's education* and *mother's father's occupation* continued to be significant despite controlling for *maternal ethnicity*.

Given these results, the next step was to remove the cases with ECM to look at cardiac only cases.

5.2 Analysis of cases without ECM, cardiac only

5.2.1 Univariate results: description of cases and controls

There were 151 cases and 242 controls without a known ECM. Univariate statistics are presented on those cardiac only cases in table 5.18 a-i.

Consanguinity (table 5.18a)

There continued to be more cases than controls who were from consanguineous unions in this analysis (56% versus 49%) however the difference remains statically non-statistically significant although the p value dropped beneath a 0.25 threshold recommended by Hosmer and Lemeshow (1998) for inclusion in the logistic regression (table 5.18a). When stratified by category we see that both the closest and the least close categories continued to be virtually the same in cases and controls (27% versus 25% and 12% versus 12%, respectively). However in the "All other (lesser) first cousins" the proportion of cases is larger than for the controls (17% versus 12%).

Table 5.18(a-i) Characteristics for cardiac only cases and controls n=393

5.18a Consanguinity

Characteristic	Stratum	Cases N (%)		Controls N (%)		Crude odds ratio (95% CI)		Chi^2 (LR) p value
Consanguinity	Yes	84	55.6	119	49.2	1.3	(0.9-2.0)	0.20
	No	67	44.4	123	50.8	1.0		
	Total	151	100.0	242	100.0			
First Cousin or closer		40	26.5	60	24.8	1.2	(0.7-2.0)	0.49
All other (lesser) First Cousins		26	17.2	30	12.4	1.6	(0.9-2.9)	
All Second and Third Cousins		18	11.9	29	12.0	1.1	(0.6-2.2)	
Non-Consanguineous		67	44.4	123	50.8	1.0		
Total		151	100.0	242	100.0			

Infant characteristics (table 5.18b)

There was no difference from the all cases analysis for *infant's sex*, *age at interview*, *birth weight* or *gestational age* (5.18b). In the cardiac only analysis *infant's age at interview* was collapsed from six to two categories and it remained significant ($p<0.001$). *Multiplicity* continued to be significant with a wide confidence interval.

5.18b Infant characteristics

Characteristic	Stratum	Cases N (%)		Controls N (%)		Crude odds ratio (95% CI)		Chi^2 (LR) p value
Infant's Sex	Male	76	50.3	120	49.6	1.0	(0.7-1.5)	0.88
	Female	75	49.7	122	50.4	1.0		
	Total	151	100.0	242	100.0			
Infant's age at interview	15 days to 3 months	39	25.8	29	12.0	1.0		< 0.001
	3 to 6 months	25	16.6	72	29.8	0.3	(0.1-0.5)	
	6 months to 1 year	27	17.9	90	37.2	0.2	(0.1-0.4)	
	1 to 1.5 years	29	19.2	30	12.4	0.7	(0.4-1.5)	
	1.5 to 2 years	14	9.3	18	7.4	0.6	(0.2-1.4)	
	More than 2 years	17	11.3	3	1.2	4.2	(1.1-16.5)	
	Total	151	100.0	242	100.0			
Infant's age at interview (collapsed)	One year or less	91	60.3	191	78.9	1.0		
	More than 1 to 4 years	60	39.7	51	21.1	2.5	(1.6-3.9)	< 0.001
	Total	151	100.0	242	100.0			
Infant's Birth weight	< 1500 grams	6	4.0	0	0.0	-		< 0.001
	1500-2499 grams	29	19.2	21	8.7	3.3	(1.7-6.2)	
	2500-3499 grams	69	45.7	163	67.4	1.0		
	3500-3999 grams	21	13.9	42	17.4	1.2	(0.7-2.1)	
	> 4000 grams	6	4.0	9	3.7	1.6	(0.5-4.6)	
	Total	131	86.8	235	97.1			
Gestational Age	31 or less weeks	6	4.1	1	.4	11.7	(1.3-101.5)	< 0.001
	32 to 36 weeks	24	16.4	12	5.0	3.9	(1.9-8.2)	
	37 or more weeks	116	79.5	227	94.6	1.0		
	Total	146	100.0	240	100.0			
Multiplicity	Singleton	144	95.4	240	99.2	1.0		0.01
	Twins or higher	7	4.6	2	.8	5.8	(1.2-28.9)	
	Total	151	100.0	242	100.0			

Maternal characteristics (table 5.18c)

Since nearly all participants were Saudi, *maternal nationality* was dropped. *Maternal ethnicity* remained elevated (table 5.18c). The association with *maternal age at infant's birth* decreased slightly which may be related to power and the removal of the Down syndrome infants. To increase power, *maternal age* was collapsed from four categories to three. The results for *gravida* and *parity* remain the same.

5.18c Maternal characteristics

Characteristic	Stratum	Cases N (%)		Controls N (%)		Crude odds ratio (95% CI)		Chi^2 (LR) p value
Mother's Ethnicity	Bedouin Ethnicity	60	40.0	52	21.6	2.4	(1.5-3.8)	< 0.001
	Urban Ethnicity	90	60.0	189	78.4	1.0		
	Total	150	100.0	241	100.0			
Mother's age at infant's birth (years) 3 Groups	14-20	12	7.9	34	14.3	0.7	(0.4-1.5)	< 0.001
	21-28	57	37.7	118	49.8	1.0		
	29+	80	53.0	85	35.9	1.9	(1.3-3.0)	
	Total	149	98.7	235	100.0			
Gravida	1 pregnancy	24	15.9	69	28.5	1.0		0.01
	2-5 pregnancies	78	51.7	124	51.2	1.8	(1.0-3.1)	
	6-8 pregnancies	38	25.2	36	14.9	3.0	(1.5-6.0)	
	9 or more pregnancies	11	7.3	13	5.4	2.4	(0.9-6.3)	
	Total	151	100.0	242	100.0			
Parity	1 birth	77	51.7	158	65.3	1.0		0.02
	2-5 births	49	32.9	56	23.1	1.7	(1.0-2.8)	
	6 or more births	23	15.4	28	11.6	2.3	(1.2-4.3)	
	Total	149	100.0	242	100.0			

Paternal characteristics (table 5.18d)

Paternal's nationality was dropped because nearly all participants were Saudi. *Paternal age* remained significant although a higher proportion of the most elderly fathers were dropped when the *ECM* infants were excluded (table 5.18d). The proportion of fathers over 45 years in the all cases analysis was 15 percent versus 11 percent in the Cardiac, only analysis (data not shown). To increase power, paternal age was collapsed from four categories to three. Similar results for *paternal ethnicity* were seen to the all case analysis.

5.18 d Paternal characteristics

Characteristic	Stratum	Cases N (%)		Controls N (%)		Crude odds ratio (95% CI)		Chi^2 (LR) p value
Father's age at infant's birth (years) 3 Categories	19-24	14	9.8	14	6.5	2.3	(1.0-5.3)	< 0.001
	25-34	53	37.1	124	57.7	1.0		
	35+	76	53.1	77	35.8	2.3	(1.5-3.7)	
	Total	143	100.0	215	100.0			
Father's Ethnicity	Bedouin Ethnicity	63	42.0	57	23.6	2.4	(1.5-3.7)	< 0.001
	Urban Ethnicity	87	58.0	185	76.4	1.0		
	Total	150	100.0	242	100.0			

The influence of *ART* dropped by one half in the CARDIAC ONLY analysis and was no longer significant at the level of 0.25 (table 5.18e). *Planning the pregnancy* is also no longer protective with this reduced dataset although *12 months or more of trying* continues to be significantly associated with increased risk.

5.18e Index pregnancy characteristics

Characteristic	Stratum	Cases N (%)		Controls N (%)		Crude odds ratio (95% CI)		Chi^2 (LR) p value
Did this pregnancy use ART?	Yes	3	2.0	3	1.2	1.6	(0.3-8.2)	0.40
	No	146	98.0	239	98.8	1.0		
	Total	149	100.0	242	100.0			
Was this pregnancy planned?	Yes	58	38.9	79	32.6	0.8	(0.5-1.1)	0.21
	No	91	61.1	163	67.4	1.0		
	Total	149	100.0	242	100.0			
How many weeks did it take to become pregnant?*	Less than 3 months	13	23.6	27	35.5	1.0		0.01
	3 to 6 months	6	10.9	22	28.9	0.6	(0.2-1.8)	
	7 to 12 months	8	14.5	6	7.9	2.8	(0.8-10.1)	
	12 months +	28	50.9	21	27.6	2.8	(1.1-6.8)	
	Total	55	100.0	76	100.0			
Severity of vaginal bleeding	None	134	89.9	232	95.9	1.0		< 0.001
	Mild/Moderate	11	7.4	7	2.9	2.7	(1.0-7.2)	
	Severe	4	2.7	3	1.2	2.3	(0.5-10.5)	
	Total	149	100.0	232	100.0			
Severity of vaginal bleeding	None to Mild	134	89.9	232	95.9	1.0		
	Moderate to Severe	15	10.1	10	4.1	2.6	(1.1-5.9)	0.02
	Total	149	100.0	242	100.0			
Estimate of Mother's BMI pre-pregnancy	Underweight (<18.5)	1	1.2	5	3.2	0.3	(0.0-3.1)	0.24
	Normal (18.5 – 24.9)	28	34.6	47	30.5	1.0		
	Overweight (25.0-29)	33	40.7	50	32.5	1.1	(0.6-2.1)	
	Obese (30+)	19	23.5	52	33.8	0.6	(0.3-1.2)	
	Total	81	100.0	154	100.0			
Diabetes	None or gest diabetes	146	96.7	239	99.6	1.0		
	Overt diabetes	5	3.3	1	0.4	8.2	(0.9-70.1)	0.02
	Total	151	100.0	240	100.0			
Major maternal health problem	Yes	35	23.5	33	13.6	1.9	(1.1-3.3)	0.01
	No	114	76.5	209	86.4	1.0		
	Total	149	100.0	242	100.0			

In order to increase power, the variable *severity of vaginal bleeding* was collapsed into two categories. "Moderate to severe vaginal bleeding" had enough power to show significance. The estimate of mother's BMI pre-pregnancy was not significant. Overt diabetes continued to be significant (p=0.02) although the odds ratio crossed one and the confidence interval remained wide (8.2, $CI_{95\%}$ = 0.9-70.1). *Major maternal health problem* with index pregnancy continued to be significant (1.9, $CI_{95\%}$ = 1.1-3.3).

Previous pregnancy characteristics (table 5.18f)

Total number of pregnancy losses was collapsed from 4 categories to 3 and "2 or more losses" was significant (table 5.18f). With the reduction of numbers the *total number of*

pregnancies with vaginal bleeding lasting more than 1 day was no longer significant but *pregnancies with a maternal health problem* continued to be so (3.8, $CI_{95\%}$ = 1.3-11.1).

5.18f Previous pregnancy characteristics

Characteristic	Stratum	Cases N (%)		Controls N (%)		Crude odds ratio (95% CI)		Chi^2 (LR) p value
Total pregnancy losses	No losses	108	72.5	190	78.5	1.0		0.01
	1 loss	18	12.1	37	15.3	0.9	(0.5-1.6)	
	2 or more losses	23	15.2	15	6.2	2.7	(1.3-5.4)	
	Total	149	100.0	242	100.0			
Total neonatal deaths (<30 days)	No neonatal deaths	145	97.3	239	98.8	1.0		0.31
	1+ neonatal deaths	4	2.7	3	1.2	2.2	(0.5-10.0)	
	Total	149	100.0	242	100.0			
Total infant deaths (31 to 365 days)	No infant deaths	144	96.6	238	98.3	1.0		0.29
	1 or more deaths	5	3.4	4	1.7	2.1	(0.5-7.8)	
	Total	149	100.0	242	100.0			
Total deceased children	No deaths	137	91.9	231	95.5	1.0		0.20
	1 or more deaths	12	8.1	11	4.5	1.8	(0.8-4.3)	
	Total	149	100.0	242	100.0			
Pregnancies w/ vaginal bleeding > 1 day	Bleeding in at most 1	143	96.0	239	98.8	1.0		0.08
	Bleeding in 2 or more	6	4.0	3	1.2	3.3	(0.8-13.7)	
	Total	149	100.0	242	100.0			
Pregnancies with maternal health problem	None to 2 pregnancies	138	92.6	237	97.9	1.0		0.01
	At least 3 pregnancies	11	7.4	5	2.1	3.8	(1.3-11.1)	
	Total	149	100.0	242	100.0			
Total pregnancies while mother suffered from a major illness	None	138	96.0	227	93.8	1.0		0.49
	1 pregnancy	2	1.3	9	3.7	0.4	(0.7-1.7)	
	2 pregnancies	2	1.3	2	.8	1.6	(0.2-11.4)	
	3 pregnancies	2	1.3	4	1.7	0.8	(0.1-4.4)	
	Total	149	100.0	242	100.0			

Fasting (table 5.18g)

Other religious, non-Ramadan, fasting within the 3+/- window drops under the 0.25 threshold for consideration in the logistic regression therefore will be included (table 5.18g). The proportion increased from 62 percent versus 59 percent (all cases) to a proportion of 66 percent versus 59 percent (cardiac only).

Environmental factors (table 5.18h)

Skin lightening creams and *kohl* were not associated with CHD (table 5.18h). *Nogd* and *saoot* were dropped from this sub-analysis of CARDIAC ONLY as the numbers were so low. The odds ratio of *chemical hair dye use* increased slightly compared with the all cases analysis with a commensurate increase in width of confidence limit (2.4, $CI_{95\%}$ = 1.3-3.7). *Vitamin use* within the window remained the same without the ECM infants. Lack of *folic acid* still continued not to predict case / control status. *Nausea, illness, fever* and *medication use* were non-significant.

5.18g Fasting Concerns

Characteristic	Stratum	Cases N (%)		Controls N (%)		Crude odds ratio (95% CI)		Chi^2 (LR) p value
Ramadan fell within 3+/- window?	Occurred	95	62.9	148	61.2	1.1	(0.7-1.6)	0.70
	Did not occur	56	37.1	94	38.8	1.0		
	Total	151	100.0	242	100.0			
Ramadan fasting in window?	Yes	92	96.8	144	97.3	0.9	(0.19-3.9)	0.83
	No	3	3.2	4	2.7	1.0		
	Total	95	100.0	148	100.0			
Other fasting* days within 3+/- window?	Yes	98	66.2	143	59.3	1.3	(0.9-2.1)	0.17
	No	50	33.8	98	40.7	1.0		
	Total	148	100.0	241	100.0			
Days fasting in window	Up to five weeks	110	72.8	189	78.1	1.0		
	More than five weeks	41	27.2	53	21.9	1.3	(0.8-2.1)	0.24
	Total	151	100.0	242	100.0			

*Other religious, non-Ramadan, fasting

Exposure to cigarette smoke had borderline significance and will thus be considered in the logistic model. Consumption of caffeinated beverages decreased in importance. *House sprayed with pesticides* and *rodenticides* continued to be associated with CHD although the confidence limit for *rodenticides* becomes very wide (17.2, $CI_{95\%}$ = 2.1-141.2). *Hyperthermia* is not associated with increased risk of CHD in this sample.

Socio-economic status characteristics (table 5.18i)

The results concerning *location of the house*, *household income* and *maternal education* remained consistent with the all case analysis as did mother's employment. The proxy variable for her early socio-economic status *mother's early SES* became less significant although her place of *residence to age 12* remained the same. *Mother's father's occupational field* remained significant.

5.18h Environmental issues

Characteristic	Stratum	Cases N (%)		Controls N (%)		Crude odds ratio (95% CI)		Chi^2 (LR) p value
Skin lightening creams?	Yes	20	13.7	39	16.3	0.8	(0.5-1.5)	0.49
	No	126	86.3	200	83.7	1.0		
	Total	146	100.0	239	100.0			
Chemical hair dye use in window	Yes	36	24.0	31	12.8	2.4	(1.3-3.7)	< 0.001
	No	114	76.0	211	87.2	1.0		
	Total	150	100.0	242	100.0			
Peroxide use in window	Yes	23	15.3	18	7.4	2.3	(1.2-4.4)	0.02
	No	127	84.7	224	92.6	1.0		
	Total	150	100.0	242	100.0			
Henna use in window	Yes	45	30.0	46	19.0	1.8	(1.1-2.9)	0.01
	No	105	70.0	196	81.0	1.0		
	Total	150	100.0	242	100.0			
Khol Bought from herbalist		8	5.3	13	5.4	1.4	(0.5-3.8)	0.49
Didn't use or commercially obtained		143	94.7	229	94.6	1.0		
Total		151	100.0	242	100.0			
Vitamin use within window	Yes	107	71.8	196	81.3	1.0		0.03
	No	42	28.2	45	18.7	1.7	(1.1-2.8)	
	Total	149	100.0	241	100.0			
Folic Acid use within window	Yes	91	60.7	133	56.6	1.0		
	No	59	39.3	102	43.4	0.8	(0.6-1.3)	0.42
	Total	150	100.0	235	100.0			
Nausea	Yes	107	71.8	184	76.3	0.8	(0.5-1.3)	0.32
	No	42	28.2	57	23.7	1.0		
	Total	149	100.0	241	100.0			
Illness during pregnancy with influenza or cold?	Yes	61	41.5	93	39.2	1.1	(0.7-1.7)	0.66
	No	86	58.5	144	60.8	1.0		
	Total	147	100.0	237	100.0			
Illness with fever	Yes	43	28.5	60	24.8	1.2	(0.8-1.9)	0.42
	No	108	71.5	182	75.2	1.0		
	Total	151	100.0	242	100.0			
Medications	Yes	68	46.3	105	43.6	1.1	(0.7-1.7)	0.61
	No	79	53.7	136	56.4	1.0		
	Total	147	100.0	241	100.0			
Passive cigarette smoke exposure	Yes	63	42.3	80	33.1	1.4	(1.0-2.3)	0.07
	No	86	57.7	162	66.9	1.0		
	Total	149	100.0	242	100.0			
Consumption of caffeinated beverages during the window	Yes	144	96.0	217	89.7	1.6	(0.2-11.6)	0.23
	No	6	4.0	25	10.3	1.0		
	Total	150	100.0	242	100.0			
House sprayed with pesticide during the window period	Yes	52	36.1	33	13.9	3.5	(2.1-5.9)	< 0.001
	No	92	63.9	205	86.1	1.0		
	Total	144	100.0	238	100.0			
House treated with rodenticides during the window period	Yes	10	6.7	1	.4	17.2	(2.1-141.2)	< 0.001
	No	140	93.3	241	99.6	1.0		
	Total	150	100.0	242	100.0			
Hyperthermia during the window period.	Yes	26	17.7	33	13.9	1.3	(0.8-2.3)	0.32
	No	121	82.3	204	86.1	1.0		
	Total	147	100.0	237	100.0			

5.18i Socioeconomic Status Characteristics

Characteristic	Stratum	Cases N (%)		Controls N (%)		Crude odds ratio (95% CI)		Chi^2 (LR) p value
Location of House	On a busy street	21	13.9	26	10.8	1.4	(0.8-2.6)	0.05
	Near an industry	4	2.6	1	.4	7.0	(0.8-64.7)	
	In a residential area	119	78.8	209	87.1	1.0		
	Rural **	7	4.6	4	1.7	3.1	(0.9-10.1)	
	Total	151	100.0	240	100.0			
Household income/capita excluding servants /month	Poor	22	16.8	26	11.9	1.7	(0.9-3.1)	0.05
	Middle	89	67.9	174	79.5	1.0		
	Well off	20	15.3	19	8.7	2.1	(1.0-4.1)	
	Total	131	100.0	219	100.0			
Mother's Education	None	23	15.3	15	6.2	2.7	(1.4-5.4)	< 0.001
	Some (includes adult)	127	84.7	227	93.8	1.0		
	Total	150	100.0	242	100.0			
Has mother ever had paid employment?	Yes	41	27.3	33	13.6	2.4	(1.4-4.0)	< 0.001
	No	109	72.7	209	86.4	1.0		
	Total	150	100.0	242	100.0			
Mother's Early SES	Her father responsible	139	92.7	212	87.6	1.0		
	Someone else	11	7.3	30	12.4	0.6	(0.3-1.2)	0.11
	Total	150	100.0	242	100.0			
Mother's residence birth to 12	City/Town	105	69.5	186	77.2	0.7	(0.4-1.1)	0.09
	Village/Desert	46	30.5	55	22.8	1.0		
	Total	151	100.0	241	100.0			
Mother's Father's Occupational Field	Military	33	26.8	106	49.3	0.4	(0.2-0.6)	< 0.001
	White Collar	60	48.8	70	32.6	1.0		
	Trade and Manual	30	24.4	39	18.1	0.9	(0.5-1.6)	
	Total	123	100.0	215	100.0			

** Rural = in a village, in the desert or on a farm

Note: Where more than 1 stratum are present stratum specific Chi square have been presented (i.e., not the Wald statistics). The overall p value is a Chi square.

5.2.2 Multivariate analysis

Correlations

In order to reduce the number of variables being considered the same method was used as in the all cases analysis to consider correlations between the 53 variables presented in the univariate analysis (data not presented).

Selection of variables for logistic regression

Of the 53 variables, 38 were significant at the level of 0.25. The following 19 variables in table 5.19 were selected from them for further analysis.

In the full regression *paternal age at infant's birth* was not considered because of the quantity of missing data. *Maternal ethnicity* was replaced with *maternal education* based on the cross tabulation of the two variables (table 5.20). Another difference with this cardiac only analysis was that the variable *infants' age at interview* was included.

Table 5.19 Variables considered for further analysis, cardiac only

	Number Table 5.13	Variable	Baseline p value
	Dependent Variable		
1	1	Consanguinity (dichotomous)	0.20
	Infant Characteristics		
2	4	Infant's age at interview (2 groups)	< 0.001
3	7	Multiplicity	0.01
	Maternal Characteristics		
4	10	Maternal age at infant's birth	< 0.001
	Paternal Characteristics		
	15	Paternal age at infant's birth	< 0.001
	Index Pregnancy Characteristics		
5	19	Planned	0.21
6	22	Severity of vaginal bleeding (2 groups)	0.02
7	30	None, versus gestational, versus overt diabetes	0.02
8	31	Major maternal health problem with index pregnancy	0.01
	Previous Pregnancy		
9	32	Total pregnancy losses	0.01
10	33	Total deceased children	0.20
11	36	Vaginal bleeding (previous pregnancy)	0.08
12	37	Maternal health problem (previous)	0.01
	Fasting Concerns		
13	42	Total fasting days	0.24
	Environmental issues		
14	44	Chemical hair dyes	< 0.001
15	50	Vitamin use	0.03
16	57	Passive cigarette smoke exposure	0.07
17	58	Caffeine use	0.23
18	59	House sprayed with pesticides	< 0.001
	Socio-Economic Status Characteristics		
19	66	Mother's education	< 0.001

Table 5.20 Comparison of maternal ethnicity with maternal education

Characteristic	Stratum	Some Education N (%)		No Education N (%)		Total N (%)	
Cases	Bedouin ethnicity	41	33	18	78	59	40
	Urban ethnicity	85	37	5	22	90	60
	Total	126	100	23	100	149	100
Controls	Bedouin ethnicity	46	20	6	40	52	22
	Urban ethnicity	180	80	9	60	189	78
	Total	226	100	15	100	241	100

5.2.3 Multivariate results

Full model

The 19 factors found to be important and with sufficient data in the univariate analysis (table 5.19) were entered into a multivariate logistic regression model following the method described in Chapter 3. The variables found to be significant from the full model were *infant's age at interview*, *multiplicity*, *use of hair dye*, *house sprayed with pesticides* and *maternal education* (table 5.21).

Table 5.21 Summary table for adjusted odds ratio with 95% confidence intervals for cardiac only cases	**Cardiac cases, only**					
	Crude n=393	**pvalue**	**Full Model n=371**	**pvalue**	**Forward Stepwise n=371**	**pvalue**
Consanguinity : Yes	1.3 (0.9-2.0)	0.20	1.2 (0.7-2.0)	0.44		
Infant's age at interview			2.1 (1.2-3.6)	< 0.001	1.9 (1.2-3.2)	0.01
Multiplicity	5.8 (1.2-28.9)	0.01	7.3 (1.1-49.1)	0.04	5.5 (1.0-31.2)	0.05
Maternal ethnicity: Bedouin	2.4 (1.5-3.8)	< 0.001	-			
Maternal age at infant's birth						
14-20	0.7 (0.4-1.5)	0.29	0.6 (0.3-1.5)	0.30		
21-28	-					
29+	1.9 (1.3-3.0)	< 0.001	1.5 (0.9-2.6)	0.11	1.9 (1.2-3.1)	< 0.001
Planned: Yes	0.8 (0.5-1.1)	0.21	0.7 (0.4-1.2)	0.24		
All non-CHD reported anomalies: Other problem	-	-	-	-		
Bleeding: Moderate to Severe			2.2 (0.7-6.9)	0.16	2.7 (1.0-7.1)	0.04
None and gestational versus overt diabetes**: Diabetes	8.2 (0.9-71.9)	0.20	5.4 (0.4-72.7)	0.21		
Major health concern during index pregnancy: Yes	1.9 (1.1-3.3)	0.01	0.6 (0.3-1.5)	0.33		
Total pregnancy losses: 2 or more	2.8 (1.4-5.5)	< 0.001	2.1 (0.9-5.0)	0.09		
Total deceased children: 1 or more			0.9 (0.2-3.5)	0.90		
Bleeding previous pregnancy: 2+			1.3 (0.2-9.5)	0.79		
3 + Maternal health problems previous pregnancy			1.4 (0.4-5.1)	0.61		
Chemical hair dyes: Yes	2.4 (1.3-3.7)	< 0.001	2.1 (1.1-3.9)	0.02	2.2 (1.2-3.9)	0.01
Days of fasting: > than 5 weeks			1.7 (0.9-2.9)	0.08		
Vitamin use: Yes	1.7 (1.1-2.8)	0.03	1.3 (0.7-2.3)	0.38		
Illness with fever: Yes	1.2 (0.8-1.9)	0.42	1.1 (0.6-1.9)	0.72		
Passive cigarette smoke: Yes	1.4 (1.0-2.3)	0.07	1.6 (1.0-2.7)	0.06		
Caffeine use: Yes	1.6 (0.2-11.6)	0.23	2.8 (1.0-7.8)	0.06		
House sprayed with pesticides: Yes	3.5 (2.1-5.9)	< 0.001	3.2 (1.8-5.8)	< 0.001	3.7 (2.2-6.4)	< 0.001
Mother's education: None			4.8 (2.0-11.3)	< 0.001	4.3 (1.9-9.4)	< 0.001

Stepwise procedure

Following the full model, a forward stepwise procedure was performed which indicated seven significant variables. The stepwise *cardiac only* model found that the five variables from the full model contributed, as well as two additional variables: *maternal age at infant's birth* and *moderate to severe vaginal bleeding* during the index pregnancy.

Table 5.22 Comparison of crude and adjusted odds ratios from Cardiac only analysis n= 369

Characteristic	Stratum	Cases N	Cases (%)	Controls N	Controls (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	p value
Consanguinity	Yes	75	53.6	114	49.8	1.2 (0.8-1.8)	1.2 (0.7-1.9)	0.57
	No	65	46.4	115	50.2	1.0		
	Total	140	100.0	229	100.0			
First cousin or closer		35	25.0	57	24.9	1.1 (0.6-1.8)	1.0 (0.5-2.2)	031
All other (lesser) first cousins		25	17.9	29	12.7	1.5 (0.8-2.8)	0.5 (0.2-1.1)	
All second and third cousins		15	10.7	28	12.2	0.9 (0.5-1.9)	0.8 (0.4-1.3)	
Non-consanguineous		65	46.4	115	50.2	1.0		
Total		140	100.0	229	100.0			
Remaining Infant, Maternal and Paternal Characteristics								
Multiplicity	Singleton	133	95.0	227	99.1	1.0	1.0	0.03
	Twins or higher	7	5.0	2	.9	6.0 (1.2-29.2)	5.7 (1.0-33.0)	
	Total	140	100.0	229	100.0			
Infant's age at interview (collapsed)	One year or less	87	62.1	181	79.0	1.0	1.0	0.01
	1 to 4 years	53	37.9	48	21.0	2.3 (1.4-3.7)	2.0 (1.2-3.3)	
	Total	140	100.0	229	100.0			
Maternal Ethnicity	Bedouin Ethnicity	55	39.3	51	22.3	2.3 (1.4-3.6)	1.7 (1.0-2.8)	0.05
	Urban Ethnicity	85	60.7	178	77.7	1.0	1.0	
	Total	140	100.0	229	100.0			
Maternal Age at Infant's Birth (years)	14-20	12	8.6	34	14.8	0.7 (0.4-1.6)	0.7 (0.3-1.5)	< 0.001
	21-28	54	38.6	114	49.8	1.0	1.0	
	29+	74	52.9	81	35.4	1.9 (1.2-3.0)	1.8 (1.1-2.9)	
	Total	140	100.0	229	100.0			
Paternal Age at Infant's Birth (years)	19-24	13	9.6	14	6.7	2.2 (1.0-5.1)	2.8 (1.1-7.4)	0.08
	25-34	50	37.0	120	57.7	1.0	1.0	
	35+	72	53.3	74	35.6	2.3 (.5-3.7)	1.5 (0.8-2.9)	
	Total	135	100.0	208	100.0			
Index Pregnancy Characteristics								
Was this pregnancy planned?	Yes	57	40.7	76	33.2	0.7 (0.5-1.1)	0.7 (0.4-1.1)	0.12
	No	83	59.3	153	66.8	1.0	1.0	
	Total	140	100.0	229	100.0			
Severity of Vaginal bleeding	No bleeding to mild	126	90.0	220	96.1	1.0	1.0	
	Moderate to severe	14	10.0	9	3.9	2.7 (1.1-6.5)	2.6 (1.0-6.8)	0.05
	Total	140	100.0	229	100.0			
Diabetes	None or GDM	136	97.1	228	99.6	1.0	1.0	
	Overt	4	2.9	1	.4	6.7 (0.7-61.6)	4.4 (0.4-50.2)	0.20
	Total	140	100.0	229	100.0			
Major maternal health problem	Yes	29	20.7	32	14.0	1.6 (0.9-2.8)	0.9 (0.5-1.8)	0.79
	No	111	79.3	197	86.0	1.0		
	Total	140	100.0	229	100.0			
Previous Pregnancy Characteristics								
Pregnancy losses	1 or fewer losses	118	84.3	214	93.4	1.0	1.0	0.22
	2 or more losses	22	15.7	15	6.6	2.7 (1.3-5.3)	1.6 (0.7-3.6)	
		140	100.0	229	100.0			
Total deceased children	No deaths	131	93.6	219	95.6	1.0	1.0	0.52
	1 or more deaths	9	6.4	10	4.4	1.5 (0.6-3.8)	0.7 (0.2-2.1)	
	Total	140	100.0	229	100.0			
Pregnancies with bleeding > 1 day+	Bleeding 0-1	126	90.0	223	97.4	1.0	1.0	
	Bleeding >1	14	10.0	6	2.6	4.1 (1.5-11.0)	1.5 (0.3-8.9)	0.65
	Total	140	100.0	229	100.0			
Maternal health problem	None to 2 preg	129	92.1	224	97.8	1.0	1.0	
	At least 3 preg	11	7.9	5	2.2	3.8 (1.3-11.2)	2.0 (0.6-6.6)	0.25
	Total	140	100.0	229	100.0			
Fasting								
Other fasting* in window	0-5 weeks	100	71.4	180	78.6	1.0	1.0	
	More than 5 weeks	40	28.6	49	21.4	3.8 (1.3-11.2)	1.4 (0.8-2.5)	0.19
	Total	140	100.0	229	100.0			

Characteristic	Stratum	Cases N (%)		Controls N (%)		Crude OR (95% CI)	Adjusted OR (95% CI)	p value
Environmental Risk Factors								
Chemical hair dye use in window	Yes	32	22.9	31	13.5	1.9 (1.1-3.3)	2.2 (1.2-4.0)	< 0.001
	No	108	77.1	198	86.5	1.0	1.0	
	Total	140	100.0	229	100.0			
Vitamin use in window	Yes	100	71.4	184	80.3	1.0	1.0	0.53
	No	40	28.6	45	19.7	1.6 (1.0-2.7)	1.2 (0.7-2.1)	
	Total	140	100.0	229	100.0			
Passive cigarette smoke exposure	Yes	59	42.1	74	32.3	1.5 (1.0-2.4)	1.6 (1.0-2.6)	0.08
	No	81	57.9	155	67.7	1.0	1.0	
	Total	140	100.0	229	100.0			
Consumption of caffeinated beverages	Yes	134	95.7	207	90.4	2.4 (0.9-6.0)	2.6 (0.9-7.2)	0.05
	No	6	4.3	22	9.6	1.0	1.0	
	Total	140	100.0	229	100.0			
House sprayed with pesticide in window	Yes	51	36.4	33	14.4	3.4 (2.1-5.6)	3.7 (2.1-6.3)	< 0.001
	No	89	63.6	196	85.6	1.0	1.0	
	Total	140	100.0	229	100.0			
Socioeconomic Status Characteristics								
Household income /month	Poor	20	16.0	21	10.1	1.9 (1.0-3.6)	1.0 (0.5-2.3)	0.23
	Middle	85	68.0	167	80.7	1.0	1.0	
	Well off	20	16.0	19	9.2	2.1 (1.0-4.1)	2.0 (0.7-5.5)	
	Total	125	100.0	207	100.0			
Mother's Education	None	23	16.4	12	5.2		4.5 (2.0-10.0)	< 0.001
	Some	117	83.6	217	94.8		1.0	
	Total	140	100.0	229	100.0			
Has mother ever had paid employment?	Yes	38	27.1	31	13.5	1.0	1.0	
	No	102	72.9	198	86.5	0.4 (0.2-0.7)	0.6 (0.3-1.1)	0.08
	Total	140	100.0	229	100.0			
Mother's Early SES	Her father responsible	129	92.1	201	87.8	0.6 (0.3-1.3)	0.4 (0.2-1.0)	0.03
	Someone else	11	7.9	28	12.2	1.0	1.0	
	Total	140	100.0	229	100.0			
Mother's residence birth to 12	City/Town	98	70.0	176	77.2	1.0	1.0	0.74
	Village/Desert	42	30.0	52	22.8	1.5 (0.9-2.3)	1.1 (0.6-1.9)	
	Total	140	100.0	228	100.0			
Mother's Father's Occupational Field	Military	31	27.2	103	50.7	0.3 (0.2-0.6)	0.4 (0.2-0.7)	0.01
	White Collar	56	49.1	65	32.0	1.0	1.0	
	Trade and Manual	27	23.7	35	17.2	0.9 (0.5-1.7)	0.7 (0.3-1.5)	
	Total	114	100.0	203	100.0			

* Other religious, non-Ramadan, fasting

- Adjusted for maternal education, infant's age at interview, maternal age, multiplicity, maternal use of hair dye, house sprayed with pesticides, and moderate to severe vaginal bleeding during index pregnancy
- p-value is from likelihood ratio test comparing the fit of the reduced model (as described above) plus v_t (8 variables) with the fit of the reduced model alone (7 variables).
- v_t = Variable to be tested / confirmed as not being relevant to model.

Adjustment

The seven variables identified through the forward stepwise procedure were used to adjust all 19 variables that had been included in the full model using the likelihood ratio test as the measure of improvement to the model (table 5.22). Seven variables of specific interest (*maternal ethnicity*, *paternal age* and several SES factors) were also examined. *Maternal ethnicity* continued to contribute (adj. OR = 1.7, $CI_{95\%}$ =1.0-2.8). Once the data were adjusted, *paternal age at infant's birth* ceased to be significant (p=0.08). Neither

whether or not the pregnancy was planned nor *diabetes* achieved significance after adjustment. *Major maternal health problem with the index pregnancy* did not contribute after adjustment. *Vaginal bleeding for more than one day* continued to add to the model (p=0.05).

After adjustment, *pregnancy losses* did not contribute to the model nor did *total deceased children*. *Chemical hair dye use* and *passive cigarette smoke exposure* contributed to the model. *Vitamin use* in the window was no longer significant. Consumption of caffeinated beverages had borderline significance (p = 0.05) but a confidence interval that crossed 1 (adj. OR = 2.6, $CI_{95\%}$ =0.09-7.2). *Mother's early SES* (adj. OR = 0.4, $CI_{95\%}$=0.2-1.0) and *mother's father's occupation* in the military continued to be significant despite controlling for *mother's education* (adj. OR = 0.4, $CI_{95\%}$ =0.2-0.07).

Interactions

An interaction was considered although this investigation was limited by the size of the dataset. Because both *maternal ethnicity* and *maternal education* were significant they were tested for an interaction. This model removed the influence of maternal education but did not affect any of the other variables (data not shown).

5.3 Analysis of embryologically earliest and latest cases

A third and fourth analysis were conducted with the data although there was very little power in the third analysis with only 44 cases. Table 5.23 presents the data split into embryological earliest and embryologically latest categories (see Chapter 1 and Chapter 4). There were 44 cases (embryologically early) that were classified as category 1 (Laterality and Looping) or category 2 (DVOAT) that did not have an associated ECM. There were 83 cases in category 6 (HD) without an ECM (embryologically late).

5.3.1 Results: embryologically earliest cases

Maternal ethnicity and *maternal education* both were still significant in univariate analysis, *paternal ethnicity*, three or more pregnancies with a *maternal health problem*, *other religious, non-Ramadan, fasting,* within the window, *vitamin use, maternal nausea, house sprayed with pesticides* and *rodenticides* were significantly associated with CHD. *Maternal age, paternal age,* and *household income* were no longer significant.

Table 5.23 Characteristics for embryologically earliest (EE) and embryologically latest (EL) cases and controls, selected from the subset of cardiac only cases

5.23a Consanguinity

Characteristic	Stratum	Controls N (%)		EE N (%)		Crude odds ratio (95% CI)	pvalue	EL N (%)		Crude odds ratio (95% CI)	pvalue
Consanguinity	Yes	119	49.2	21	47.7	0.9 (0.5-1.8)	0.86	47	56.6	1.3 (0.8-2.2)	0.24
	No	123	50.8	23	52.3	1.0		36	43.4	1.0	
	Total	242	100.0	44	100.0			83	100.0		
First Cousin or closer		60	24.8	8	18.2	0.7 (0.3-1.7)	0.62	26	31.3	1.5 (0.8-2.7)	0.35
All other (lesser) First Cousins		30	12.4	5	11.4	0.89 (0.3-2.5)		14	16.9	1.6 (0.8-3.3)	
All Second and Third Cousins		29	12.0	8	18.2	1.5 (0.6-3.6)		7	8.4	0.8 (0.3-2.0)	
Non-Consanguineous		123	50.8	23	52.3	1.0		36	43.4	1.0	
Total		242	100.0	44	100.0			83	100.0		

5.23b Infant characteristics

Characteristic	Stratum	Controls N (%)		EE N (%)		Crude odds ratio (95% CI)	p value	EL N (%)		Crude odds ratio (95% CI)	pvalue
Infant's Sex	Male	120	49.6	26	59.1	1.5 (0.8-2.8)	0.25	37	44.6	0.8 (0.5-1.3)	0.70
	Female	122	50.4	18	40.9	1.0		46	55.4	1.0	
	Total	242	100.0	44	100.0			83	100.0		
Infant's age at interview (collapsed)	One year or less	191	78.9	34	77.3	1.0		42	50.6	3.6 (2.2-6.2)	0.00
	1 to 4 years	51	21.1	10	22.7	1.2 (0.5-2.8)	0.63	41	49.4	1.0	
	Total	242	100.0	44	100.0			83	100.0		
Multiplicity	Singleton	240	99.2	42	95.5	1.0		80	96.4	1.0	
	Twins +	2	.8	2	4.5	5.7 (0.8-41.7)	0.09	3	3.6	4.5 (0.7-25.4)	0.10
	Total	242	100.0	44	100.0			83	100.0		

5.23c Maternal characteristics

Characteristic	Stratum	Controls N (%)		EE N (%)		Crude odds ratio (95% CI)	p value	EL N (%)		Crude odds ratio (95% CI)	pvalue
Maternal Ethnicity	Bedouin Ethnicity	52	21.6	23	50.0	4.0 (2.0-7.8)	0.00	30	36.1	2.1 (1.2-3.5)	0.02
	Urban Ethnicity	189	78.4	21	50.0	1.0		53	63.9	1.0	
	Total	241	100.0	44	100.0			83	100.0		
Maternal Age at Infant's Birth	14-20	34	14.3	5	11.6	0.9 (0.3-2.5)	0.73	6	7.3	0.6 (0.2-1.6)	0.02
	21-28	118	49.8	20	46.5	1.0		33	40.2	1.0	
	29+	85	35.9	18	41.9	1.2 (0.6-2.5)		43	52.4	1.8 (1.1-3.1)	
	Total	237	100.0	43	100.0			82	100.0		

Characteristic	Stratum	Controls N (%)		EE N (%)		Crude odds ratio (95% CI)	p value	EL N (%)		Crude odds ratio (95% CI)	pvalue
Gravida	1 pregnancy	69	28.5	7	15.9	1.0	0.19	16	19.3	1.0	0.05
	2-5 pregnancies	124	51.2	24	54.5	1.9 (0.8-4.7)		38	45.8	1.3 (0.7-2.5)	
	6-8 pregnancies	36	14.9	11	25.0	3.0 (1.1-8.4)		21	25.3	2.5 (1.2-5.4)	
	9 + pregnancies	13	5.4	2	4.5	1.5 (0.3-8.1)		8	9.6	2.7 (0.9-7.5)	
	Total	242	100.0	44	100.0			83	100.0		
Parity	1 birth	79	32.6	9	20.9	1.0	0.30	20	24.4	1.0	0.14
	2-5 births	125	51.7	25	58.1	1.8 (0.8-4.0)		42	51.2	1.3 (0.7-2.4)	
	6 or more births	38	15.7	9	20.9	2.1 (0.8-5.7)		20	24.4	2.1 (1.0-4.3)	
	Total	242	100.0	43	100.0			82	100.0		

5.23d Paternal characteristics

Characteristic	Stratum	Controls N (%)		EE N (%)		Crude odds ratio (95% CI)	pvalue	EL N (%)		Crude odds ratio (95% CI)	pvalue
Paternal Ethnicity	Bedouin Ethnicity	57	23.6	22	50.0	3.2 (1.7-6.3)	0.00	33	39.8	2.1 (1.3-3.7)	0.01
	Urban Ethnicity	185	76.4	22	50.0	1.0		50	60.2	1.0	
	Total	242	100.0	44	100.0			83	100.0		
Paternal Age at Infant's Birth	19-24	14	6.5	2	5.0	0.8 (0.2-4.0)	0.71	9	11.3	3.5 (1.3-8.9)	0.00
	25-34	124	57.7	21	52.5	1.0		23	28.8	1.0	
	35+	77	35.8	17	42.5	1.3 (0.6-2.6)		48	60.0	3.1 (1.9-6.0)	
	Total	215	100.0	40	100.0			80	100.0		

5.23e Index pregnancy characteristics

Characteristic	Stratum	Controls N (%)		EE N (%)		Crude odds ratio (95% CI)	pvalue	EL N (%)		Crude odds ratio (95% CI)	pvalue
Was this pregnancy planned?	Yes	79	32.6	17	39.5	0.7 (0.4-1.4)	0.38	33	40.2	0.7 (0.4-1.2)	0.21
	No	163	67.4	26	60.5	1.0		49	59.8	1.0	
	Total	242	100.0	43	100.0			82	100.0		
Diabetes	No Diabetes or Gestational	239		43		1.0	0.25	79	95.2	1.0	0.01
	Overt	1		1		5.6 (0.3-90.6)		4	4.8	12.1 (1.3-109.9)	
	Total	240	100.0	44	100.0			83	100.0		
Major maternal health problem with index pregnancy	Yes	33	13.6	5	11.6	0.8 (0.3-2.3)	0.72	26	31.7	2.9 (1.6-5.3)	0.00
	No	209	86.4	38	88.4	1.0		56	68.3	1.0	
	Total	242	100.0	43	100.0			82	100.0		

5.23f Previous pregnancy characteristics

Characteristic	Stratum	Controls N (%)		EE N (%)		Crude odds ratio (95% CI)	pvalue	EL N (%)		Crude odds ratio (95% CI)	pvalue
Total number of pregnancy losses[+]	1 or fewer losses	227	93.8	19	90.7	1.0	0.47	67	81.7	1.0	0.00
	2 ore more losses	15	6.2	4	9.3	1.6 (0.5-4.9)		15	18.3	3.3 (1.6-7.3)	
	Total	242	100.0	43	100.0			82	100.0		
Total number of neonatal deaths (<30 days)	No neonatal deaths	239	98.8	43	100.0	-		78	95.1	1.0	0.07
	1+ neonatal deaths	3	1.2	0	0.0			4	4.9	4.1 (0.9-18.7)	
	Total	242	100.0	43	100.0			82	100.0		
Total number of infant deaths (31 to 365 days)	No infant deaths	238	98.3	42	97.7	1.0	0.77	78	95.1	1.0	0.13
	1 or more deaths	4	1.7	1	2.3	1.4 (0.5-13.0)		4	4.9	3.1 (0.7-12.5)	
	Total	242	100.0	43	100.0			82	100.0		
Total number of lost children, any cause	No deaths	231	95.5	42	97.7	1.0		71	86.6	1.0	0.01
	1 or more deaths	11	4.5	1	2.3	0.5 (0.06-4.0)	0.47	11	13.4	3.3 (1.4-7.8)	
	Total	242	100.0	43	100.0			82	100.0		
Total number of pregnancies with bleeding lasting > 1 day[++]	No bleeding	208	86.0	33	76.7	1.0	0.34	65	79.3	1.0	0.01
	1 pregnancy	28	11.6	8	18.6	1.8 (0.7-4.3)		8	9.8	0.9 (0.4-2.1)	
	2+ pregnancies	6	2.5	2	4.7	2.1 (0.4-10.9)		9	11.0	4.8 (1.6-14.0)	
	Total	242	100.0	43	100.0			82	100.0		
Total number of pregnancies with a maternal health problem	2 or few pregnancies	237	97.9	39	91.7	1.0	0.03	77	93.9	1.0	0.09
	3 or more pregnancies	5	2.1	4	9.3	4.9 (1.3-18.9)		5	6.1	3.1 (0.9-10.9)	
	Total	242	100.0	43	100.0			82	100.0		
Total number of pregnancies while mother suffered from a major illness	None	227	93.8	43	100.0	-		76	92.7	1.0	0.73
	1 or more pregnancies	15	6.2	0	0.0			6	7.3	1.2 (0.4-3.2)	
	Total	242	100.0	43	100.0			82	100.0		

5.23g Fasting concerns

Characteristic	Stratum	Controls N (%)		EE N (%)		Crude odds ratio (95% CI)	pvalue	EL N (%)		Crude odds ratio (95% CI)	pvalue
Ramadan fell within 3+/- window?	Occurred	148	61.2	30	68.2	1.4 (0.7-2.7)	0.37	53	63.9	1.1 (0.7-1.8)	0.66
	Did not occur	94	38.8	14	31.8	1.0		30	36.1	1.0	
	Total	242	100.0	44	100.0			83	100.0		
Ramadan fasting in window?	Yes	144	97.3	28	93.3	0.4 (0.1-2.2)	0.32	52	98.1	1.4 (0.2-13.2)	0.74
	No	4	2.7	2	6.7	1.0		1	1.9	1.0	
	Total	148	100.0	30	100.0			53	100.0		
Other fasting* days within 3+/- window?	Yes	143	59.3	34	77.3	2.3 (1.1-4.9)	0.02	47	58.8	1.0 (0.6-1.6)	0.93
	No	98	40.7	10	22.7	1.0		33	41.3	1.0	
	Total	241	100.0	44	100.0			80	100.0		
Number of days of fasting in window	Up to five weeks	189	78.1	31	70.5	1.5 (0.7-3.1)	0.28	61	73.5	1.3 (0.7-2.3)	0.40
	More than five weeks	53	21.9	13	29.5	1.0		22	26.5	1.0	
	Total	242	100.0	44	100.0			83	100.0		

* Other religious, non-Ramadan, fasting

5.23h Environmental issues

Characteristic	Stratum	Controls N (%)		EE N (%)		Crude odds ratio (95% CI)	pvalue	EL N (%)		Crude odds ratio (95% CI)	pvalue
Skin lightening creams?	Yes	39	16.3	5	11.6	0.7 (0.2-1.8)	0.42	13	16.5	1.0 (0.5-2.0)	0.98
	No	200	83.7	38	88.4	1.0		66	83.5	1.0	
	Total	239	100.0	43	100.0			79	100.0		
Chemical Hair dyes use in window	Yes	31	12.8	9	20.5	1.8 (0.7-4.0)	0.19	21	25.0	2.3 (1.3-4.4)	0.01
	No	211	87.2	35	79.5	1.0		61	75.0	1.0	
	Total	242	100.0	44	100.0			82	100.0		
Peroxide use in window	Yes	18	7.4	4	9.1	1.2 (0.4-3.9)	0.71	16	19.5	3.0 (1.5-6.2)	0.00
	No	224	92.6	40	90.9	1.0		66	80.5	1.0	
	Total	242	100.0	44	100.0			82	100.0		
Henna use in window	Yes	46	19.0	13	29.5	1.8 (0.9-3.7)	0.13	23	28.0	1.7 (0.9-3.0)	0.09
	No	196	81.0	31	70.5	1.0		59	72.0	1.0	
	Total	242	100.0	44	100.0			82	100.0		
Khol Bought from herbalist		13	5.4	2	4.5	0.8 (0.2-3.9)	0.81	5	6.0	1.1 (0.4-3.3)	0.82
Didn't use or commercially obtained		229	94.6	42	95.5	1.0		78	94.0	1.0	
Total		242	100.0	44	100.0			83	100.0		
Vitamin use within window	Yes	196	81.3	28	63.6	1.0		66	81.5	1.0	0.97
	No	45	18.7	16	36.4	2.4 (1.2-5.0)	0.01	15	18.5	1.0 (0.5-1.9)	
	Total	241	100.0	44	100.0			81	100.0		

Characteristic	Stratum	Controls N (%)		EE N (%)		Crude odds ratio (95% CI)	pvalue	EL N (%)		Crude odds ratio (95% CI)	pvalue
Folic Acid use within window	Yes	133	56.6	20	45.5	1.0		54	65.9	1.0	0.18
	No	102	43.4	24	54.5	1.6 (0.8-3.0)	0.17	28	34.1	0.7 (0.4-1.1)	
	Total	235	100.0	44	100.0			82	100.0		
Nausea	Yes	184	76.3	27	61.4	0.5 (0.3-1.0)	0.04	62	76.5	1.0 (0.6-1.8)	0.97
	No	57	23.7	17	38.6	1.0		19	23.5	1.0	
	Total	241	100.0	44	100.0			81	100.0		
Illness during pregnancy with a influenza or cold?	Yes	93	39.2	18	41.9	1.1 (0.6-2.2)	0.70	35	43.2	1.2 (0.7-2.0)	0.96
	No	144	60.8	25	58.1	1.0		46	56.8	1.0	
	Total	237	100.0	43	100.0			81	100.0		
Was there any fever?	Yes	60	24.8	12	27.3	1.1 (0.6-2.4)	0.70	26	31.3	1.4 (0.7-2.4)	0.25
	No	182	75.2	32	72.7	1.0		57	68.7	1.0	
	Total	242	100.0	44	100.0			83	100.0		
Medications	Yes	105	43.6	20	47.6	1.2 (0.6-2.3)	0.62	40	49.4	1.2 (0.8-2.1)	0.36
	No	136	56.4	22	52.4	1.0		41	50.6	1.0	
	Total	241	100.0	42	100.0			81	100.0		
Exposed to cigarette smoke at any time in window?	Yes	80	33.1	17	38.6	1.3 (0.7-2.5)	0.51	36	44.4	1.6 (1.0-2.7)	0.07
	No	162	66.9	27	61.4	1.0		45	55.6	1.0	
	Total	242	100.0	44	100.0			81	100.0		
Consumption of caffeinated beverages during the window	Yes	217	89.7	44	100.0	-		77	93.9	1.8 (0.7-4.8)	0.23
	No	25	10.3	0	0.0			5	6.1	1.0	
	Total	242	100.0	44	100.0			82	100.0		
House sprayed with pesticide during the window period	Yes	33	13.9	16	36.4	3.5 (1.7-7.3)	0.00	25	32.9	3.0 (1.7-5.6)	0.00
	No	205	86.1	28	63.6	1.0		51	67.1	1.0	
	Total	238	100.0	44	100.0			76	100.0		
House treated with rodenticides during the window period	Yes	1	.4	3	6.8	17.6 (1.8-173.7)	0.01	5	6.1	15.6 (1.8-136.0)	0.00
	No	241	99.6	41	93.2	1.0		77	93.9	1.0	
	Total	242	100.0	44	100.0			82	100.0		
Hyperthermia during the window period.	Yes	33	13.9	7	15.9	1.2 (0.5-2.8)	0.73	16	20.3	1.6 (0.8-3.0)	0.19
	No	204	86.1	37	84.1	1.0		63	79.7	1.0	
	Total	237	100.0	44	100.0			79	100.0		

5.23i Socioeconomic status characteristics

Characteristic	Stratum	Controls N (%)		Embryologically Earliest N (%)		Crude odds ratio (95% CI)	pvalue	Embryologically Latest N (%)		Crude odds ratio (95% CI)	pvalue
Household income/capita excluding servants /month	Poor	26	11.9	9	22.0	2.3 (1.0-5.5)	0.10	11	16.2	1.6 (0.8-3.6)	0.07
	Middle	174	79.5	26	63.4	1.0		45	66.2	1.0	
	Well off	19	8.7	6	14.6	2.1 (0.8-5.8)		12	17.6	2.4 (1.1-5.4)	
	Total	219	100.0	41	100.0			68	100.0		
Mother's Education	None	15	93.8	34	77.3	4.4 (1.8-10.9)	0.00	70	85.4	2.6 (1.2-5.8)	0.01
	Some (includes adult)	227	6.2	10	22.7	1.0		12	14.6	1.0	
	Total	242	100.0	44	100.0			82	100.0		
Has mother ever had paid employment?	Yes	33	13.6	5	11.4	1.0	0.70	27	32.9	1.0	0.00
	No	209	86.4	39	88.6	0.8 (0.3-2.2)		55	67.1	3.1 (1.7-5.6)	
	Total	242	100.0	44	100.0			82	100.0		
Mother's Early SES	Her father responsible	212	87.6	41	93.2	1.0	0.26	75	91.5	1.0	0.33
	Someone else	30	12.4	3	6.8	0.5 (0.2-1.7)		7	8.5	0.7 (0.3-1.6)	
	Total	242	100.0	44	100.0			82	100.0		
Mother's residence birth to 12	City/Town	186	77.2	28	63.6	0.5 (0.3-1.0)	0.06	58	69.9	1.5 (0.8-2.5)	0.19
	Village/Desert	55	22.8	16	36.4	1.0		25	30.1	1.0	
	Total	241	100.0	44	100.0			83	100.0		
Mother's Father's Occupational Field	Military	106	49.3	10	29.4	0.4 (0.2-1.0)	0.09	20	29.4	0.4 (0.2-0.8)	0.01
	White Collar	70	32.6	16	47.1	1.0		33	48.5	1.0	
	Trade and Manual	39	18.1	8	23.5	0.9 (0.4-2.3)		15	22.1	0.8 (0.4-1.7)	
	Total	215	100.0	34	100.0			68	100.0		

Correlations

Correlations were considered between the 46 variables presented in univariate analysis following the same method as for the entire dataset to assist in variable reduction (data not shown).

Selection of variables for logistic regression

Of the 46 variables, 17 were significant at the level of 0.20. However, because of the correlations and small numbers *gravida*, *paternal ethnicity*, *henna use*, *folic acid*, *rodenticides* and *household income* were not considered. *Diabetes* was considered even though it did not meet the new threshold. However it had to be discarded because of lack of data. Similarly, *multiplicity* had to be discarded for lack of data. *Consanguinity* was considered but as it was not significant in this data set either it was discarded. Also, *infant's age at interview* was no longer significant for the embryological early group. There were therefore 10 variables entered into the full model.

Multivariate results

Full model and stepwise procedure

The model was reduced from 286 observations to 272. The results (table 5.24, Full Model) show that 5 of the 10 variables were statistically significant: *major maternal health problem* in a previous pregnancy, *other religious, non-Ramadan, fasting, nausea, house sprayed with pesticides* and *mother's father's occupation*. The stepwise procedure confirmed these results.

Adjustment

The five variables identified through the full model and the forward stepwise procedure were used to adjust all 10 variables that had been used in the full model using the likelihood ratio test as the measure of improvement to the model (table 5.24). The adjusted odds ratio for maternal health problem in a previous pregnancy (adj. OR = 8.7, $CI_{95\%}$ =1.8-42.9), for other religious, non-Ramadan, fasting, days within the window (adj. OR = 3.7, $CI_{95\%}$=1.3-11.1), nausea (adj. OR = 0.3, $CI_{95\%}$=0.1-0.9), house sprayed with pesticides (adj. OR = 3.7, $CI_{95\%}$=1.5-9.2) and mother's father's occupation being in the military (adj. OR = 0.3, $CI_{95\%}$ =0.1-0.8).

Table 5.24 Summary table for adjusted odds ratio with 95% confidence intervals for earliest embryological cases	Embryologically Earliest n=286					
	Crude n=286	pvalue	Full Model n=272	pvalue	Forward Stepwise n=272	P value
Maternal ethnicity: Bedouin	4.0 (2.0-7.8)	< 0.001	2.5 (1.0-6.4)	0.06		
Major maternal health problem (previous): 3 or more	4.9 (1.3-18.9)	0.03	6.3 (1.2-33.4)	0.03	8.1 (1.7-39.5)	0.01
Other religious, non-Ramadan, fasting	2.3 (1.1-4.9)	0.02	4.7 (1.4-15.1)	0.01	3.7 (1.2-10.9)	0.02
Chemical hair dyes: Yes	1.8 (0.7-4.0)	0.19	2.1 (0.6-4.4)	0.17		
Vitamin use	2.4 (1.2-5.0)	0.01	1.6 (0.6-4.5)	0.34		
Nausea during pregnancy	0.5 (0.3-1.0)	0.04	0.3 (0.1-0.9)	0.03	0.4 (0.2-0.9)	0.03
House sprayed with pesticides: Yes	3.5 (1.7-7.3)	< 0.001	3.1 (1.3-7.8)	0.01	3.7 (1.5-9.2)	0.01
Mother's education	4.4 (1.8-10.9)	< 0.001	1.8 (0.3-9.7)	0.52		
Mother's residence until 12	0.5 (0.3-1.0)	0.06	1.4 (0.5-4.0)	0.52		
Mother's father's occupation:						
Military	0.4 (0.2-1.0)	0.09	0.3 (0.1-0.8)	0.01	0.3 (0.1-0.8)	0.01
Trade and manual	0.9 (0.4-2.3)		0.6 (0.2-1.7)		0.8 (0.3-2.5)	

Table 5.25 Comparison of crude and adjusted odds ratios from analysis of embryologically earliest cases n=272

Characteristic	Stratum	Cases N (%)		Controls N (%)		Crude OR (95% CI)	Adjusted OR (95% CI)	p value
Maternal Ethnicity	Bedouin Ethnicity	23	53.5	51	22.3	3.9 (2.0-7.5)	2.5 (1.0-6.2)	0.06
	Urban Ethnicity	20	46.5	178	77.7	1.0	1.0	
	Total	43	100.0	229	100.0			
Maternal health problem (previous)	None to 2 pregnancies	39	90.7	224	97.8	1.0	1.0	0.01
	At least 3 pregnancies	4	9.3	5	2.2	4.7 (1.2-18.4)	8.7 (1.8-42.9)	
	Total	43	100.0	229	100.0			
Other fasting* days within window?	Yes	34	79.1	138	60.3	2.3 (1.1-4.8)	3.7 (1.3-11.1)	0.01
	No	9	20.9	91	39.7	1.0		
	Total	43	100.0	229	100.0			
Chemical hair dye use in window	Yes	9	20.9	31	13.5	1.7 (0.7-3.9)	2.4 (0.9-6.8)	0.10
	No	34	79.1	198	86.5	1.0	1.0	
	Total	43	100.0	229	100.0			
Vitamin use in window	Yes	27	62.8	184	80.7	1.0	1.0	0.26
	No	16	37.2	44	19.3	2.5 (1.2-5.0)	1.8 (0.7-4.7)	
	Total	43	100.0	228	100.0			
Nausea	Yes	26	60.5	174	76.3	0.5 (0.3-1.0)	0.3 (0.1-0.9)	0.03
	No	17	39.5	54	23.7	1.0	1.0	
	Total	43	100.0	228	100.0			
House sprayed with pesticides	Yes	15	34.9	33	14.4	3.5 (1.7-7.3)	3.7 (1.5-9.2)	0.01
	No	28	65.1	196	85.6	1.0	1.0	
	Total	43	100.0	229	100.0			
Mother's Education	None	33	76.7	217	94.8	4.3 (1.8-10.4)	4.2 (0.8-21.5)	0.10
	Some (includes adult)	10	23.3	12	5.2	1.0	1.0	
	Total	43	100.0	229	100.0			
Mother's residence birth to 12	City/Town	27	62.8	175	76.8	1.0	1.0	0.18
	Village/Desert	16	37.2	53	23.2	1.6 (1.0-2.5)	2.0 (0.8-5.2)	
	Total	43	100.0	228	100.0			
Mother's Father's Occupational Field	Military	10	30.3	102	50.2	0.4 (0.2-1.0)	0.3 (0.1-0.8)	0.03
	White Collar	16	48.5	66	32.5	1.0	1.0	
	Trade and Manual	7	21.2	35	17.2	0.9 (0.4-2.3)	0.8 (0.3-2.5)	
	Total	33	100.0	203	100.0			

- Adjusted for major maternal health problem (previous), other religious, non-Ramadan, fasting, house sprayed with pesticides, nausea during pregnancy and mother's father's occupation.
- p-value is from likelihood ratio test comparing the fit of the reduced model (as described above) plus v_t (6 variables) with the fit of the reduced model alone (5 variables).
- v_t = Variable to be tested / confirmed as not being relevant to model.

*Other religious, non-Ramadan, fasting

5.3.2 Results: embryologically latest cases

Of the 46 variables (table 5.23), 29 were significant at the level of 0.20. *Infant's age at interview* was one of these.

Selection of variables for logistic regression

Due to correlations and small numbers only 11 of the 29 factors were considered for entrance into the full model.

Multivariate results

Full model and stepwise procedure

After initial exclusions there were 311 observations available. The results (table 5.26, Full Model) showed that 5 of the 11 variables were statistically significant: *infant's age at interview, major maternal health problem* in 3 or more previous pregnancies, *use of chemical hair dyes, house sprayed with pesticides* and *mother's father's occupation*. However, to fit this model there were an additional 43 observations excluded. The model was therefore run again without *mother's father's occupation* since it was responsible for

Table 5.26 Summary table for adjusted odds ratio with 95% confidence intervals for latest embryological cases	Embryologically Latest n=311					
	Crude n=311	pvalue	Full Model n=268	pvalue	Full Model (w/o mother's father's occupation) n=308	pvalue
Infant's age at interview	3.2 (1.8-5.5)	< 0.001	3.1 (1.5-6.2)	< 0.001	2.8 (1.5-5.1)	< 0.001
Multiplicity	4.7 (0.8-9.2)	0.10	2.2 (0.2-23.1)	0.53	4.3 (0.6-29.7)	0.14
Mother's ethnicity: Bedouin	2.0 (1.1-3.5)	0.02	0.9 (0.4-2.1)	0.88	1.1 (0.6-2.1)	0.75
Mother's age at infant's birth 14-20	0.6 (0.3-1.7)	0.34	0.6 (0.2-1.9)	0.37	0.6 (0.2-1.7)	0.35
21-28	1.0		1.0		1.0	
29+	1.7 (1.0-3.0)	0.03	1.2 (0.6-2.5)	0.61	1.2 (0.7-2.3)	0.52
Major maternal health problem with index pregnancy (Yes/No)	2.9 (1.6-5.3)	< 0.001	0.4 (0.2-0.9)	0.02	0.6 (0.3-1.2)	0.14
Pregnancy losses 2 or more	3.3 (1.6-7.3)	< 0.001	1.8 (0.7-4.9)	0.24	2.1 (0.9-5.2)	0.10
3 or more previous pregnancies with major maternal health problem	3.1 (0.9-10.9)	0.09	1.7 (0.3-8.3)	0.54	1.4 (0.3-5.7)	0.67
Chemical hair dyes: Yes	2.3 (1.3-4.4)	0.01	2.4 (1.0-5.3)	0.04	2.5 (1.2-5.1)	0.01
House sprayed with pesticides: Yes	3.0 (1.7-5.6)	< 0.001	2.5 (1.2-5.2)	0.01	2.6 (1.3-5.0)	< 0.001
Mother's education	2.6 (1.2-5.8)	0.01	2.6 (0.7-9.0)	0.14	3.0 (1.1-7.8)	0.03
Mother's father's occupation : Military	0.4 (0.2-0.8)	< 0.001	0.4 (0.2-0.9)	0.03	-	
: Trade and manual	0.8 (0.4-1.7)	0.58	0.7 (0.3-1.7)	0.33		
			Forward Stepwise n=268	pvalue	Forward Stepwise n=308	pvalue
Infant's age at interview			3.3 (1.7-6.2)	< 0.001	2.9 (1.6-5.1)	< 0.001
Major maternal health problem (index pregnancy)			0.3 (0.2-0.7)	< 0.001		
Pregnancy losses 2 or more					2.7 (1.2-6.3)	0.02
Chemical hair dyes: Yes					2.4 (1.2-4.8)	0.02
House sprayed with pesticides: Yes			2.7 (1.4-5.5)	< 0.001	2.8 (1.5-5.4)	< 0.001
Mother's education					3.1 (1.2-7.9)	0.02
Mother's father's occupation : Military			2.0 (1.1-3.7)	0.03	-	
: Trade and manual						

40 of the observations being excluded. With this full model three of the variables remained significant, and judging by their p values more strongly so, with the addition of *maternal education*. The stepwise procedure was then run with both the smaller dataset which included *mother's father's occupation* (n=268) and the larger dataset which did not (n=308). With the forward step model including *mother's father's occupation* we see that *infant's age at interview* enters the model but that *chemical hair dyes* does not. In the larger dataset we see that *chemical hair dyes* is significant but that also *pregnancy losses* of 2 enters the model. *Major maternal health problem* with the index pregnancy is no longer significant.

Adjustment

The five variables identified through the forward stepwise procedure with the larger dataset were then used to adjust the 10 variables plus *paternal age* that had been used in the full model using the likelihood ratio test as the measure of improvement to the model (table 5.27). The adjusted odds ratio for *infant's age at interview* was OR = 2.9, ($CI_{95\%}$=1.6-5.1), for *pregnancy losses* it was OR = 2.7, ($CI_{95\%}$ =1.2-6.3), for *hair dyes* OR = 2.4, ($CI_{95\%}$=1.2-4.8), for *house sprayed with pesticides* OR = 2.8, ($CI_{95\%}$=1.5-5.4) and for *maternal education* OR = 3.1 ($CI_{95\%}$=1.2-7.9). *Paternal age* (35+) was significantly associated with CHD in this model (adj. OR = 1.9, $CI_{95\%}$ =1.4-4.9) but young age was not.

Table 5.27 Comparison of crude and adjusted odds ratios from analysis of embryologically latest cases n=308

Characteristic	Stratum	Cases N (%)		Controls N (%)		Crude OR (95% CI)	Adjusted OR (95% CI)	p value
Infant's age at interview	One year or less	41	53.9	183	78.9	1.0	1.0	< 0.001
	1 to 4 years	35	46.1	49	21.1	3.2 (1.8-5.5)	2.9 (1.6-5.1)	
	Total	76	100.0	232	100.0			
Multiplicity	Singleton	73	96.1	230	99.1	4.7 (0.8-29.2)	5.7 (0.9-36.5)	0.06
	Twins or higher	3	3.9	2	.9	1.0	1.0	
	Total	76	100.0	232	100.0			
Mother's Ethnicity	Bedouin	27	35.5	51	22.0	2.0 (1.1-3.5)	1.2 (0.6-2.3)	0.56
	Urban	49	64.5	181	78.0	1.0	1.0	
	Total	76	100.0	232	100.0			
Mother's Age at Infant's Birth (years)	14-20	6	7.9	34	14.7	0.6 (0.3-1.7)	0.6 (0.2-1.6)	0.20
	21-28	31	40.8	115	49.6	1.0	1.0	
	29+	39	51.3	83	35.8	1.7 (1.0-3.0)	1.4 (0.8-2.5)	
	Total	76	100.0	232	100.0			
Father's Age	19-24	8	10.7	14	6.6	3.2 (1.2-8.4)	2.8 (0.9-8.1)	0.01
	25-34	22	29.3	122	57.8	1.0	1.0	
	35+	45	60.0	75	35.5	1.9 (1.9-6.0)	1.9 (1.4-4.9)	
	Total	75	100.0	211	100.0			
Index Pregnancy Characteristics								
Major maternal health problem	Yes	22	28.9	32	13.8	2.5 (1.4-4.7)	2.0 (1.0-3.9)	0.06
	No	54	71.1	200	86.2	1.0	1.0	
	Total	76	100.0	232	100.0			
Previous Pregnancy Characteristics								
Pregnancy losses	1 or <	61	80.3	217	93.5	1.0	1.0	0.02
	2 +	15	19.7	15	6.5	3.5 (1.6-7.8)	2.7 (1.2-6.3)	
	Total	76	100.0	232	100.0			
Maternal health problem	None to 2	71	93.4	227	97.8	1.0	1.0	0.37
	At least 3	5	6.6	5	2.2	3.2 (0.9-11.3)	1.9 (0.5-7.7)	
	Total	76	100.0	232	100.0			
Environmental Risk Factors								
Chemical hair dye use in window	Yes	18	23.7	31	13.4	2.0 (1.1-3.9)	2.4 (1.2-4.8)	0.02
	No	58	76.3	201	86.6	1.0	1.0	
	Total	76	100.0	232	100.0			
House sprayed with pesticide in window	Yes	25	32.9	33	14.2	3.0 (1.6-5.4)	2.8 (1.5-5.4)	< 0.001
	No	51	67.1	199	85.8	1.0	1.0	
	Total	76	100.0	232	100.0			
Socioeconomic Status Characteristics								
Mother's Education	None	64	84.2	220	94.8	3.5 (1.5-8.0)	3.1 (1.2-7.9)	0.02
	Some	12	15.8	12	5.2	1.0	1.0	
	Total	76	100.0	232	100.0			

- Adjusted for Infant's age at interview, house sprayed with pesticides, previous pregnancy losses, use of chemical hair dyes and maternal education.
- p-value is from likelihood ratio test comparing the fit of the reduced model (as described above) plus v_t (6 variables) with the fit of the reduced model alone (5 variables).
- v_t = Variable to be tested / confirmed as not being relevant to model.

Summary of Results Chapter 5

1. Consanguinity was not found to be associated with CHD in any of the analyses.
2. Diabetes was not found to be associated with CHD in any of the analyses.
3. In adjusted analysis of ALL CHD the following variables were found to be statistically significantly associated with increased risk:
    - twins or higher multiplicity
    - maternal Bedouin ethnicity
    - high maternal age
    - low paternal age
    - presence of an extra-cardiac malformation
    - maternal use of chemical hair dye within the exposure window
    - maternal heartburn
    - house sprayed with pesticides within the exposure window
    - no maternal education
    - mother's father's occupational field being "white collar"
4. In adjusted analysis of CARDIAC ONLY cases the following variables were statistically significantly associated with increased risk:
    - twins or higher multiplicity
    - later infant's age at interview
    - maternal Bedouin ethnicity
    - higher maternal age
    - moderate to severe vaginal bleeding
    - maternal use of chemical hair dye within the exposure window
    - drinking caffeinated beverages within the exposure window
    - house sprayed with pesticides within the exposure window
    - no maternal education
    - mother's early SES being other than the responsibility of her father
    - mother's father's occupation being "white collar"
5. In adjusted analysis of EMBRYOLOGICALLY EARLIEST cases the following variables were found to be statistically significantly associated with increased risk:
    - major maternal health problem in 3 or more previous pregnancies
    - other religious, non-Ramadan, fasting within the exposure window

- maternal nausea
- house sprayed with pesticides within the exposure window
- mother's father's occupation being "white collar"

6. In adjusted analysis of EMBRYOLOGICALLY LATEST cases the following variables continued to be statistically significantly associated with increased risk:
    - later infant's age at interview
    - higher paternal age
    - two or more previous pregnancy losses
    - maternal use of chemical hair dyes within the exposure window
    - house sprayed with pesticides within the exposure window
    - no maternal education

CHAPTER 6 DISCUSSION

6.1 Overview

The aims of this study were to describe live born cases registered with the Riyadh CHD Registry, and to use these cases and conduct a case-control study within the Riyadh population in Saudi Arabia to investigate risk factors for CHD. Consanguinity, which is prevalent in this region, was of particular interest as a potential risk factor, and this was extensively reviewed. A systematic review of the literature describing risk factors for CHD, was also conducted.

A high proportion of the Registry cases (62%) were diagnosed at birth, suggesting a high degree of severe CHD conditions in this population. This compares to 30 percent for the BWIS group (Ferencz et al., 1993). Indeed, in the total BWIS case group it was four weeks before 60 percent of the cases had been diagnosed.

Classification of the cases was made according to whether they had one or more than one CHD diagnosis (i.e., isolated versus parallel defects) and whether or not they had other non-CHD extra-cardiac (ECM) defects. This stratification showed that thirty-five percent had more than one CHD diagnosis without an ECM, and a minority (15%) had an isolated defect in the presence of an ECM. The implications of these findings are discussed in more depth in the following sections.

Considerable effort was spent investigating the various systems for the classification and grouping of CHD cases. Special attention was paid to the BWIS and EUROCAT systems, both of which were found to be useful methods for describing cases and allowing comparisons with published information of these case-groups. In very general terms, the distribution of study cases was similar to that found among the EUROCAT cases. However there were differences between the Riyadh registry data and the BWIS data. These results are discussed further in the following section.

The case-control study using Registry cases did not confirm an association between consanguinity and risk of CHD. Factors which were found to increase the risk of ALL CHD in this population were *multiplicity*, *maternal ethnicity*, *maternal age*, *presence of*

ECM, *use of chemical hair dyes* and *house sprayed with pesticides*. In the first sub-analysis, where the 151 CARDIAC ONLY cases were analyzed, the risk factors were *multiplicity*, *use of chemical hair dyes*, *house sprayed with pesticides*, *maternal education* and *infant's age at interview*. The latter factor was not included in the ALL CHD analysis and should be regarded as a consequence of the design, rather than a true risk factor for CHD. It is interesting that the forward-stepwise procedure yielded two additional variables: *maternal age* and moderate to severe *vaginal bleeding*. These results will be discussed in more detail, later in this chapter.

Further analyses were conducted on cases defined according to the methodology of the BWIS group. The CARDIAC ONLY cases were divided into two groups: EMBRYOLOGICALLY EARLIEST cases (n=44) and the EMBRYOLOGICALLY LATEST cases (n=83), leaving aside those 24 cases in the middle embryological categories. Several risk factors were identified from the adjusted case-control analyses of the EMBRYOLOGICALLY EARLIEST cases: *major maternal health problem in three or more previous pregnancies*; *other religious, non Ramadan, fasting*; *nausea during pregnancy*; *house sprayed with pesticides* and *mother's father's occupation*. In the analyses using EMBRYOLOGICALLY LATEST cases, *infant's age at interview*, *pregnancy losses greater than two*, *chemical hair dyes*, *house sprayed with pesticides*, and *mother's education* were identified as risk factors. There were discrepancies in some of the findings of these sub-analyses according to the regression method used, providing evidence that that these analyses, using small numbers of cases, were unstable. The implications of low power are discussed in section 6.3.

6.2. Description of cases and their lesions (Chapter 4) - Summary and discussion of results

Of the 235 cases, a minority (15%) had both a parallel CHD defect and an ECM (table 4.3). This could be explained by a relatively higher foetal mortality in this group. For cases with no ECM, the presence of parallel defects is proportionally more common than isolated defects. This could be due to the greater relative survival of cases with parallel defects than those with isolated defects only. One explanation for the increased survival in these apparently more diseased infants may be the example of the infant with TAPVR whose "second" defect of VSD ensures post-term survival and registration. This would mean there was a percentage of parallel cases who were more severely damaged and

others whose live birth status was attributable to the second defect. This later group, if identifiable, might more sensibly be considered as "isolated" cases.

The finding that 19 percent of cases had Down syndrome and 36 percent had ECM (table 4.4) is an indication that the case population may be biased in some way towards a greater proportion of ECM referrals. The BWIS reported only 9 percent of cases with Down syndrome (385 of 4390). Of course the total of 4390 in this denominator includes PDA and cardiomyopathies which the Saudi Arabian study did not include.[1] The inclusion in this study of a case-control analysis made up of CARDIAC CASES ONLY ensured that any possible bias associated with the inclusion of Down syndrome cases (or indeed any other ECM) was eliminated.

Extra-cardiac malformations

While this study reported that 36 percent of all cases had an ECM, the BWIS study reported 28 percent (Ferencz et al., 1993). The majority of this difference is explained by the high proportion of chromosomal syndromes in the current cases (19%) compared to that reported for the BWIS cases (Ferencz et al., 1993). Also, while this Saudi Arabian study found 5 percent *heritable syndromes* in the case population, the BWIS found 7 percent. This study also found 12 percent *anomalies of organs* while the BWIS found 5 percent. Finally, this study found *no toxic embryopathies, infective embryopathies* or *deformations, non-structural and miscellaneous* anomalies whereas BWIS reported some of these conditions (5 percent, <1 percent, < 1 percent respectively).

Three explanations for these reported differences are possible: (1) The findings reflect bias given that KFSH&RC is a tertiary referral centre so the cases may not be representative of all CHD cases in the Riyadh population; (2) The cases are representative of all cases, but the Riyadh population has a higher proportion of ECM in the CHD population compared to the BWIS source population; (3) Since the time of the BWIS effort 10 years ago, the ability to detect ECM has improved. Undoubtedly, the third option is suspect, given that the ECM in question is Down syndrome. With the unique facies associated with Down syndrome, it is unlikely that it would have been under-diagnosed in the BWIS population.

[1] The BWIS data are not presented with sufficient detail to calculate the percentage of ECM for only the 3,885 structural defects.

On the other hand, the two populations might look more similar if we could compare for maternal age. The proportion of mothers aged 29 or more is greater for both the cases and controls in the Riyadh population than in the BWIS (59% and 36% versus 34% and 30%). This may partially explain the higher proportion of cases with ECM in the current study compared to that in the BWIS registry although this difference would probably not double the proportion of Down syndrome cases.

A few other studies have reported the number of ECMs in their CHD population (table 1.2). Although Olshan, Schnitzer, Baird (1994) do not report the actual chromosomal aberrations, they did report that a large proportion (94 percent of cases) were free of them. This is comparable to Bassili et al., (2000) who reported only 4 percent with ECM and is far different from the Riyadh registry result. Although most studies did not report the percentage of ECM, the range of those which did was from a low of 4 percent to a high of 28 percent (BWIS group).

BWIS classification system for cases

Using the BWIS "embryological" classification system, we were able to compare the distribution of cases within the 6 groups (9 including subgroups) between the present study and the BWIS study (see table 4.5). The rank ordering of the proportions of cases by embryological category is presented in table 6.1. It is reassuring that despite the differences in case definition there was comparability between the proportions in the Riyadh registry data and the BWIS data in a number of embryological defect categories including *laterality and looping*, *mesenchymal cell* and *extracellular matrix defects*. Given that mortality is higher in the embryologically-earlier categories perhaps even the small difference between 4.7 percent and 5.5 percent in the *laterality and looping* category can be explained by the BWIS's superior ability to follow-up the cases – especially those who were deceased.

It was also reassuring that the most common lesion in both datasets was *septal defects* and the least common was *targeted growth defects*. The second most common category for both datasets was *left-sided flow lesions*. These similarities indicate that the populations of cases are comparable and that the method of classification was conducted similarly in both studies. However, the differences between the data in the categories of *complete*

transposition (2b), *right sided flow lesions* (6a) and *cell death defects* (5) raise unanswered questions.

Table 6.1 Rank order comparing the Riyadh registry case data to the BWIS data

	BWIS Category	Riyadh data %	Rank	BWIS data %	Rank
6c	HD: Septal defects	36.2	1	33.0	1
6b	HD: Left-sided flow lesions	11.9	2	14.2	2
2b	DVOAT: Complete transposition	10.6	3	4.9	8
2a	DVOAT: Mesenchymal cell	9.4	4	10.1	5
3	Extracellular matrix defects	8.5	5	7.6	6
6a	HD: Right-sided flow lesions	8.1	6	12.0	3
5	Cell death defects	7.2	7	11.3	4
1	Laterality and looping	4.7	8	5.5	7
4	Targeted growth defects	3.4	9	1.4	9
	Total	100.0		100.0	

The graphical depiction of the distribution of cases using the embryological *meta-nosology* demonstrates how strongly the data are dominated by the hemodynamic category (figure 4.1). This is to be expected due to the finding that septal defects (VSD and ASD II) are the most common CHD. The Riyadh data were composed of 56 percent hemodynamic defects which compares to 59 percent in the BWIS data.

Table 4.6 and figure 4.2 tell the same stories using different methods. It was expected that the *extracellular matrix defect* category would be largely composed of the Down syndrome infants with AVSD and this was the case. The possible explanation for the dearth of ECM cases in the *laterality* category (and to a lesser extent the DVOAT category) may be that in a live birth study these cases would not appear. It could be that the excessive load of both an early embryological defect (such as those in categories 1, 2a and 2b) coupled with an ECM, tips the balance of survival and leads to spontaneous termination. Only further studies which are sophisticated enough to include spontaneous terminations, can answer this question.

Lesion Analysis – comparison with other published studies

This study found 531 lesions in the 235 Registry cases described by 29 lesion groups (table 4.7). These data show that ASD II is the most common lesion, making up almost one quarter of all the diagnoses, followed by all VSD at one fifth. Together, septal defects make up almost half of all lesions diagnosed in the 235 cases. One partial explanation for

the deficit of VSD could be that when the registry code, VSD was not permitted in combination with TOF. Another is that in lesion analysis, VSD is not actually the most common defect after all.

It is difficult to compare the Saudi Registry data to other studies as there is very little consistency in the published literature. Table 1.2 includes six studies which used the method of lesion analysis. Unfortunately, upon closer inspection, the first of these studies is not comparable. Lian et al., (1986) using the MACDP registry states that "[i]f a baby had two or more defects, he or she was counted in each relevant defect group" – which is the common principal of lesion analysis. However detailed data are not presented and only 12 of the CHD lesions are included in the publication. The second possible comparison would be with Bassili et al. (2000) who portended to present the types of lesions in the 931 index patients. However, again, they do not present the detail necessary for a comparison. The third lesion analysis study was by Olshan, Schnitzer, Baird (1994) using data from British Columbia, Canada investigating the effect of paternal age on CHD. Their dataset is not useful for comparison because they chose only to present data for those lesions where there were at least 100 cases thus restricting the number of cardiac lesions analyzed to 8. More interestingly, they report no cases of AVSD in either the *with chromosomal aberration* data or the *without chromosomal aberration* data.

Pradat (1992a) presented a table listing his lesion analysis data. The 1,605 infants had 2,849 lesions providing a ratio of 1.8:1 lesions per case (versus the ratio of 2.3 per case among the Riyadh data). However, Pradat used the ISC coding system rather than ICD-9. After converting the lesion codes to two digits, the dataset reduced from 2,849 lesions to 2,063. A comparison between the EUROCAT data and that of Cordier et al., (1997) was not possible because they did not present the data with sufficient detail.

Results from Pradat et al.'s 1992 study are presented in table 6.2 as a comparison to the Riyadh data. Because there were so many ties among the Riyadh data after rank 9 but no ties among the Swedish data, it was decided only to compare those defects ranked 1 to 9. This was deemed an acceptable adjustment because *dextrocardia* was not presented in the Swedish data.

Looking at ranks 1 to 9, we see that there are some correlations between the Swedish and the Riyadh data if the rank of plus or minus 1 is used as the threshold. VSD is first in the Swedish dataset and second in the Riyadh dataset. TGV is fourth for the Swedish dataset and fifth for the Riyadh dataset. What Pradat refers to as *endocardial cushion defects* (and this study refers to as AVSD and ASD I) is sixth for both datasets. Lastly *AV stenosis* (Pradat's *AV anomalies*) is eighth for the Swedish dataset and ninth for the Riyadh dataset. One intriguing difference was HLHS, one of the more severe and lethal defects, which was seven times as prevalent in the live birth Swedish population.

Table 6.2 Rank ordering comparing Pradat's Swedish data to the registry case data

		Riyadh Data			Swedish Data		
Defect or lesion	ICD 9 Code	N	%	Rank	N	%	Rank
ASD II	745.5	122	23.0	1	65	3.2	10
VSD	745.4	105	19.8	2	276	13.4	1
PDA	747.0	93	17.5	3	39	1.9	16
PV anomalies	746.01/2 745.0	37	7.0	4	274	13.3	2
d-TGV and l-TGV	745.10	28	5.3	5	205	9.9	4
AVSD/ ASD I	745.61 745.69	27	5.1	6	178	8.6	6
COA	747.1	19	3.6	7	212	10.3	3
DORV	745.11	13	2.5	8	44	2.1	14
AV stenosis	746.3	9	1.7	9	78	3.8	8
Dextrocardia	746.87	9	1.7	9	0	0	-
Bicuspid aortic valve (BAV)	746.4	8	1.5	10	0	0	-
Pulmonary artery hypoplasia/stenosis	747.3	8	1.5	10	36	1.7	17
DILV	745.3	6	1.1	12	63	3.1	11
HLHS	746.7	6	1.1	12	130	7	6.3
TAPVR	747.41	6	1.1	12	0	0	-
PAPVR	747.42	5	0.9	13	0	0	-
IAA	747.21	5	0.9	13	0	0	-
Sub-aortic stenosis	746.81	5	0.9	13	0	0	-
Truncus	745.0	3	0.6	14	51	2.5	13
DCRV	746.83	3	0.6	14	0	0	-
HRHS	746.9	3	0.6	14	0	0	-
Tricuspid valve atresia	746.1	3	0.6	14	43	2.1	15
Sinus ASD	745.8	2	0.6	14	0	0	-
Mitral stenosis	746.5	2	0.4	15	33	1.6	18
Ebstein's anomaly	746.2	1	0.4	15	18	0.9	19
Other anomalies of great veins	747.49	1	0.4	15	0	0	-
Other truncus anomaly		0	0	-	3	0.1	20
ASD+VSD		0	0	-	73	3.5	9
Aortic malformations (except COA)		0	0	-	63	3.1	12
Other malformations		0	0	-	179	8.7	5

Pradat presented "endocardial cushion defect" rather than AVSD. TOF included in pulmonary valve anomalies categories

Lastly, we make a comparison with the Stoll et al., (1989) French dataset (table 6.3). The authors report 949 anomalies in 801 children giving 1.2 lesions per case. They found no cases of DORV, BAV, *PA anomalies*, TAPVR, PAPVR, IAA, *sub-aortic stenosis*, *truncus* or DCRV; these were therefore excluded from the ranking. Like Pradat (1992a), Stoll et al., (1989) used the ISC coding system.

PDA is third for both the French and Riyadh datasets, and Ebstein's anomaly is the most rare in both populations. Using the same criteria of plus or minus one, as in the Swedish data, we see that ASDII, VSD, PDA, COA, *AV stenosis*, DILV, *TV atresia* and Ebstein's anomaly are comparable in frequency.

Table 6.3 Rank ordering comparing Stoll's French data to the registry case data

		Riyadh Data			French Data		
Defect or lesion	ICD 9 Code	N	%	Rank	N	%	Rank
ASD II	**745.5**	**122**	**23.0**	**1**	**137**	**14.4**	**2**
VSD	**745.4**	**105**	**19.8**	**2**	**393**	**41.4**	**1**
PDA	**747.0**	**93**	**17.5**	**3**	**73**	**7.7**	**3**
d-TGV and l-TGV	745.10	28	5.3	4	46	4.8	6
AVSD	745.69	20	3.8	5	34	3.6	7
COA	**747.1**	**19**	**3.6**	**6**	**51**	**5.4**	**5**
PV stenosis	746.02	17	3.2	7	71	7.5	4
TOF	745.2	11	2.1	8	23	2.4	11
AV stenosis	**746.3**	**9**	**1.7**	**9**	**33**	**3.5**	**8**
Dextrocardia	746.87	9	1.7	10	11	1.2	13
DILV/Single ventricle	**745.3**	**6**	**1.1**	**11**	**28**	**3.0**	**10**
HLHS	746.7	6	1.1	12	31	3.3	9
Tricuspid valve atresia	**746.1**	**3**	**0.6**	**13**	**14**	**1.5**	**12**
Ebstein's anomaly	**746.2**	**1**	**0.4**	**14**	**4**	**0.4**	**14**

Other Comparisons

Ideally, we would compare the study data with the two Saudi Arabian studies: Becker et al., (2001) and Abbag (1998). Becker et al., (2001) should make a very useful comparison as these data were also abstracted from the Saudi Arabian CHD registry. However, as their results were classified by the predominant lesion – a method for which no evidence exists that it is replicable – the comparison was impossible. We could also not compare these data to Abbag (1998). Firstly his data were hospital-based rather than registry-based and secondly although he does not declare his meta-nosology it is likely that he used the predominant lesion method.

In table 4.8 the Saudi Arabian CHD data for 2001 to 2002 is compared with the Riyadh study data, and EUROCAT data. In the table's orange section we see that for the meta-categories of anomalies of *septa*, *arteries and veins*, *valves* and *chamber*, the frequencies are comparable. All nine datasets have similar distributions, with the exception of NORCAS, Oxford and Wessex which each have one category out of step.

In conclusion, the profile of cases obtained from the registry and used in the case-control study was found to be comparable with other studies despite the differences in case ascertainment and definition.

6.3 Case-control study (Chapter 5) - Summary and discussion of results

With the exception of multiplicity, the distribution of potential risk factors (exposure data) in controls was as expected (table 5.1a-j). With regard to multiplicity, we found only one set of twins among the controls. The prevalence of twins is estimated to be 14 per 1000 in Saudi Arabia (Kurdi et al., 2004) therefore we expected 2 to 3 sets in a sample of 247. Most likely this deficit is an effect of sampling error.

Comparing the crude distributions of potential risk factors, *maternal age* was found to be greater for case infants than for control infants, (as was *maternal parity* and *gravidity*). *Paternal age* was higher for cases than controls, which was not surprising since this is highly correlated with *maternal age*. There were far more ECM in case infants than in control infants. Most often these were Down syndrome cases. Not unexpectedly, we found a low 2 percent of control infants with any ECM. This is due to the selection of controls from a 'Well-Baby Clinic'. For the same reason, there were no cases of Down syndrome in the control population. The prevalence of Down syndrome in the Saudi Arabian population has been estimated at 1.8 per 1000 live births (Niazi et al., 1995), so we would have been unlikely to find any cases in a population of 247 infants even if the source was not a well-baby clinic.

Artificial reproductive therapies were more common in cases than in controls and it took longer to conceive a case than a control. Cases also displayed a higher frequency of reported *vaginal bleeding* lasting more than 1 day, and more *maternal diabetes* than controls. Case mothers reported more *major maternal health problems* with the index pregnancy than the control mothers.

In summary, comparing the distributions of factors in cases and controls to those of other researchers this study population looked reassuringly similar with respect to the criteria of *gestational age*, *birth weight*, *parity*, *gravida*, *paternal age* and ECM (Rosenthal et al., 1991; Tikkanen, Heinonen, 1992; Lian, Zack, Erickson, 1986; Savitz, Schwingl, Keels, 1991; Olshan, Schnitzer, Baird, 1994; Anthony et al., 2002; Kramer et al., 1987; Eskedal et al., 2004).

6.3.1 Consanguinity

This study did not find an association between the independent variable of consanguinity and risk of CHD and thus has not confirmed findings from previous studies which reported an association (Gev et al., 1986; Bassili et al., 2000; Nabulsi et al., 2003; Badaruddoza et al., 2004; Becker et al., 2001). This result is unlikely to be explained by low statistical power since the study has good power to detect a 1.7 times increase in risk or more, should it exist in the population. This study also took considerable care to develop a methodology for collection of consanguinity data. Data collection methods were highly structured and interviewers well-trained, ensuring that data were collected from both cases and controls with equal precision and without bias.

Having said that, it could be that even the phylogram method is flawed. While it captures the relationship of the proband it does not capture the relationships of the proband's parents. Also, while some double and triple relationships were described perhaps not all of them were identified. We do not know that it is reasonable to assume that 5 percent of the control population had a second relationship (data not shown) because the data have not been presented at this level of detail in other studies (table 1.6). The phylogram method would have to be adapted to include such previous relationships. As Bittles et al., (1991) wrote, "Manifestly, when considering the level of inbreeding cited for a population, and especially one with a long tradition of consanguinity, the cumulative depth of inbreeding would be expected to greatly exceed the F value calculated for a single generation." Ideally, a genetic study where DNA could be studied would answer this question more precisely. Currently, however a genetic study is not possible in this population. The Saudi Arabian is suspicious regarding the risks of having their genome studied therefore the phylogram was the only method available (Personal communication, William Greer, Scientist, Biostatistics, Epidemiology and Scientific Computing

Department, KFSH&RC and Brian Meyer, Scientist, Department of Medical Genetics Department, Research Centre, KFSH&RC, 2005).

One primarily methodological study from Kuwait suggests that consanguinity data at the level of third cousins is not reliable (Radovanovic, Shah, Behbehani, 1998). This was a cross-sectional random sample of 25 percent of all Kuwaiti national households which compared an urban area with a rural area. More than 1400 individuals were interviewed with 959 current or previous marriages. These couples provided information about their parental blood relationship in addition to their own marital consanguinity. The authors defined collection of consanguinity data well and used phylograms. The methodological point under investigation was the inter-observer variation after one year. The results showed that there was indeed inter-observer variation-at the level of third cousins. However, they do not explain exactly what is meant about the responses taken in the second interview being "inconsistent". Although inter-rater reliability is scored as if it were a 'test' with right and wrong answers, in this instance we are interested rather in an estimate of bias which would influence the estimate of risk. There is inconsistency to *generation* and inconsistency of *exact* relationship (i.e., the partner is a third cousin (consistent) but the informant does not report that is it the same great-great-grandparents who are the siblings (inconsistent)). The authors explain the uncertainty of the respondents by saying that it has to do with the total number of family members and the authors suggest that a respondent would have to keep track of 2,016 first cousins, first cousins once removed and second cousins; 10,584 second cousins once removed; and 16,464 third cousins taking into consideration large family sizes and the potential for polygamy. The logic in this is unclear because it would seem that one would only keep track of the relatives considered for marriage. A society like Saudi Arabia has familial specialists who have the task of researching this topic before a proposal of marriage is made and therefore individual parents rely on obtaining this information from a recognized informed source (Nyrop, 1977).

Marriage is entered into thoughtfully within Saudi Arabian society which again supports the idea that the phylograms were accurately collected. Marriages are arranged by elders of the family after *considering* the blood relationship if it exists. The proposed marriage is discussed in depth among the relations before the boy visits the girl's house. These factors suggest that the informant knows to whom she is married.

However, if consanguinity studies of CHD are conducted in different populations and they produce results which disagree, they could still all be correct. Consanguinity as a risk factor for a genetic disease can be a different entity for each population since it depends on which genes are contained within the consanguineous group.

In conclusion, it is unlikely that the consanguinity result found here can be explained by methodological limitations in the data collection method; there may be some degree of (non-differential) misclassification, but that is unlikely to explain the result. Using a simple sensitivity analysis, the author has estimated that if the true odds ratio was 2.0, then 50 percent random misclassification in consanguinity would be required in order to produce the finding reported here. This level of misclassification using the phylogram method is highly unlikely. The sensitivity model also predicted that thirty percent misclassification in either the case or the control exposure status (differential misclassification) could also explain a negative result (if the true odds ratio was 2.0) but again this does not seem likely since there is no reason to expect a differential measurement error in this study population.

Potential that SES was a confounder for consanguinity

Another item to consider as an explanation for this result is the presence of uncontrolled confounding. If the study controls were from a lower SES strata, then their rates of consanguinity could have been unnaturally elevated which would have obfuscated the relationship between consanguinity and CHD. We know that consanguinity has been found to be associated with lower SES although these studies were mostly carried out among sub-continent Indian peoples or in other Middle Eastern countries poorer than Saudi Arabia (Shami Grant, Bittles, 1994; Bener et al., 1996; Bittles et al., 2002; Sallam, Mahfouz, Dabbous, 2001; Tamim et al., 2003). The definition of socio-economic status is difficult to validate even in countries such as the UK where efforts are regularly made to quantify this factor (McLaren, Bain, 1998). There may be greater success looking at the individual parts of SES (i.e., *net income, paternal education, maternal education, paternal occupation, maternal occupation*) until a composite can be developed for Saudi Arabia.

One important component of SES is education. Khoury and Massad (1992) found a negative correlation between education (categorized into six levels) and consanguinity in

Jordan. Illiterate males were more likely to marry consanguineously than the next three levels of education. However, university educated males were also likely to marry consanguineously. For females however, the university-educated were more likely not to marry consanguineously. In this Saudi Arabian research, for the ALL CHD analysis we found that a higher proportion of the cases than controls had no education (13% versus 6%) and the levels of income were both poorer and richer among the cases compared to the controls. For confounding to exist, the controls should be from a lower SES, consanguinity should be associated with lower SES and consanguinity should be associated with CHD. We found no evidence for confounding associated with educational level or income, and adjusting for these factors had no effect on the findings, although a discussion of the problems of measuring SES in this society follows in section 6.6.

As a reminder of the difficulties in doing cross-cultural research, the fact that the women covered themselves made it impossible to obtain even a flavour of any disparities between the cases and controls in terms of SES. The advantage of the covering of course (from the perspective of the study) was that the study was blinded from investigator bias using visible clues to SES.

6.3.2 Infant characteristics

Infant's age at interview

The purpose of controlling for this variable, either by design or by analysis, was to protect against information bias where the cases could have a fresher memory of exposures than controls. Despite attempting to control for this factor in the design this was not successful and the factor emerged as a significant predictor of case control status in the analysis, control infants being younger than cases at time of interview. For consanguinity the length of time from birth to interview would be unlikely to be influenced by recall since mothers would know their status regardless. There were few divorces among either the case or control parents and the interviewers were careful to remind the mothers that they were interested in the mother's relationship to the father of the baby included in the study. Use of specific time windows of exposure in the interview schedule may also have reduced the possibility of bias. However there may have been some degree of recall bias resulting from the differential age of the infant at interview. However, even where recall bias may have been present, the tendency would have been for the bias to work against

finding a positive association with disease risk, should it exist (with controls recalling exposure more accurately than cases) rather than finding one spuriously.

Multiplicity

Because of the mechanisms of shared circulation in the womb, the reduced cell mass divided between twins and disturbances of laterality (Burn, 2002), the finding that twins were more at risk for CHD than the singleton birth was expected, well-established and plausible (Doyle et al., 1991; Berg et al., 1989; Hajdu et al., 2006; Caputo et al., 2005; Burn, 2002; Kuehl, Loffredo, 2002; Karatza et al., 2002). We see the increased risk associated with *multiplicity* even after controlling for *maternal age*, moderate to severe *vaginal bleeding*, *maternal use of hair dye*, *house sprayed with pesticides*, *mother's education* and *infant's age at interview*.

Multiplicity and artificial reproductive therapies

Although an association between multiplicity and ART has been found previously, this was not the case here (Kozinszky et al., 2003; Beral et al., 1990). This may be confounded by the fact that some proportion of twins with CHD die *in utero* - the phenomenon of the 'vanishing twin' (Hajdu et al., 2006; Chasen et al., 2006). Also, the numbers exposed were small, hence the analysis had low statistical power.

6.3.3 Maternal characteristics

Maternal age at infant's birth

It was expected that maternal age at infant's birth would be a significant predictor of increased risk of CHD, and this was confirmed here. This factor was also significant in the analysis without the ECM (CARDIAC ONLY) cases as was found by other researchers (Rotherman, Fyler, 1976, McBride et al., 2005; Forrester, Merz, 2004).

Maternal ethnicity

While it is recognized that it is difficult to define the concept of ethnicity, and in this study ethnicity was self-defined by the participants, other researchers may want to pursue this line of inquiry. A difference in consanguinity prevalence by ethnicity was observed (table 5.3). It is difficult to gauge the influence of ethnicity given our current understanding of this factor, although we surmise that it could be related to genetics, to patterns of consanguinity (including tribal affiliations) or lifestyle choices (periods spent in the outdoors, dietary habits and use of traditional medicines).

6.3.4 Paternal characteristics

Father's occupation

Father's occupation was of interest primarily as an indicator of socio-economic status, although there are published reports that paternal occupation has been linked to an increased risk of CHD in the offspring of firemen (Olshan, Teschek, Baird, 1990) and birth defects to the offspring of some agricultural workers (Ronda et al., 2005). The major contributor of risk in this instance could be through connection to the military (via hazardous exposures) and exposure to the petrochemical industry. To date, the results of studies looking at various paternal occupational exposures have not shown an increased risk for CHD (Aschengrau, Monson, 1990; Erickson et al., 1984; Doyle, Maconochie, Ryan, 2006; Oliveira et al., 2002; Bhopal et al., 1999). Of course, these types of studies associating birth defects and generalized exposures are fundamentally difficult to do.

In this study, despite the percentage of missing cases for father's occupation being low (7 cases and 0 controls) the usefulness of the information provided by the mothers was limited. While we expected a high percentage of the fathers to be employed by the military, we expected that the mothers would know what they actually did as a job. Since they did not, the value for understanding socio-economic status diminished. One example is the job of *mutasabib* which some translate as "business man", "broker" or "trader" and some translate as "itinerate worker". The mothers could not or would not describe what was involved in this work therefore it was difficult to assign a SES category. A comparison occupation, *tajr*, will illustrate this problem. The *tajr* too is a "business man" who is an "entrepreneur", "broker" or "trader". Some of my Saudi Arabian colleagues said that the *tajr* was wealthy and the *mutasabib* was poor but there was not complete consensus on this distinction.

6.3.5 Index pregnancy characteristics

Vaginal bleeding

The elevated risk found for vaginal bleeding was intriguing. Islam distinguishes between menstruation (*haidh*), bleeding after child birth (*nifaas*) and any other vaginal bleeding (*istihaada*). There is controversy among scholars regarding the topic of vaginal bleeding with some arguing that during *haidh* women must not pray, have sexual intercourse, fast or even touch the Qur'an but during *nifaas* and *istihaada* they may engage in these activities. Because of the religious rules which apply to the three different types of

vaginal bleeding it is reasonable to assume that Saudi Arabian women would be good informants regarding if and when it occurred.

In the ALL CASES crude analysis, vaginal bleeding was found to be present for more than one day in 11 percent of cases versus 4 percent of controls with an odds ratio of 2.9 (CI $_{95}$=1.3-6.1). After adjustment for multiplicity, mother's ethnicity, ECM, mother's age, maternal use of hair dye and maternal exposure to pesticides it was associated with a borderline contribution with an odds ratio of 2.5 (CI $_{95}$=1.0-6.3) (p=0.06). Vaginal bleeding may be associated with the unknown contribution of the 'vanishing twin' (Saidi, 1988). Up to 29 percent of twin pregnancies include the loss of one foetus (Sampson, de Crespigny, 1992).

Severity of vaginal bleeding

Moderate to severe vaginal bleeding was found to influence the risk of CHD. Other studies which have shown this effect are Loffredo et al., (2000) and Tikkanen, Heinonen, (1992). It is reasonable that this would be a factor since vaginal bleeding may be the body's natural way of sloughing off a foetus with a defect as a very early spontaneous miscarriage. This idea was explored by Anderson (2002) who proposes that the reason why we see more Down syndrome in older mothers may have to do with the body's weakened ability to miscarry rather than increased age of the egg as is more commonly hypothesized.

Diabetes

No control mothers had type 2 diabetes while 7 percent of cases did. Thirteen percent of cases had gestational diabetes versus 12 percent of controls. The treatment of the gestational diabetes for the majority was diet although a large proportion of these mothers also received insulin injections: 4 case mothers and 3 control mothers. This result was surprising since gestational diabetes would not normally be treated with insulin injections (Personal communication, Liam Smeeth, Reader in Clinical Epidemiology, LSHTM, 2006). This raises the concern that when the mothers were asked question number 70 "Have you ever been told that you had diabetes," there may have been miscommunication. When the response was, "Only when pregnant," in the absence of access to medical records we coded this as "gestational diabetes". It is possible that some "gestational" diabetics were truly diabetic. However, the prevalence of gestational

diabetes in Saudi Arabia has been reported to be 12.5 percent (Ardawi et al., 2000). Since we found a prevalence of 12.2 percent in the controls this criticism does not seem likely. Nevertheless, because Saudi Arabian mothers have high fecundity it is possible that they may never have had a chance to be tested for the return to normal glucose levels, the hallmark of the gestational diabetic. Because the test is never completed, the mother's understanding of the diagnosis is that she is "only diabetic when she is pregnant".

The prevalence of diabetes in females of reproductive age is not easy to estimate with precision because most studies include older ages and not necessarily those women who are pregnant or planning pregnancies. In Chapter 1 we reported the figures collected by Warsy and El-Hazmi (1999) that 6 to 7 percent of Saudi Arabian females in the ages of 14-44 can be expected to have type 1 or type II diabetes. Compared to these figures, the findings in this study indicate a low prevalence for both cases and controls. However, the Warsy and El-Hazmi figures may not be relevant to us because they are not from the population of women having babies. Small numbers and sampling error may have also contributed to this finding of fewer diabetics than expected.

After adjustment, diabetes was not found to be a risk factor for CHD in this study. This contradicts the BWIS work although they had the power to look at specific defects (aortic stenosis, ASD, AVSD, bicuspid aortic valve, COA, Ebstein's anomaly, HLHS, laterality and looping defects, left-sided obstructive defects, VSD, outflow tract, TAPVR and TA) (Ferencz et al., 1997) while we did not. We expect that our finding is related to sampling error, and/or possible exposure misclassification whereby the mother did not report her diabetes through ignorance or denial, rather than a true finding against diabetes in adjusted analysis.

6.3.6 Previous pregnancy characteristics

Pregnancy losses of 2 or more

For the EMBRYOLOGICALLY LATEST cases we see that in the larger dataset with 308 observations, a *previous loss of 2 or more pregnancies* is a significant risk factor. It was interesting that *maternal age* was still not significant in the adjusted analysis for EMBRYOLOGICALLY LATEST cases.

Large family size and burden of disease in the population

The total fertility rate for Saudi Arabian women is high at 4 per woman placing it 53rd of 222 nation states (CIA, 2006). In this study, parity ranged from 1 to 12 in the cases and 1 to 13 among the controls. The familial disease burden appeared high as well. In the cases, 14 mothers had had at least one previous child with CHD, two had had a previous child with Down syndrome and 10 had had a child with a major birth defect. In the controls, 12 of the mothers had had at least one child previously with CHD. Three more controls had had a previous child with a major birth defect. These figures appear greater than were reported by Adams, Mulinare, Dooley (1989) and Gill et al., (2003). Gill found a recurrence rate of 2.7 percent in pregnancies following an initial CHD. The analysis on repeat cases and sibling anomalies is not presented in this thesis.

Condition, illness or previous history affecting this pregnancy

While the results of table 5.10 can be better codified using a multivariate regression technique, a combination variable of several variables affecting this pregnancy (see Section 3.14.2, *Major maternal health problems (index pregnancy)*) quickly highlighted the number of case mothers with "warning signs". Sixty-three of 235 (27%) case mothers had a serious condition, illness or previous history which made the result of the CHD infant "non-surprising" albeit tragic. It should also be noticed that these problems were found in 34 of 247 control mothers (14%). Thyroid disease was particularly common in the control mothers (table 5.12). The number of controls with a previous CHD child (10 of 247 or 4%) was striking in its magnitude as it gives a raw prevalence of 40 per 1000.

6.3.7 Environmental factors

Chemical hair dyes

The finding that hair dyes are related to CHD risk is intriguing. Blackmore-Prince et al. (1999) found no association in adjusted analysis between the use of chemical hair straighteners and preterm and low birth-weight babies. Zhu et al. (2006) looked at pregnancy outcomes (specifically congenital malformations) in a population-based cohort study of 550 hairdressers and 3216 shop assistants using data from the Danish National Birth Cohort and did not find a relationship using logistic analysis. However no other published studies have investigated this suspected risk factor.

Chemical hair dye use may be related to age. Do older mothers colour their hair more frequently than younger mothers? In any case, because both *maternal age* and *use of chemical hair dyes* were in the logistic regression model *use of hair-dyes* has been adjusted *for maternal age*. Unfortunately, because of the small numbers involved we could not test if an interaction existed between use of chemical dyes and maternal age. As most of the women covered themselves even during the interview we could not assess even anecdotally the type of hair colouring being used, although the question was in reference to the exposure-window rather than the time of interview.

House sprayed with pesticides

There have been several studies regarding pesticide use in Saudi Arabia (Al-Saleh et al., 2003; Al-Saleh, Al-Doush, Echeverria-Quevedo, 1999; Badawy, 1998) although no studies have looked specifically at exposure to pesticides in the home. Pesticides are used in fairly large quantities to keep the natural population of vermin (particularly cockroaches and rats) controlled. Riyadh has several date groves within the city limits and these especially attract vermin which the human denizens want controlled. The level of education of household workers is low and there is little public health information broadcast about the importance of covering food and work-surfaces when houses are being sprayed with pesticides. The Sanitation Department regularly sends pesticide control vehicles through the streets spraying pesticides – usually in the morning when the streets are empty. Nevertheless, it is not unreasonable to expect that there could be a high exposure to pesticides. Of course, the question asked was specifically about household exposure and generalized spraying would not explain the excess which was identified among case mothers.

Al-Saleh et al., (2003) conducted a cross sectional study comparing breast milk from lactating mothers from Al-Hassa region with breast milk from Riyadh region mothers to test for levels of DDT and its metabolites. They found that - despite the fact that DDT was banned by the government in 1982 - mothers from both the Al-Hassa and Riyadh regions were delivering milk estimated to be much higher in DDT than the FAO/WHO recommended levels. They estimated that 98 percent of infants living in the Riyadh region had DDT daily intakes that exceeded the recommended levels. In another study, Al Saleh, Al-Doush, Echeverria-Quevedo (1999) looked at 50 samples of wheat grains grown locally in seven areas in Saudi Arabia. Although the residual values of pesticides

were well below the maximum residue limit proposed by the FAO/WHO, the exposure to pesticides is likely to be additive. If they are simultaneously sprayed in the house, sprayed in the air and used on the food then this deserves further investigation.

Although Badawy's (1998) study of airborne suspended particulates (ASP) near Mecca is not directly relevant to the question of generalized pesticide exposure to our Riyadh-based mothers, nonetheless his work does highlight some of these mechanisms at work. For example, in Mecca in 1995, to control mosquitoes, cockroaches, houseflies and other insects seven tons of insecticides which included PCB's, organophosphorus and pyrethorid pollutants were used for the Hajj. Human exposure via dermal as well as inhalational routes should be considered in assessing the risk of pesticide exposure. The absorption rate could be aggravated by high temperatures and relative humidity that cause sweating and enhance the deposition of the soluble compounds. These substances can have a synergistic effect associated with the presence of other contaminants. The effect of covering (i.e., with the *abaya* , *niqab* and *hijab*) could be protective or the cloth could absorb the ASP and women could continue breathing the particulates throughout the day. Once in the body, it has been estimated that PCB's take three years to clear (WHO, 1993).

Whether the mother attended Omra[2] and/or Hajj in the window period were not questions that were asked in this study. We therefore do not know whether case mothers visited Mecca within the window period of exposure more than control mothers (and therefore might have been further exposed to pesticides). Mecca is a popular destination for Saudi Arabians throughout the year and this is another area of potential exposure which should be pursued by future researchers.

6.4 Case-control results from analysis using Cardiac cases only

It is well established (Kramer et al., 1987; Eskedal et al., 2004; Ferencz et al., 1989) and it was borne out with these data, that ECM are highly associated with CHD. Most frequently, the anomaly is Down syndrome. In fact, the original study design called for ECM infants to be excluded. However, the thesis upgrading committee suggested that this would be unwise given the time constraints of the thesis, and the fact that it was unclear

[2] Omra - a visit to Mecca similar to Hajj but which can be taken at any time during the year or at any time in a person's lifetime and as often as liked.

how they could be identified prior to interview. Additionally, with only two years of Registry data available there was no stable estimate of the prevalence of ECM. However, at upgrading it was suggested that a second analysis might be conducted without these cases. Fortunately, the power results presented in Chapter 3 supported this sub-analysis.

Additionally, in terms of the primary, independent, variable of consanguinity it was hoped that without the "noise" provided by the ECM cases, the CARDIAC ONLY cases would provide a "cleaner" result. As it turned out, the result was similar, and consanguinity was not found to be a risk factor in this analysis either (table 5.17a).

Other results from the analysis using CARDIAC ONLY cases were also similar to those from the analysis using ALL CASES. *Paternal age* remained significant although a higher proportion of the most elderly fathers were dropped when the *ECM* infants were excluded. The proportion of fathers over 45 years in the ALL CASES analysis was 15 percent versus 11 percent in the CARDIAC ONLY.

6.5 Case-control results from analysis using embryological earliest and latest cases

As described in the introduction, the BWIS Group implemented a meta-nosology from some of the work of Clark (1994, 1990, 1987) which followed embryological/mechanistic principles to group cardiac defects together. This system considers the parallel CHD in an infant and categorizes him/her according to the defect which would have occurred earliest in gestation; any other defects are assumed to be spurious in terms of aetiology. The 54 defects (according to ICD – 9 nosology) are reduced to seven embryological groups (six here, because cardiomyopathies were excluded).

It has been postulated that some cardiac defects (although phenotypically differentiated) are actually different paths arising from an insult or a series of insults. For example, in the category DVOAT, Mesenchymal cell, TOF would be one expression of an insult which occurred on *Day X* of gestation, DORV would be another and Truncus a third (Appendix 4A). Convinced by the elegance of the BWIS meta-nosology (and the fact that a systematic method was necessary to group the patterns of defects for analysis and comparisons to other populations) the Riyadh data were coded into the six relevant groups. However, these groups were small to provide statistical significance. To increase

the numbers the data were collapsed into two parts: EMBRYOLOGICALLY EARLIEST and EMBRYOLOGICALLY LATEST with the remaining 16 percent (the middle categories) not considered at this time. Although there was very little power in the analysis of the "earliest" (with only 44 cases), the full model and forward stepwise regression both suggested that a *major maternal health problem in a previous pregnancy* (3 or more) was associated with CHD. Other risk factors included *other religious, non Ramadan, fasting, house sprayed with pesticides* and *mother's father's occupation* in the military. *Nausea during pregnancy* was protective. The two results that will be discussed further are the *major maternal health problem in a previous pregnancy* (3 or more) and *other religious, non-Ramadan, fasting.*

Major maternal health problem (previous): 3 or more pregnancies

With this set of EMBRYOLOGICALLY EARLIEST cases we expected to see influence due to grave insults during the earliest days of pregnancy. This is the time when miscarriage is most likely. It is estimated that 25 percent of all pregnancies are miscarried, some so early that there is no recognized pregnancy (Regan, Rai, 2000; Wilcox et al., 1988). The finding that a major maternal health problem in three or more previous pregnancies is a risk factor in the EMBRYOLOGICALLY EARLIEST CHD is intuitively appealing (table 5.23e). Those infants who were not miscarried may have been exposed to an insult which resulted in CHD; the insult being the mother's compromised health status from her major health problem.

It is further intriguing that there were no EMBRYOLOGICALLY EARLIEST cases where the mother suffered from a major illness (table 5.23e). This could be an indication that these pregnancies were so compromised that they were naturally aborted or ended in stillbirths which were not registered by the CHD Registry.

Other religious, non-Ramadan, fasting

Given a highly borderline diabetic population, the dramatic shifts in glucose from hypoglycaemic to hyperglycaemic conditions during Ramadan in the critical plus or minus 3 month period of gestation could tip the balance so that the correct metabolism was not maintained, potentially resulting in the same increased risk as is seen in true diabetes. This phenomenon could be exacerbated by obesity. While we did not find this in the overall population, it is possible that a more appropriate analysis would have been to

focus only on those women who experienced Ramadan in the first three months of pregnancy rather than including the whole window period of six months. However, we did observe an increased risk with women reporting *other religious, non-Ramadan, fasting* (for a definition of these days of fasting see Section 1.1.3).

There is a paucity of literature on the possible connection between fasting and negative pregnancy outcomes. The articles to-date have investigated fasting which falls towards the end of pregnancy and sequelae such as reduced foetal breathing movement and accelerated starvation (Prentice et al., 1983; Mirghani et al. 2003). Reduced IQ in children aged 4 to 13 has also been related to fasting at Ramadan (Azizi et al., 2004). But, fasting at the end of pregnancy would not cause structural CHD given that the heart forms early in gestation. The early nutritional status of the mother has been shown to be implicated in other neural crest malfunctions such as the relationship between folic acid and neural tube defects which could be another outcome of the same insult that occurred at *Day X*. The effect on early gestational fasting and pregnancy outcomes should be an area of further research.

If it is true that *other religious, non-Ramadan, fasting* is associated with Wahabi/Salafist Sunni Islam and/or Shi'a Islam (as suggested in Section 1.1.3) it is possible that this is merely another proxy variable for SES. It has been hypothesized that these sects draw a higher proportion of their congregations from economically stressed communities although this too is an area which requires further research by local scholars.

Severity

In analyzing the EMBRYOLOGICALLY EARLIEST cases there was no significant relationship between age at interview and CHD however with the EMBRYOLOGICALLY LATEST cases a difference was found. We hypothesized that this reflected a difference between these two groups: the EMBRYOLOGICALLY EARLIEST cases were more serious and therefore were diagnosed earlier. If they were not interviewed in the first weeks after birth then in this study they were likely to be lost to follow-up (due to death). Unfortunately, this theory was not supported by the data which showed that only fifty to seventy-six percent of the types of CHD (as categorized by the BWIS method) were diagnosed at birth (table 4.2) (diagnosis pre-natally would not reflect severity). Nevertheless, diagnoses at birth may reflect symptomology rather than severity. Some of these defects are "easily" diagnosed

at birth even when the defect itself is not the most serious in terms of treatment possibilities. Although Samanek (1992, 2000) has done some work in this area, using survival as a gross criterion for severity, there remains much more to do. Definitions of CHD severity are, like so many of the other aspects of this work, still being refined.

Other Lost to Follow up

Another type of infant who was "lost to follow up" was the one who turned 4 during the course of the study. If a child was registered at 3 years of age, for example, but it wasn't possible to complete the interview prior to the 4th birthday then that infant was considered "lost" and efforts were stopped to contact that family. However, there were only four of these children who became too old during the course of the study and therefore it would be unlikely that they would have had an effect on the odds ratio.

6.6 Problems with identifying residence and measuring SES

Infant's residence in Riyadh was a requirement for case inclusion. This variable was considered carefully (Appendix 6A). Because of *Shari'a* laws regarding divorce and the residence of offspring it was fortunate that over 99 percent of the mothers were married to the father as the process of collecting the interviews might have been even further complicated.

SES Measurement

As mentioned previously, there is no established method of assessing SES in the Saudi Arabian framework. We tried to develop a composite SES score using the following variables:

- location of house
- household income
- paternal, maternal and mother's father's education
- paternal, maternal and mother's father's occupation
- mother's early SES
- mother's residence from her birth to age 12 years

plus additional variables concerning land ownership and livestock (data not shown). It was thought that income would not be the only criterion by which to define SES, since some government jobs have perquisites such as paid housing and electricity, company

cars, educational allowance for children and other travel allowances that would not be captured in a monthly salary figure. Family and tribal resources also have to be considered. However without support from local experts knowledgeable in the local economic culture (as described below in the section on Father's Occupation) the task of creating an indicator for SES was unachievable.

Nevertheless, we were aware that twice as many infants in the cases came from the wealthiest category of 2500 Saudi riyals or more, per capita (excluding servants) per month. This might possibly indicate bias. Despite KFSH&RC being a referral hospital whose access is freely available to all Saudi Arabian infants suspected of CHD, instead, it may be the wealthier and more educated families who eventually make their way through the system. The study may therefore have suffered from selection bias whereby the cases were from a different socio-economic strata than the controls. This is potentially a limitation of the study method, but we do not think that can explain the main finding of no association of risk with consanguinity (section 6.3.1).

6.7 Missing data

Overall, the dataset was fairly complete with few missing data points (table 5.12). However, there were two important variables that were more difficult to capture than had been anticipated: paternal age and pre-pregnancy weight.

Paternal age

Among the cases there were 7 percent with missing data for *paternal age* and among controls the figure was 11 percent. This reduced the size of the dataset significantly so that the variable *paternal age* could not be tested within the logistic regression. In the pilot study this problem did not appear. One explanation was that the Saudi Arabian identification card was initially thought to be an acceptable source for age (which is how it is routinely collected by the Registry) but it turned out that source is prone to error. In Saudi Arabia research has shown that despite the problems with last-digit preference error (encountered through self-reporting of age) that official documents cannot be relied upon either (Greer, Sandridge, Chehabbedine, 2003; Chasteland, 1970). The father was also not always present at the interview and he would be the one who would carry the Saudi Arabian identification card for the family.

Accepting *paternal age* from *either* the mother *or* from the Saudi Arabian identification card was considered. However, it was decided that this could have lead to bias since there is no evidence that they correspond well – especially for the over-thirty age-group. It was less common to deliver in hospital 30 years ago and therefore the date of birth may not have been recorded. Later, the date of birth for the father would be estimated when it was time for him to obtain travel documents or when the Saudi Arabian identification card was introduced in the 1990's. At the "Well Baby" control hospital we did not expect fathers to be present for the interviews given the nature of the visit. Therefore it was decided that the mother would be asked directly for this information.

It was thought that a population of women of reproductive age (born between 1957 and 1990 for cases and 1960 and 1987 for controls) would know the age of their husband especially after probing to consider the number of years they had been married. There is little evidence of bias in the characteristics of the mothers who did not report *paternal age* (data not shown). Regarding *maternal age at infant's birth*: mothers might deflate their own ages but it would be unusual for the reverse to occur. However, given that we collected a complete pregnancy history it was difficult for them to introduce fabrication.

Pre-pregnancy BMI

Information about pre-pregnancy weight was only obtained from 61 percent of cases and 65 percent of controls. Partly this was due to the question being introduced late in the study. Of the cases with missing data, 33 percent were obese at the time of the interview versus 36 percent of the controls, suggesting that they might also have been overweight prior to this pregnancy. The difficulties which the mothers experienced in estimating their pre-pregnancy weight may be related to their not having a scale at home and / or not being conscious of weight and outward physical appearance given the cultural values placed on chastity and modesty.

In any case, it does not appear that the missing data contributed to bias although it did reduce the statistical power in some of the analyses.

6.8 Other study limitations

Limitations to this work include incomplete case ascertainment and errors in case diagnosis. The CHD Registry may not have yet reached a level of proven stability

although we provided some evidence that it was (Greer et al., 2004). It originated in 1998 and the data used for this present study was abstracted from 2001-2002 – only three years from inception. Registries should be well established with validation procedures in place and surveillance of trends before their data can be considered without reservation.[3] Unlike cancer registration there is no standardized training programme to prepare CHD registrars for their jobs. The Saudi Arabian CHD registrars learned "on the job" how to code defects – under the supervision of a paediatric cardiologist – but to date there is little evidence that paediatric cardiologists know how to code data (work in progress.) The field of birth defects is also a very broad area and the CHD registrars' training focused only on one small aspect (i.e., CHD) despite the fact that they were also asked to code ECM.

The first language of the Registrars was Arabic not English. The patient interviews were conducted in Arabic by research assistants from an Arabic culture. Thus, there is always the possibility that some questions were not fully understood or communicated. However, the close supervision should have minimized this possibility. Some Registrars had never previously held paid employment and most did not choose to become CHD registrars. It is likely that some chose to work because of the benefits involved in working for KFSH&RC rather than the job description. The motivation and ability to "do the job well" probably differs for staff of an entity such as EUROCAT in Europe, staff working for the BWIS in Washington D.C. and staff at the Saudi Arabian CHD Registry.

We have assumed that the CHD Registry is a regional registry, for Riyadh at least. Unfortunately, the evidence for that is only being collected now. The CHD registry now includes the two major cardiac centres in Riyadh: KFSH&RC and the Prince Salmon Cardiac Centre. A comparison of the current data with the next Registry report would therefore be useful.

With respect to the case control results, the results are only generalizable to the live birth population of Riyadh. BWIS made this restriction to live births too. It is likely that the inclusion of stillbirths would have provided a broader variety of cases, and thus have been more representative of the total cases incident in the source population.

[3] The author led the Cancer Surveillance Section, Information and Statistics Division, Scottish Health Service from 1995-1998 and is aware that the data from the earliest 5-10 years were never fully utilized.

While home birth is now rare in Riyadh (Molina and Sandridge, 2000; Khoja and Farid, 2000) we may have lost cases in early neo-natal deaths who were not reported to the registry. This would have introduced bias if these early losses were more frequently to consanguineous families. The measure of effect would have been biased downwards. At present, we have no way of estimating whether such a selection bias exists. Additionally, we are aware that only 80 percent of the eligible, registered population were interviewed. Of the 20 percent who were not interviewed we only know the outcome for 4 percent (neo-natal death).

Selection bias among the controls is an important issue to consider when interpreting the results of any case-control study. Because only one well-baby clinic was chosen as a source of the controls for this study, it is possible that the cases and the controls did not come from one underlying population; the controls may have come from a unique sub-section of the greater Riyadh population. We know, for example, that the control fathers were mainly drawn from the military (90%); since the hospital from which they were selected was initially designed for members of the Armed Forces this is not surprising.[4] However since the schema of hospitals being associated with professions was initiated over 25 years ago there has been a substantial mixing of boundaries including the concept of "health care shopping". This emphasis on comparing hospitals, and seeking the best care (and the best prognosis) is particularly apparent in the case of life threatening illnesses among children (Unpublished communication, M. Al Jufan, Paediatric Cardiologist, King Faisal Heart Institute, 2004). Nonetheless, the large number of fathers who were in the military among the controls versus the smaller number among the cases (34%) remains cause for concern. On the other hand, the military is the largest single employer in Saudi Arabia (Nyrop, 1977). One means of addressing this issue was by comparing the *hiy'* of residence for cases and controls as discussed in Appendix 6A and this showed that cases and controls came from all sections of the city.[5] Another analysis which could be done would be to look at the average income reported by *hiy'*.

[4] Riyadh Armed Forces Hospital was originally designed for members of the military as King Faisal Specialist Hospital was designed for members of the Royal Family, Security Forces was designed for employees of the Ministry of Interior and King Fahd National Guard was designed for employees of the National Guard. Shamasi Hospital was designed to care for persons not associated with one of these four groups. Other private hospitals have been built in Riyadh since the 1980's including Al Yamamah, Dallah, Kingdom and Al Meshari.

[5] These data could be explored further using a GIS a map of the city.

In conclusion, while there is some evidence that the controls were representative of the general population of Riyadh infants this has not been definitively proven. If the controls could have been selected randomly from all births we would have more assurance that they were representative of the general population.

Could selection bias in the controls explain the results this study has found? The primary aim of the study was to investigate the association between consanguinity and risk of CHD. Since we did not find an association, we would need to postulate that the controls had a higher prevalence of consanguinity than that in the general population (ie that the controls were biased with respect to this primary exposure). In fact we have some evidence against this hypothesis since the level of consanguinity in the controls was similar to that found in previous studies (49%) (Table 1.6).

Another concern is the actual selection of the controls, given that a strict random selection could not be enforced. During data collection it was noted that the gravidity of the case mothers was higher than that of the control mothers. It is possible that the research assistant pre-selected controls who she thought would be less likely to have had complicated pregnancy histories. She might have done this by choosing a chart from the stack that was obviously brand new. However, this would not have influenced consanguinity status.

With regard to exposure measurement, some data were validated as described in the methods section, but it was not possible to check all reported exposures. The absence of validation of reported exposure to *house sprayed with pesticides*, *maternal use of chemical hair dyes* and *length of fasting*, especially where the exposure was intended to be *within the six month window,* is a recognised limitation. However, it is likely that any misclassification, if present, would have been non-differential, which would have biased the odds ratio towards unity. By itself, this cannot explain the reported findings for these factors. However, it was also shown that control mothers had a stronger belief that environmental toxins could be responsible for birth defects (table 5.1j). The results implicating *pesticides*, *chemical hair dyes* and *fasting* should therefore be considered cautiously until replicated.[6]

[6] Although, it is unlikely that either Saudi case mothers or control mothers would associate hair-dye use with environmental toxins.

The ± 3 months exposure-window surrounding conception was chosen in order to follow the methodology of Ferencz and colleagues. The three months following conception are the period in which the mother's exposure to teratogens are most likely to cause harm to the developing foetus. The three month window prior to pregnancy is more difficult to justify. It is used for two reasons. Firstly, it is believed that conception itself is not well marked and what a woman was exposing herself to at *that moment* would not be well-remembered. Therefore, giving a woman a range of time should increase the chances of obtaining accurate data. Research into the problem of conception and pregnancy related recall bias is fraught (Rockenbauer et al., 2001; Werler et al., 1989; Werler, Mitchell, Shapiro, 1989; Zieler, Rothman, 1985) for even basic indicators such as birth weight (Sanderson et al.,1998). Secondly (as has been suggested with the reduction of spina bifida in mothers who take folic acid pre-conceptionally), the weeks and months leading up to pregnancy dictate the chemical milieu in which gestation begins and therefore are crucial when trying to understand birth defects (Smithells et al., 1980; Berry et al., 1999; Czeizel, Dudas, 1992; MRC Vitamin Study Research Group, 1991).

One further limitation of this study is that although a number of fathers were involved in the military it was impossible to categorize precisely their occupation and therefore their exposure to toxic substances may have been missed. In fact, many of the responses regarding the paternal influences (age, occupation, education, smoking history) have uncertainty associated with them as they were obtained through the proxy of the mother.[7]

As an indicator of socio-economic status, paternal employment was to be complemented by the collection of data on mother's father's occupation. One of the hypotheses of the *Aberdeen Children of the 1950s* cohort study was that it would be the SES the mother experienced as a child that would determine her long term health risks rather than her SES as an adult (Unpublished communication, Susan Morton, PhD candidate, Non-communicable Disease Epidemiology, LSHTM, 2003).

[7] Although there is no evidence that this uncertainty would have been differential between cases and controls.

There may have been tribal affiliations underlying the consanguineous relations that escaped notice. For example, within the consanguineous group there theoretically could have been a cluster within a tribe that was not identified using this methodology.

There were missing data for some of the key variables of interest such as maternal pre-pregnancy weight and paternal age as described in Section 6.7. Also, despite efforts to ensure good statistical power, some results were unstable with wide confidence limits. This was especially true for the EMBRYOLOGICALLY EARLIEST analysis. Even though the overall study was well-powered there were still opportunities for type I errors. Additionally, given the number of odds ratios calculated and the size of the dataset it is possible that some of the positive results were spurious (multiple testing). Although, because the majority of hypotheses were established *a priori* this is unlikely. Furthermore, although the statistical power was sufficient for the majority of analyses which were conducted, there was not enough power to consider all potential interactions.

6.9 Strengths of study

This study has numerous strengths. The consanguinity prevalence found in the controls was similar to that reported in the previous literature (Khoja, Farid, 2000; Al Husain, Al Bunyan, 1997; El Hazmi et al., 1995), indicating that the controls were likely to be representative of the background population. This study is also the only one of its kind in this unique Middle Eastern population. The population is unique because of the high frequency of well documented consanguineous marriages. The *phylogram* methodology which was used to assess consanguinity is painstaking in its thoroughness. The population is understudied and interesting because the use of controversial substances such as street drugs, alcohol and tobacco are at a minimum especially among the pregnant population normally resident in Riyadh.

Women in Riyadh generally work in non hazardous occupations - such as teaching or the health care industry. Their participation in household "Do it Yourself" activities (e.g., painting the interior walls or the baby's crib) is not common therefore exposure to heavy metals and other toxic substances is unlikely. High parity, young and mature maternal ages and religious fasting practices are also unique to this region but with migrations from East to West these factors may soon be more commonly found in the UK which makes

this study of some interest to the UK scientific community. Finally, the self-determined distinction between Bedouin and urban makes this study exceptional in its scope.

Validation of the phylograms was available for nearly 100 percent of the cases (data not shown), but only 2 minor errors were discovered. Other items were validated using the patient's medical records or the CHD registry (sex of the infant, maternal age, history of maternal diabetes, maternal epilepsy, maternal thyroid conditions, extra-cardiac malformations in the infant, age of diagnosis of the infant, and place of residence). Obtaining accurate responses to other exposures such as kohl and nausea medications were assisted through the use of samples.

Because the population of cases and controls are naïve in that they are unlikely to have participated in many research studies and do not live in the same "media savvy" culture of the West it is unlikely that the responses of the cases would have been differentially biased through feelings of guilt and/or shame at having a child with a birth defect. This is coupled with the fatalistic nature of Islam. Islam is a religion that does not accept feelings of guilt or personal responsibility in the face of a child with a birth defect: all is the will of Allah. The mothers do not look for blame, and thus responses to questions about exposure to possible hazards are unlikely to be biased according to case or control status.

The study was well-powered, with the response rate for cases approaching 99 percent and for controls almost 94 percent. Only newly registered, incident cases were used. Although recall of past exposure is always a problem in case-control studies, the fact that 63 percent of the case mothers and 79 percent of the control mothers were interviewed within 1 year of the infant's birth, minimizes the problem of recall of exposures within the window around conception.

For cases it was simple, through use of the registry's family number (Section 3.3.1) and careful exploration by the research assistant, to protect against a second affected child in the family being included in the study. This ensured independence of measurement. Theoretically, however, there could have been more distantly related relatives who were unaware of one another's condition. Similarly, in the design only one infant per control family was included.

There were little missing data for many of the variables including: detailed consanguinity, maternal characteristics, index pregnancy characteristics (with the exception of estimated pre-pregnancy BMI), previous pregnancy characteristics, fasting and environmental exposures. The study was meticulously conducted with frequent observation by the P.I., regular coding of the interviews, rapid first entry of the data, double-data entry and easy access to co-investigators for medical questions concerning obstetric, paediatric and cardiology matters arising.

Lastly, this study provided an opportunity to use data from an important Registry (the Saudi Arabian CHD Registry) and to compare these data to two world class efforts (EUROCAT and the BWIS). Despite the publication of the BWIS study ten years ago, few researchers have implemented their useful method of classification and still rely on "quick and dirty" alternatives such as "predominant lesion". Similarly, the wealth of the EUROCAT data has not yet been exploited to its full potential.

CHAPTER 7 Conclusions and Recommendations

Conclusions

As outlined in the Aims and Objectives, this study achieved its purpose. The type of, and risk factors for congenital heart defects in a population of Saudi Arabian infants were successfully investigated. To accomplish these aims a thorough understanding of the classification systems of congenital heart defects was achieved. The differences between the defects were understood, from a descriptive vantage; the methods of defining them were investigated; and the methods of grouping them were distinguished. Extra-cardiac malformations had to be understood to some extent as well. The literature on prevalence of CHD was reviewed so that an understanding could be developed for the seriousness of the disease and also to understand that there is variation throughout the world. It is tempting to conclude that this variation is a reflection of the inconsistency in the definitions of the defects and the methods of grouping them. However, it is also recognized that there are other factors not studied in this thesis that are at play and these include varying ability to diagnose cases and resources to count them.

Secondly, the literature on risk factors for CHD was reviewed. It was found that the research conducted to date in the field of CHD while copious, is muddled. There has been little consensus on how to define cases or how to present the data. Therefore, few studies are comparable. Partly this is of course the fault of journals who do not demand higher standards for the reporting of study methods. Many studies were under powered and many appeared to be opportunistic: a hospital-based pediatric cardiology clinic collects 8 years worth of data and publishes it as being from a "registry". The definition of a registry is very specific and should remain so: it should be population based and include all cases of a disease collected for the purposes of surveillance and research studies.

Despite the limitations of the CHD risk factor literature it did suggest hypotheses that were of interest and the case-control study could be designed. Given that this study was to be conducted in Saudi Arabia the author drew on her years of experience living in that culture to shape the questionnaire to make it appropriate for general and specific use. Culture specific questions included those on consanguinity, traditional medicines,

traditional cosmetics, religious fasting, ethnicity and socio-economic status. Although not all the culture specific risk factors investigated proved to be indicative of risk this effort was a pilot study for future work.

Thirdly, with respect to consanguinity a review of the literature was conducted to understand its prevalence and the nature of the risk estimated. From this review it was concluded that the evidence does not warrant public health measures warning against this practice for the general public in the absence of specific familial evidence to the contrary – such as deafness, thalessemia, sickle cell anemia, inborn errors of metabolism, or recurrent CHD in the extended family. These disorders are known to be, or likely to be, single gene disorders.

Fourthly, the review of the literature on consanguinity revealed that much of it has been hampered by data that was collected using a hard coded method rather than a phylogram. Data on consanguinity is likely to be invalid if not obtained by native speaking, local staff who have been trained in collection methods.

Fifthly, as the study was implemented in a developing area attention had to be paid to its management. Careful attention to research methods is vital. Training sessions must be held with staff members. The more the research assistants understand about the study the better they will collect the data. Logs must document case ascertainment and study refusals. Reports should be sent to all co-investigators to keep them up to date. Where coding is required documentation must be kept so that consistency can be maintained. We found that research could be successfully conducted with the CHD Registry staff based at King Faisal Specialist Hospital and Research Centre and the Riyadh Al Kharj Armed Forces Hospital with adequate research resources. Tools that were used in this endeavor included epidemiological skills and reasoning, data management techniques, and the use of software: primarily EXCEL (for the log), SPSS, JMP and STATA.

Sixthly, this study reported cases from the Riyadh registry which had comparable distributions to two other large efforts: the BWIS and the EUROCAT system indicating that these two methods of analyzing CHD cases are useful. More standardization by other investigators would improve this field and make it easier to draw conclusions. We should all be using the BWIS and EUROCAT datasets for comparison purposes.

Lastly, we found no evidence that consanguinity is a risk factor for CHD in this population. Despite the limitations of the study we would have had to have had substantial misclassification bias to obtain the results that we did for the ALL CHD and for the CARDIAC ONLY analyses. The study did confirm previously reported associations with increased risk: maternal age and extra-cardiac malformations.

Recommendations

1. An international web-based registry specializing in congenital heart defects should be established. International centres should be developed which have staff to abstract CHD cases for their area and maintain their details centrally. Access to the data should be available freely upon written request. EUROCAT and The Clearinghouse are steps towards this. These efforts need to be supported and the data from them needs to be used.
2. Systematic coding to ICD 9 or ICD 10 for CHD and extra-cardiac malformations and presentation of the results in this format should be the requirement for all journals. Using established coding systems will standardize a research area that is currently ambiguous and full of maverick researchers. Similarly, journal editors must require more detail from authors. If ALL CHD is to be analyzed then the readers should be informed of the make up of the CHD and the types of parallel defects seen. If prevalent cases are included rather than restricting to incident cases the discussion must include statements about how the results would be affected through differential survival for different types of CHD.
3. The embryological meta-nosology is an excellent method for data presentation. It makes intuitive sense and the BWIS and this study have shown that with it interesting results are obtained. Only through time will we see if these results hold up to scrutiny and actually contribute to the knowledge bank regarding CHD. Some other meta-nosologies must either be codified by their proponents (such as the "predominant" lesion method) or discarded.
4. The lesion analysis method, for parallel CHD, needs further scrutiny. For example, are functional defects counted? Clear guidelines should be developed by paediatric cardiologists as to how to code CHD. As in cancer registration, registrars responsible for CHD coding should have access to standard materials.

5. A national population based case-control study should be conducted in Saudi Arabia following the methodology of the BWIS as closely as possible. This study will have a sample size large enough to answer the questions raised in this study: is pesticide exposure a risk factor for CHD?; what is the role of toxic exposures such as chemical hair colouring?; do the mothers of embryologically early cases fast significantly more during the crucial early days of pregnancy?
6. Attention must be paid to the development of the infrastructure for research in Saudi Arabia. Data management is learned by experience and therefore trained field epidemiologists should be recruited, from countries with established research departments and Schools of Public Health to train local personal in the conduct of research studies. The development of the infrastructure could include investigative studies into areas which need further research such as defining the various ethnicities (Bedouin and Urban; Nejd and Hijazi); further research into tribal organization; and development of a socio-economic indicator.

REFERENCES

Abbag F (1998). Pattern of congenital heart disease in the Southwestern region of Saudi Arabia. Ann Saudi Med 18(5): 393-395.

Abdallah H (1999). http://www.thic.com/hyporight.htm last accessed August 12, 2006. The Heart Institute for Children.

Abdulrazzaq YM, Bener A, Al-Gazali LI, Al-Khayat AI, Micallef R, Gaber T (1997). A study of possible deleterious effects of consanguinity. Clinical Genetics 51: 167-173.

Abu-Harb M, Hey E, Wren C (1994). Death in infancy from unrecognised congenital heart disease. Arch Disease Child 71: 3-7.

Abu-Rezq HAS, Al-Tarkait AAH, Husien NIK, Qasrawi B, Radovanovic Z (1995). Multihandicap and consanguinity in Kuwait: a case-control study (letter). Ann Saudi Med 15(2): 189-91.

Abushaban L, Al-Hay A, Uthaman B, Salama A, Selvan J (2004). Impact of the Gulf war on congenital heart diseases in Kuwait. Int J Cardiol 93: 157-162.

Adams MM, Mulinare J, Dooley K (1989). Risk factors for conotruncal cardiac defects in Atlanta. J Am Coll Cardiol 14(2): 432-42.

Afzal M (1988). Consequences of Consanguinity on Cognitive Behavior. Behavior Genetics 18(5): 583-594.

Agrawal N, Sinha SN, Jensen AR (1984). Effects of Inbreeding on Raven Matrices. Behavior Genetics 14(6): 579-585.

Al Khabori M (2004). Causes of severe to profound deafness in Omani paediatric population. J Ped Otorhinolaryngology 68: 1307-1313.

Alabdulgader AAA (2001). Congenital heart disease in 740 subjects: epidemiological aspects. Ann Trop Paed 21: 111-118.

Al-Abdulkareem AA, Ballal S (1998). Consanguineous marriage in an urban area of Saudi Arabia: rates and adverse health effects on the offspring. J Community Health 23(1):75-83.

Al-Awadi SA, Naguib KK, Moussa MA, Farag TI, Teebi AS, El-Khalifa MY (1986). The effect of consanguineous marriages on reproductive wastage. Clinical Genetics 29: 384-388.

Alfi OS, [El-Alfi OS], Shaker YK, Shaath R, Salam TA (1968). Congenital Malformations in Kuwait. J Kwt Med Assoc 2: 99-108.

Alfi OS, Chang R, Azen SP (1980). Evidence for genetic control of nondisjunction in man. Am J Human Genetics 32: 477-483.

Al-Gazali LI, Bener A, Abdulrazzaq YM, R. Micallef, Al-Khayat AI, Gaber T (1997). Consanguineous marriages in the United Arab Emirates. J Biosoc Sci 29: 491-497.

Al-Gazali LI, Dawodu HA, Sabarinathan K, Varghese M (1995). The profile of major congenital abnormalities in the United Arab Emirates (UAE) population. J Med Genetics 32: 7-13.

Al-Husain M, Al-Bunyan M (1997). Consanguineous marriages in a Saudi population and the effect of inbreeding on prenatal and postnatal mortality. Ann Trop Paed 17: 155-160.

Al-Saleh I, Al-Doush I, Echeverria-Quevedo A (1999). Residues of pesticides in grains locally grown in Saudi Arabia. Bull Environ Contam Toxicol 63: 451-9.

Al-Saleh IA, Shinwari N, Basile P, El-Doush I, Al-Zahrani M, Al-Shanshoury M, Mohammed GE (2003). DDT and its metabolites in breast milk from two regions in Saudi Arabia. J Occup Environ Med 45: 410-427.

Al-Salem M, Rawashdeh N (1993). Consanguinity in North Jordan: Prevalence and Pattern. J Biosoc Sci 25: 553-556.

Alzamora V, Rotta A, Battilana G, Abugattas R, Rubio C, Bouroncle J, Zapata C, Santa-Maria E, Binder T, Subiria R, Paredes D, Pando B, Graham GG (1953). On the possible influences of great altitudes on the determination of certain cardiovascular anomalies. Pediatrics 12: 259-62.

Anderson RH, Baker EJ, Macartney FJ, Rigby ML, Shinebourne EA, Tynan M (2002). Paediatric cardiology.

Anokute CC (1992). Suspected synergism between consanguinity and familial aggregation in Type 2 Diabetes Mellitus in Saudi Arabia. J Roy Soc Health.

Anthony S, Buitendijk SE, Dorrepaal CA, Lindner K, Braat DDM, den Ouden AL (2002). Congenital malformations in 4224 children conceived after IVF. Human Repro 17(8): 2089-2095.

Araneta MR, Schlangen KM, Edmonds LD, Destiche DA, Merz RD, Hobbs CA, Flood TJ, Harris JA, Krishnamurti D, Gray GC (2003). Prevalence of birth defects among infants of Gulf War veterans in Arkansas, Arizona, California, Georgia, Hawaii, and Iowa, 1989-1993. Birth Defects Res A Clin Mol Teratol 67: 246-260.

Ardawi MSM, Nasrat HA, Jamal HS, Al-Sagaaf HM, Mustafa BE (2000). Screening for gestational diabetes mellitus in pregnant females. Saudi Med J 21(2): 155-160.

Aschengrau A, Monson RR (1990). Paternal military service in Vietnam and the risk of late adverse pregnancy outcomes. Am J Public Health 80: 1218-1224.

Aslam M, Wilson JV (1992). Medicines, health and the fast of Ramadan. J Roy Soc Health: 135-136.

Azizi F, Sadeghipour H, Siahkolah B, Rezaei-Ghaleh N (2004). Intellectual development of children born of mothers who fasted in Ramadan during pregnancy. Int J Vita Nutr Res 74: 374-380.

Badaruddoza, Afzal M, Akhtaruzzaman (1994). Inbreeding and congenital heart diseases in a North Indian population. Clinical Genetics 45: 288-291.

Badawy MI (1998). Organic insecticides in airborne suspended particulates. Bull Environ Contam Toxicol 60: 693-701.

Bagley SC, White H, Golomb BA (2001). Logistic regression in the medical literature: standards for use and reporting, with particular attention to one medical domain. J Clin Epi 54: 979-985.

Balarajan R, Soni Raleigh V, Botting B (1989). Sudden infant death syndrome and postneonatal mortality in immigrants in England and Wales. BMJ 298: 716-720.

Bannerman CH, Mahalu W (1998). Congenital heart disease in Zimbabwean children. Ann Trop Paed 18: 5-12.

Barth F (1953). Principles of social organization in Southern Kurdistan. Universitetets Etnografiske Museum Bulletin n. 7, Oslo, cited in Murphy and Kasdan, 1959.

Basaran N, Hassa H, Basaran A, Artan S, Stevenson JD, Sayli BS (1989). The effect of consanguinity on the reproductive wastage in the Turkish population. Clinical Genetics 36: 168-173.

Bashi J (1977). Effects of inbreeding on cognitive performance. Nature 266: 440-442.

Bassili A, Mokhtar SA, Dabous NI, Zaher SR, Mokhtar MM, Zaki A (2000). Risk factors for congenital heart diseases in Alexandria, Egypt. Eur J Epi 16: 805-814.

BBC News (2004). Laws on forced marriages pondered. http://news.bbc.co.uk/1/hi/uk/3956399.stm October 24. Last accessed August 13, 2006.

Becerra JE, Khoury MJ, Cordero JF, Erickson JD (1990). Diabetes mellitus during pregnancy and the risks for specific birth defects: a population-based case-control study. Pediatrics 85(1): 1-9.

Becker S, Al Halees Z (1999). First-cousin matings and congenital heart disease in Saudi Arabia. Comm Genetics 2: 69-73.

Becker SM, Al Halees Z, Molina C, Paterson RM (2001). Consanguinity and congenital heart disease in Saudi Arabia. Am J Med Genetics 99: 8-13.

Ben Arab S, Masmoudi S, Beltaief N, Hachicha S, Ayadi H (2004). Consanguinity and endogamy in Northern Tunisia and its impact on non-syndromic deafness. Genetic Epi 27: 74-79.

Bener A, Abdulrazzaq YM, Al-Gazali LI, Micallef R, al-Khayat AI, Gaber T (1996). Consanguinity and associated socio-demographic factors in the United Arab Emirates. Hum Heredity 46: 256-64.

Bener A, Alali KA (2006). Consanguineous marriage in a newly developed country: the Qatari population. J Biosoc Sci 38: 239-46.

Bener A, Hussain R (2006). Consanguineous unions and child health in the State of Qatar. Paediatr Perinat Epidemiol 20(5):372-8.

Bener A, El Hakeem AAM, Abdulhadi K (2005). Is there any association between consanguinity and hearing loss? Int J Pediatric Otorhinolaryngology 69: 327-333.

Beral V, Doyle P (1990). Births in Great Britain resulting from assisted conception, 1978-87. BMJ 300: 1229-33.

Berg KA, Astemborski JA, Boughman JA, Ferencz C (1989). Congenital cardiovascular malformations in twins and triplets from a population-based study. Am J Dis Child 143: 1461-1463.

Bhopal RS, Tate JA, Foy C, Moffatt S, Phillimore PR (1999). Residential proximity to industry and adverse birth outcomes. Lancet 9182: 920-1.

Bitar FF, Baltaji N, Dbaibo G, El-Jawad MA, Yunis KA, Obeid M (1999). Congenital heart disease at a tertiary care center in Lebanon. Middle East J Anesthes 15(2): 159-164.

Bittles AH (1994). The Role and Significance of Consanguinity as a Demographic Variable. Pop Dev Review 20(3): 561-584.

Bittles AH (1998). Empirical estimates of the global prevalence of consanguineous marriage in contemporary societies, Paper number 0074, Centre for Human Genetics, Edith Cowan University, Perth, Western Australia.

Bittles AH, Grant JC, Shami SA (1993). Consanguinity as a Determinant of Reproductive Behaviour and Mortality in Pakistan. Int J Epi 22(3): 463-467.

Bittles AH, Mason WM, Greene J, Appaji Rao N (1991). Reproductive behavior and health in consanguineous marriages. Science 252: 789-794.

Bittles AH, Savithri HS, Appaji Rao N (2002). Community genetics in developing countries. Comm Genetics 5: 151-2.

Bizarro RO, Callahan JA, Feldt RH, Kurland LT, Gordon H, Brandenburg RO (1970). Familial atrial septal defect with prolonged atrioventricular conduction: a syndrome showing the autosomal dominant pattern of inheritance. Circulation 41: 677-683.

Black S, Sandridge AL (2001). Congenital Heart Disease Registry, Third Annual Report, Riyadh, KFSH &RC.

Blackmore-Prince C, Harlow SD, Gargiullo P, Lee MA, Savitz DA (1999). Chemical hair treatments and adverse pregnancy outcome among black women in central North Carolina. Am J Epi 149(8): 712-716.

Boneva RS, Moore CA, Botto L, Wong LY, Erickson JD (1999). Nausea during pregnancy and congenital heart defects: a population-based case-control study. Am J Epi 149(8): 717-725.

Botto L, Correa A, Erickson JD (2001). Racial and temporal variations in the prevalence of heart defects. Pediatrics 107(3): E32.

Botto LD, Khoury MJ, Mulinare J, Erickson JD (1996). Periconceptional multivitamin use and the occurrence of conotruncal heart defects: results from a population-based, case-control study. Pediatrics 98(5): 911-917.

Botto LD, Loffredo C, Scanlon KS, Ferencz C, Khoury MJ, Wilson PD, Correa A (2001). Vitamin A and cardiac outflow tract defects. Epi 12(5): 491-496.

Botto LD, Lynberg MC, Erickson JD (2001). Congenital heart defects, maternal febrile illness, and multivitamin use: a population-based study. Epi 12(5): 485-490.

Botto LD, Mulinare J, Erickson JD (2000). Occurrence of congenital heart defects in relation to maternal multivitamin use. Am J Epi 151(9): 878-84.

Bove FJ, Fulcomer MC, Klotz JB, Esmart J, Dufficy EM, Savrin JE (1995). Public drinking water contamination and birth outcomes. Am J Epi 141(9): 850-62.

Bundey S, Alam H (1993). A five-year prospective study of the health of children in different ethnic groups, with particular reference to the effect of inbreeding. Eur J Hum Genetics 1: 206-219.

Burn J (2002). The aetiology of congenital heart disease. Paediatric Cardiology. Anderson RH, Baker EJ, Macartney FJ et al. London, Churchill Livingstone. 1: 141-213.

Caputo S, Russo MG, Capozzi G, Morelli C, Ariento P, DiSalvo G, Sarubbi B, Santoro G, Pacileo G, Calabro R (2005). Congenital heart disease in a population of dizygotic twins: an echocardiographic study. Int J Cardiol 102:293-6.

Cedergren MI, Selbing AJ, Kallen BAJ (2002a). Risk factors for cardiovascular malformation - a study based on prospectively collected data. Scand J Work Environ Health 28(1): 12-17.

Cedergren M, Selbing A, Kallen B (2002b). Geographic variations in possible risk factors for severe cardiac malformations. Acta Paediatr 91: 222-228.

Centers for Disease Control (CDC) (1998). Diabetes during pregnancy - United States, 1993-1995. MMWR (Morb Mortal Wkly Rep) 47: 408-14.

Centers for Disease Control (CDC) (2001). State birth defects surveillance programs directory. Teratology 64 (Supp): S47-S116.

Central Intelligence Agency (2006). The CIA World Factbook, Office of Public Affairs, Washington, DC, USA, last updated 14 June 2006.

Chaleby K, Tuma TA (1987). Cousin marriages and schizophrenia in Saudi Arabia. J Psych 150: 547-549.

Chasen ST, Perni SC, Predanic M, Kalish RB, Chervenak FA (2006). Does a vanishing twin affect first-trimester biochemistry in Down syndrome risk assessment? Am J Obstet Gynecol 1: 236-9.

Chasteland JC (1970). Problems of demographic data collecting in Arab countries of the Middle East. Egypt Pop Fam Plan Rev, in French 3: 29-40.

Cheng TO (1984). Prevalence of cardiovascular diseases among the national minorities of China. Ann Int Med 101: 562-563.

Chin AJ. (2006). Interrupted Aortic Arch, http://www.emedicine.com/ped/topic2515.htm, last accessed September 6, 2006.

Chitty LS, Winter RM (1989). Perinatal mortality in different ethnic groups. Arch Disease Child 64: 1036-41.

Clark EB (1987). Mechanisms in the pathogenesis of congenital heart defects The genetics of cardiovascular disease. Pierpont ME and M. J. (eds). Boston: 3-11.

Clark EB (1990). Growth, Morphogenesis, and Function: The Dynamics of Cardiac Development. Fetal, neonatal and infant cardiac disease. James H. Moller and William A. Neal. Norwalk, Connecticut, Appleton & Lange.

Cohen EN, Brown BW, Bruce D, Cascorbi HF, Corbett TH, Jones TW, Whitcher CE (1974). Occupational disease among operating room personnel. Anesthesiology 41(4): 321-340.

Cook R, Hanslip A (1966). Mortality among offspring of consanguineous marriage in a rural area of East Jordan. J Trop Ped March: 95-99.

Cordier S, Bergeret A, Goujard J, Ha MC, Ayme S, Bianchi F, Calzolari E, De Walle HEK, Knill-Jones R, Candela S, Dale I, Dananche B, de Vigan C, Fevotte J, Kiel G, Mandereau L, for the Occupational Exposure and Congenital Malformations Working Group (1997). Congenital malformations and maternal occupational exposure to glycol ethers. Epi 8(4): 355-363.

Correa-Villasenor A, David Wilson P, Loffredo CA, Ferencz C and R. JD (1993). Risk Factor Analysis. Epidemiology of Congenital Heart Disease. R. J. Ferencz C, Loffredo CA, Magee CA. Armonk NY, Futura. 4: 233-247.

Correa-Villasenor A, Ferencz C, Boughman JA, Neill CA and BWIS Group (1991a). Total anomalous pulmonary venous return: familial and environmental factors. Teratology 44: 415-428.

Correa-Villasenor A, McCarter R, Downing J, Ferencz C and BWIS Group (1991b). White-black differences in cardiovascular malformations in infancy and socioeconomic factors. Am J Epi 134(4): 393-402.

Denic S, Bener A, Sabri S, Khatib F, Milenkovic J (2005). Parental consanguinity and risk of breast cancer: a population-based case-control study. Med Sci Monitor 11: CR415-9. Epub 2005 Aug 26.

Dickinson DF, Arnold R, Wilkinson JL (1981). Congenital heart disease among 160 480 liveborn children in Liverpool 1960 to 1969. Br Heart J 46: 55-62.

Dorsten LE, Hotchkiss L, King TM (1999). The effect of inbreeding on early childhood mortality: twelve generations of an Amish settlement. Demography 36(2): 263-271.

Doyle P, Maconochie N, Ryan M (2006). Reproductive health of Gulf War veterans. Phil Trans R. Soc B 361: 571-584.

Doyle PE, Beral V, Botting B, Wale CJ (1991). Congenital malformations in twins in England and Wales. J Epi Comm Health 45: 43-8.

Dronamraju KR, Meera Khan P (1963). The frequency and effects of consanguineous marriages in Andhra Pradesh. J Genetics 58: 387-401.

Durkin MS, Khan NZ, Davidson LL, Huq S, Munir S, Rasul E, Zaman SS (2000). Prenatal and postnatal risk factors for mental retardation among children in Bangladesh. Am J Epi 152(11): 1024-33.

El Hag AI (1994). Pattern of congenital heart disease in Sudanese children. East African Med J 71(9).

El-Hazmi MAF, Al-Swailem AR, Warsy AS, Al-Swailem AM, Sulaimani R, Al-Meshari AA (1995). Consanguinity among the Saudi Arabian population. J Med Genetics 32: 623-626.

Erickson JD, Mulinare J, McClain PW, Fitch TG, James LM, McClearn AB, Adams MJ (1984). Vietnam veterans' risks for fathering babies with birth defects. JAMA 252(7): 903-912.

Eskedal L, Hagemo P, Eskild A, Aamodt G, Seiler KS, Thaulow E (2004). A population-based study of extra-cardiac anomalies in children with congenital cardiac malformations. Cardiol Young 14: 600-607.

EUROCAT (2005a). Website Database: http://eurocat.ulster.ac.uk/pubdata/tables.html (data uploaded 07/11/2005) University of Ulster, last accessed August, 2006.

EUROCAT (2005b). EUROCAT Guide 1.3 and reference documents, Instructions for the Registration and Surveillance of Congenital Anomalies.

Feldt RH, Avasthey P, Yoshimasu F, Kurland LT, Titus JL (1971). Incidence of congenital heart disease in children born to residents of Olmsted Country, Minnesota, 1950-1969. Mayo Clin Proc 46: 794-799.

Ferencz C, Correa-Villasenor A (1993). Overview and Research Implications, Chapter 15. Epidemiology of Congenital Heart Disease. Ferencz C, Rubin J, Loffredo CA and Magee CA, Futura Publishing Company. 4: 249-255.

Ferencz C, Correa-Villasenor A (1995). Overview: the epidemiologic approach to the study of congenital cardiovascular malformations. Developmental Mechanisms of Heart Disease. Clark EB, Markwald RR and Takao A. Armonk, NY, Futura: 629-638.

Ferencz C, Boughman JA, Neill CA, Brenner JI, Perry LW and the Baltimore-Washington Infant Study Group (1989). Congenital Cardiovascular Malformations: Questions on Inheritance. J Am Coll Cardiol 14: 756-63.

Ferencz C, Loffredo CA, Correa-Villasenor A, Wilson PD (eds.) (1997). Genetic and Environmental Risk Factors of Major Cardiovascular Malformations: The Baltimore-Washington Infant Study 1981-1989. Armonk, NY, Futura Publishing Co., Inc.

Ferencz C, Matanoski GM, Wilson PD, Rubin JD, Neill CA, Gutberlet R (1980). Maternal hormone therapy and congenital heart disease. Teratology 21: 225-239.

Ferencz C, Rubin J, McCarter RJ, Clark EB (1990). Maternal diabetes and cardiovascular malformations: predominance of double outlet right ventricle and truncus arteriosus. Teratology 41: 319-326.

Ferencz C, Rubin JD, Loffredo CA, Magee CA (eds.) (1993). Epidemiology of Congenital heart disease. Armonk, NY, Futura Publishing Co., Inc.

Ferencz C, Rubin JD, McCarter RJ, Boughman JA, Wilson PD, Brenner JI, Neill CA, Perry LW, Hepner SI, Downing JW (1987). Cardiac and non-cardiac malformations: observations in a population-based study. Teratology 35: 367-378.

Ferencz C, Rubin JD, McCarter RJ, Brenner JI, Neill CA, Perry LW, Hepner SI, Downing JW (1985). Congenital heart disease: prevalence at live birth. The Baltimore-Washington Infant Survey. Am J Epi 121(1): 31-36.

Fixler DE, Threlkeld N (1998). Prenatal exposures and congenital heart defects in Down Syndrome infants. Teratology 58: 6-12.

Fixler DE, Pastor P, Chamberlin M, Sigman E, Eifler CW (1990). Trends in congenital heart disease in Dallas County births 1971-1984. Circulation 81: 137-142.

Forrester MB, Merz RD (2004). Descriptive epidemiology of selected congenital heart defects, Hawaii, 1986-1999. Paed Peri Epi 18: 415-424.

Francannet C, Lancaster PAL, Pradat P, Cocchi G, Stoll C (1993). The epidemiology of three serious cardiac defects a joint study between five centres. Eur J Epi 9(6): 607-616.

Franklin RCG, Anderson RH, Daniels O, Elliott M, Gewillig MHML, Ghisla R, Krogmann OIN, Ulmer HE, Stocker FP (1999). Report on the coding committee of the association for European Paediatric Cardiology. Cardiol Young 9: 633-657.

Freundlich E, Hino N (1984). Consanguineous marriage among rural Arabs in Israel. Israel J Med Sci 20: 1035-1038.

Fyler DC, Buckley LP, Hellenbrand WE, Cohn HE (1980). Report of the New England Regional Infant Cardiac Program. Pediatrics 65(Number 2 (supplement)): 375-461.

Gensburg LJ, Marshall EG, Druschel CM (1993). Examining potential demographic risk factors for congenital cardiovascular malformations on a time-developmental model. Paed Peri Epi 7: 434-449.

Gev D, Roguin N, Freundlich E (1986). Consanguinity and congenital heart disease in the rural Arab population in Northern Israel. Hum Heredity 36: 213-217.

Gill HK, Splitt M, Sharland GK, Simpson JM (2003). Patterns of recurrence of congenital heart disease: an analysis of 6,640 consecutive pregnancies evaluated by detailed fetal echocardiography. J Am Coll Cardiol 42: 923-9.

Goldberg SJ, Lebowitz MD, Graver EJ, Hicks S (1990). An association of human congenital cardiac malformations and drinking water contaminants. J Am Coll Cardiol 16: 155-64.

Gordon LS (1990). Cardiac conditions. Clinical Perspectives in the Management of Down Syndrome. L. D. Van Dyke DC, Heide F, van Duyne S, Soucek MJ (eds). New York:, Springer-Verlag: 55-71.

Govinda Reddy P (1983). Effects of consanguineous marriages on fertility among three endogamous groups of Andhra Pradesh. Soc Bio 34: 68-77.

Govinda Reddy P (1988). Consanguineous marriages and marriage payment: a study among three South Indian caste groups. Ann Hum Bio 15: 263-268.

Grabitz RG, Joffres MR, Collins-Nakai RL (1988). Congenital heart disease: Incidence in the first year of life: the Alberta Heritage Pediatric Cardiology Program. Am J Epi 128(2): 381-8.

Grech V (1998). Epidemiology and diagnosis of ventricular septal defect in Malta. Cardiol Young 8: 329-336.

Grech V (1998). History, diagnosis, surgery and epidemiology of pulmonary stenosis in Malta. Cardiol Young 8: 337-343.

Grech V (1999). Trends in presentation of congenital heart disease in a population-based study in Malta. Eur J Epi 15: 881-887.

Greer W, Sandridge AL, Chehabeddine RS (2003). The frequency distribution of age at natural menopause among Saudi Arabian women. Maturitas 46: 263-72.

Greer W, Sandridge AL, Al-Menieir M, Al Rowais A (2005). Geographical distribution of congenital heart defects in Saudi Arabia. Ann Saudi Med 25:63-69.

Gruber PJ, Epstein JA (2004). Development gone awry: congenital heart disease. Circulation Research 94: 273-283.

Gunaid AA, Hummad NJ, Tamim KA (2004). Consanguineous marriage in the capital city Sana'a, Yemen. J Biosoc Sci 36: 111-121.

Hajdu J, Beke A, Marton T, Hruby E, Pete B, Papp Z (2006). Congenital heart diseases in twin pregnancies. Fetal Diagnostic Therapy 21: 198-203.

Hakosalo J, Saxen L (1971). Influenza epidemic and congenital defects. Lancet 1971: 1346-1347.

Hamamy HA, Al-Hakkak ZS (1989). Consanguinity and reproductive health in Iraq. Hum Heredity 39: 271-275.

Harlap S, Davies AM, Haber M, Rossman H, Prywes R, Samueloff N (1971). Congenital malformations in the Jerusalem perinatal study. Israel J Med Sci 7(12): 1520-1528.

Hashmi MA (1997). Frequency of consanguinity and its effect on congenital malformation - a hospital based study. J Pak Med Assoc 47(3): 75-78.

Hassan I, Haleem AA, Bhutta ZA (1997). Profile and risk factors for congenital heart disease. J Pak Med Assoc 47(3): 78-81.

Heinonen OP (1976). Risk factors for congenital heart disease a prospective study. Birth defects: risks and consequences. S. Kelly, Hook EB, Janerich DT, Porter IH: 221-264.

Heinonen OP, Slone D, Monson RR, Hook EB, Shapiro S (1977). Cardiovascular birth defects and antenatal exposure to female sex hormones. NEJM 296: 67-70.

Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA (2001). Neural tube defects in relation to use of folic acid antagonists during pregnancy. Am J Epi 153(10): 961-968.

Hoffman JIE (2002). Incidence, mortality and natural history. Paediatric Cardiology. Anderson RH, Baker EJ, McCartney FJ et al. London, Churchill Livingstone. 1: 111-140.

Hosmer DW, Lemeshow S (1989). Applied Logistic Regression. Chichester, UK, Wiley.

Hussain R, Bittles AH, Sullivan S (2001). Consanguinity and early mortality in the Muslim populations of India and Pakistan. Am J Hum Bio 13: 777-787.

International Centre for Birth Defects (2000). International Clearinghouse for Birth Defects monitoring systems annual report 2000. Roma, Int Centre Birth Defects.

International Society of Cardiology (1970). Classification of Heart Disease in Childhood, VRB Offsetdrukkerij, Groningen.

Jaber L, Bailey-Wilson JE, Haj-Yehia M, Hernandez J, Shohat M (1994). Consanguineous matings in an Israeli-Arab community. Arch Pediatr Adolesc Med 148: 412-415.

Jaber L, Merlob P, Bu X, Rotter JI, Shohat M (1992). Marked parental consanguinity as a cause for increased major malformations in an Israeli Arab Community. Am J Med Genetics 44: 1-6.

Jaber L, Shohat M, Halpern GJ (1996). Demographic characteristics of the Israeli Arab community in connection with consanguinity. Israel J Med Sci 32: 1286-9.

Jain VK, Nalini P, Chandra R, Srinivasan S (1993). Congenital malformations, reproductive wastage and consanguineous mating. Aust NZ J Obstet Gyne 33(1): 33-36.

Jaiyesimi F, Ruberu DK, Misra VK (1993). Pattern of congenital heart disease in King Fahd Specialist Hospital, Buraidah. Ann Saudi Med 13(5): 407-411.

Kallen K (1999). Maternal smoking and congenital heart defects. Eur J Epi 15: 731-737.

Kapusta L, Haagmans MLM, Steegers EAP, Cuypers MHM, Blom HJ, Eskes TKAB (1999). Congenital heart defects and maternal derangement of homocysteine metabolism. J Pediatr 135: 773-4.

Karatza AA, Wolfenden JL, Taylor MJO, Wee L, Fisk NM, Gardiner HM (2002). Influence of twin-twin transfusion syndrome on fetal cardiovascular structure and function: prospective case-control study of 136 monochorionic twin pregnancies. Heart 88: 271-277.

Kenna AP, Smithells RW, Fielding DW (1975). Congenital heart disease in Liverpool: 1960-69. Q J Med New Series, XLIV, 173: 17-44.

Khalil A, Aggarwal R, Thirupuram S, Arora R (1994). Incidence of congenital heart disease among hospital live births in India. Indian Pediatrics 31: 519-527.

Khattab MS, Khan MY, al-Khaldi YM, al-Gamal MN (2000). The need for traditional birth attendants (dayas) in Saudi Arabia. East Mediterr Health J(6): 13-24.

Khlat M (1988). Social correlates of consanguineous marriages in Beirut: a population-based study. Hum Bio 60(4): 541-548.

Khlat M, [Klat M], A. Khudr (1986). Religious Endogamy and consanguinity in marriage patterns in Beirut, Lebanon. Soc Bio 33(1-2): 138-145.

Khlat M, Halabi S, Khudr A, Der Kaloustian VM (1986). Perception of consanguineous marriages and their genetic effects among a sample of couples from Beirut. Am J Med Genetics 25: 299-306.

Khlat M, Khoury M (1991). Inbreeding and Diseases: Demographic, Genetic, and epidemiologic perspectives. Epi Reviews 13: 28-41.

Khoja TA, Farid SM (2000). Saudi Arabia Family Health Survey. Riyadh.

Khoshnood B, De Vigan C, Volovar V, Goujard J, Lhomme A, Bonnet D, Goffinet F (2005). Trends in prenatal diagnosis, pregnancy termination, and perinatal mortality of newborns with congenital heart disease in France, 1983-2000: a population-based evaluation. Pedatrics 115: 95-101.

Khoury MJ, Beaty TH, Cohen BH (1993). Fundamentals of Genetic Epidemiology. New York, Oxford University Press.

Khoury MJ, Cohen BH, Diamond EL, Chase GA, McKusick VA (1987). Inbreeding and pre-reproductive mortality in the old order Amish. III. Direct and indirect effects of inbreeding. Am J Epi 125(3): 473-83.

Khoury SA, Massad D (1992). Consanguineous Marriage in Jordon. Am J Med Genetics 43: 769-775.

Khoury SA, Massad DF (2000). Consanguinity, fertility, reproductive wastage, infant mortality and congenital malformations in Jordan. Saudi Med J 21(2): 150-54.

Kidd SA, Lancaster PAL, McCredie RM (1993). The incidence of congenital heart defects in the first year of life. J Paediatr Child Health 29: 344-349.

Kir T, Gulec M, Bakir B, Hosjgonul E, Tumerdem N (2005). The frequency and effecting factors of consanguineous marriage in a group of soldiers in Ankara. J Biosoc Sci. 37: 519-23.

Kirby ML (1987). Cardiac morphogenesis. Recent research advances. Pediatric Research 21: 219-224.

Kirkwood BR, Sterne JAC (2003). Essential medical statistics. Malden, MA, Blackwell Science.

Kleinman C (1997). Heart Disease in the Young. Yale University School of Medicine Heart Book. M. M. Zaret BL, Cohen LS. New York, Hearst. 1: 247-262.

Kozinszky Z, Zadori J, Orvos H, Katona M, Pal A, Kovacs L (2003). Obstetric and neonatal risk of pregnancies after assisted reproductive technology: a matched control study. Acta Obstet Gynecol Scand 82: 850-6.

Kramer H-H, Majewski F, Trampisch HJ, Rammos S, Bourgeois M (1987). Malformation patterns in children with congenital heart disease. Am J Dis Child141: 789-795.

Kuehl KS, Loffredo C (2002). Risk factors for heart disease associated with abnormal sideness. Teratology 66: 242-248.

Kuehl KS, Loffredo CA (2003). Population-based study of l-transposition of the great arteries: possible associations with environmental factors. Birth Defects Res A Clin Mol Teratol 67: 162-167.

Kurdi AM, Mesley RA, Al-Hakeem MM, Khashoggi TY, Khalifa HM (2004). Multiple pregnancy and preterm labor. Saudi Med J 25: 632-7.

Laegried L, Olegard R, Wahlstrom J, Conradi N (1987). Abnormalities in children exposed to benzodiazepines in utero. Lancet: 10 January.

Laursen HB (1980). Some epidemiological aspects of congenital heart disease in Denmark. Acta Paediatr Scand 69: 619-624.

Levy EP, Cohen A, Fraser FC (1973). Hormone treatment during pregnancy and congenital heart defects. Lancet 1: 611.

Lian Z, Zack MM, Erickson JD (1986). Paternal age and the occurrence of birth defects. Am J Hum Genetics 39: 648-660.

Loffredo CA, Ferencz C, Wilson PD, Lurie IW (2000). Interrupted aortic arch: an epidemiologic study. Teratology 61: 368-375.

Loffredo CA, Hirata J, David Wilson P, Ferencz C, Lurie IW (2001a). Atrioventricular septal defects: possible etiologic differences between complete and partial defects. Teratology 63: 87-93.

Loffredo CA, Silbergeld EK, Ferencz C, Jianyi Z (2001b). Association of transposition of the great arteries in infants with maternal exposures to herbicides and rodenticides. Am J Epi 153(6): 529-36.

Loffredo CA, Wilson PD, Ferencz C (2001c). Maternal diabetes: an independent risk factor for major cardiovascular malformations with increased mortality of affected infants. Teratology 64: 98-106.

Macintosh MCM, Fleming KM, Bailey JA, Doyle P, Modder J, Acolet D, Golightly S, Miller A (2006). Perinatal mortality and congenital anomalies in babies of women with type 1 and type 2 diabetes in England, Wales and Northern Ireland: a population based study. BMJ 333: 157-8.

MacMahon B (1952). Association of congenital malformation of the heart with birth rank and maternal age. Br J Soc Med 6: 178-182.

Martin MS, Adams MM, Mortensen ML (1990). Descriptive epidemiology of selected malformations of the aorta, Atlanta, 1970-1983. Teratology 42: 273-283.

Martinez-Frias ML, Garcia Marario MJ, Feito Caldas C, Conejero Gallego MP, Bermejo E, Rodriguez-Pinilla E (2001). High maternal fever during gestation and severe congenital limb disruptions. Am J Med Genetics 98: 201-203.

Mastroiacovo P, Mazzone T, Addis A, Elephant E, Carlier P, Vial T, Garbis H, Robert E, Bonati M, Ornoy A, Finardi A, Schaffer C, Caramelli L, Rodriguez-Pinilla E, Clementi M (1999). High vitamin A intake in early pregnancy and major malformations: a multicenter prospective controlled study. Teratology 59: 7-11.

McBride KL, Marengo L, Canfield M, Langlois P, Fixler D, Belmont JW (2005). Epidemiology of noncomplex left ventricular outflow tract obstruction malformations (aortic valve stenosis, coarctation of the aorta, hypoplastic left heart syndrome) in Texas, 1999-2001. Birth Defects Res A Clin Mol Teratol 73: 555-561.

McKusick VA (1998). Mendelian Inheritance in Man; A Catalog of Human Genes and Genetic Disorders. Baltimore, MD, The Johns Hopkins University Press.

McLaren G, Bain M (1998). Deprivation and health in Scotland-Insights from NHS Data. Edinburgh, ISD Publications.

McLaren MJ, Lachman AS, Barlow JB (1979). Prevalence of congenital heart disease in black schoolchildren of Soweto, Johannesburg. Br Heart J 41: 554-558.

Meberg A, Otterstad JE, Froland G, Hals J, Sorland SJ (1999). Early clinical screening of neonates for congenital heart defects: the cases we miss. Cardiol Young 9: 169-174.

Miao C, Li W, Gen D, Tao L, Zuberbuhler JS, Zuberbuhler JR (1988). Effect of high altitude on prevalence of congenital heart disease. Chinese Med J 101(6): 415-418.

Miao C, Zuberbuhler JS, Zuberbuhler JR (1988). Prevalence of congenital cardiac anomalies at high altitude. J Am Coll Cardiol 12(1): 224-228.

Mikhail LN, Walker CK, Mittendorf MD (2002). Association between maternal obesity and fetal cardiac malformations in African Americans. J National Medical Assoc 94(8): 695-700.

Mills JL, Knopp RH, Simpson JL, Jovanovic-Peterson L, Metzger BE, Holmes LB, Aarons JH, Brown Z, Reed GF, Bieber FR, Van Allen M, Holzman I, Ober C, Peterson CM, Withiam MJ, Duckles A, Mueller-Heubach E, Polk BF, and the National Institute of Child Health and Human Development Diabetes in Early Pregnancy Study (1988). Lack of relation of increased malformation rates in infants of diabetic mothers to glycemic control during organogenesis. NEJM 318: 671-6.

Mirghani HM, Weerasinghe DSL, Ezimokhai M, Smith JR (2003). The effect of maternal fasting on the fetal biophysical profile. Int J Gynecol Obstetr 81: 17-21.

Mitchell SC, Korones SB, Berendes HW (1971). Congenital heart disease in 56,109 births. Circulation 43: 323-32.

Mitchell SC, Sellmann AH, Westphal MC, Park J (1971). Etiologic correlates in a study of congenital heart disease in 56,109 births. Am J Cardiol 28: 653-657.

Mitri W, Sandridge AL, Subhani S, Greer W (2002). The Design and Development of an Internet Registry for Congenital Heart Disease. Teratology 65(2): 78-87.

Mokhtar MM, Abdel-Fattah MM (2001). Consanguinity and advanced maternal age as risk factors for reproductive losses in Alexandria, Egypt. Eur J Epi 17: 559-565.

Molina C, Sandridge AL (2000). KFSH &RC, Congenital Heart Disease Registry, Second Annual Report, KFSH&RC.

Montana E, Khoury MJ, Cragan JD, Sharma S, Dhar P, Fyfe D (1996). Trends and outcomes after prenatal diagnosis of congenital cardiac malformations by fetal echocardiography in a well defined birth population, Atlanta, Georgia, 1990-1994. J Am Coll Cardiol 28(7): 1805-1809.

Murphy RF, Kasdan L (1959). The Structure of Parallel Cousin Marriage. Am Anthropologist 61: 17-29.

Nabulsi MM, Tamim H, Sabbagh M, Obeid MY, Yunis KA, Bitar FF (2003). Parental consanguinity and congenital heart malformations in a developing country. Am J Med Genetics 116A: 342-347.

Narchi H, Kulaylat N (1997). Congenital malformations: are they more prevalent in populations with a high incidence of consanguineous marriages? Ann Saudi Med 17: 254-256.

Naval Intelligence Division (1946). Handbook of Western Arabia and the Red Sea, Admiralty London.

Niazi MA, Al-Mazyad AS, Al-Husain MA, Al-Mofada SM, Al -Zamil FA, Khashoggi TY, Al-Eisa YA (1995). Down's syndrome in Saudi Arabia: incidence and cytogenetics. Hum Heredity 45: 65-9.

Nora AH, Nora JJ (1975). A syndrome of multiple congenital anomalies associated with tertogenic exposure. Arch Environ Health 30: 17-21.

Nora JJ, Nora AH (1973). Birth defects and oral contraceptives. Lancet 1: 941-942.

Nyrop RF (1984). Persian Gulf States country studies. Washington, D., American Univ.

Nyrop RF, Benderly BL, Carter LN, Eglin DR, Kirchner RA (1977). Area handbook for Saudi Arabia. Washington, DC, American Univ.

Ober C, Hyslop T, Hauck WW (1999). Inbreeding effects on fertility in humans: evidence for reproductive compensation. Am J Hum Genetics 64: 225-231.

Oliveira LM, Stein N, Sanseverino MTV, Vargas VMF, Vachel JMG, Schuler L (2002). Reproductive outcomes in an area adjacent to a petrochemical plant in southern Brazil. Rev Saude Publica 36: 81-7.

Olshan AF, Schnitzer PG, Baird PA (1994). Paternal age and the risk of congenital heart defects. Teratology 50: 80-84.

Olshan AF, Teschke K, Baird PA (1990). Birth defects among offspring of firemen. Am J Epi 131(2): 312-321.

ONS (2001). Congenital anomaly statistics notifications. London, Office for National Statistics.

O'Rahily R, Muller F (2001). Human embryology & teratology, Wiley-Liss.

Ottenheimer M (1996). Forbidden Relatives: the American myth of Cousin Marriage.

Parkin R (1997). Kinship: an introduction to the basic concepts. UK, Blackwell.

Patterson DF (1991). Genes and the Heart: Congenital Heart Disease. Academy of Veterinary Cardiology Proceedings, 58th Annual Meeting of the AAHA and the Ontario Veterinary Medical Association Meeting, Toronto, Ontario, Canada.

Penaloza D, Arias-Stella J, Sime F, Recavarren S, Marticorena E (1964). The heart and pulmonary circulation in children at high altitudes. Pediatrics 34: 568-582.

Pharoah POD, Alberman E, Doyle P, Chamberlain G (1977). Outcome of pregnancy among women in anaesthetic practice. Lancet 1: 34-36.

Pitt DB, Samson PE (1961). Congenital malformations and maternal diet. Aust Ann Med 10: 268-74.

Pradat P (1992a). Epidemiology of major congenital heart defects in Sweden, 1981-1986. J Epi Comm Health 46: 211-215.

Pradat P (1992b). A case-control study of major congenital heart defects in Sweden 1981-1986. Eur J Epi 8(6): 789-796.

Pradat P (1992c). Effect of fathers' age and birth order on occurrence of congenital heart disease. J Epi Comm Health 46: 460.

Pradat P (1997). Noncardiac malformations at major congenital heart defects. Pediatr Cardiol 18: 11-18.

Prentice AM, Prentice A, Lamb WH, Lunn PG, Austin S (1983). Metabolic consequences of fasting during Ramadan in pregnant and lactating women. Hum Nutr Clin Nutr 47: 283-294.

Pyle RL, Paterson DF, Chacko S (1976). The genetics and pathology of discrete subaortic stenosis in the Newfoundland Dog. Am Heart J 92(3): 324-334.

Queisser-Luft A, Stolz G, Wiesel A, Schlaefer K, Spranger J (2002). Malformations in newborn: results based on 30940 infants and fetuses from the Mainz congenital birth defect monitoring system (1990-1998). Arch Gynecol Obstet 266: 163-167.

Radovanovic Z, Shah N, Behbehani J (1998). On the Reliability of Assessing Consanguinity in a highly fertile population: a Kuwaiti example. Kuwait Med J 30(3): 201-205.

Ransom J, Srivastava D (2007). The genetics of cardiac birth defects. Seminars in Cell and Developmental Biology.

Rittler M, Liascovich, Lobez-Camelo J, Castilla EE (2001). Parental consanguinity in specific types of congenital anomalies. Am J Med Genetics 102: 36-43.

Ritz B, Yu F, Fruin S, Chapa G, Shaw GM, Harris JA (2002). Ambient air pollution and risk of birth defects in Southern California. Am J Epi 155(1): 17-25.

Robida A, Folger GM, Hajar HA (1997). Incidence of congenital heart disease in Qatari children. Int J Cardiol 60: 19-22.

Ronda E, Regidor E, Garcia AM, Dominguez V (2005). Association between congenital anomalies and paternal exposure to agricultural pesticides depending on mother's employment status. J Occup Environ Med 47: 826-8.

Roodpeyma S, Kamali Z, Afshar F, Naraghi S (2002). Risk factors in Congenital heart disease. Clinical Pediatrics 41(9): 653-658.

Rose V, Hewitt D, Milner J (1972). Seasonal influences on the risk of cardiac malformation. Nature of the problem and some results from a study of 10,077 cases. Int J Epi 1(3): 235-244.

Rosenberg L, Mitchell AA, Shapiro S, Slone D (1982). Selected birth defects in relation to caffeine-containing beverages. JAMA 247(10): 1429-1432.

Rosenquist TH, Ratashak SA, Selhub J (1996). Homocysteine induces congenital defects of the heart and neural tube; effect of folic acid. Proc Natl Acad Sci 93: 15227-15232.

Rosenthal GL, Wilson PD, Permutt T, Boughman JA, Ferencz C (1991). Birth weight and cardiovascular malformations: a population-based study. Am J Epi 133(12): 1273-81.

Rothman KJ, Fyler DC (1976). Sex, birth order, and maternal age characteristics of infants with congenital heart defects. Am J Epi 104(5): 527-534.

Saedi-Wong S, Al-Frayh AR, Wong HYH (1989). Socio-Economic Epidemiology of Consanguineous Matings in the Saudi Arabian Population. J Asian African Studies: 247-252.

Saidi MH (1988). First-trimester bleeding and the vanishing twin. A report of three cases. J Repro Med 33: 831-4.

Sailer S (2003). Cousin marriage conundrum. Am Conservative: 20-22.

Sallam SA, Mahfouz AA, Dabbous NI (2001). Reproductive health of married adolescent women in squatter areas in Alexandria, Egypt. East Mediterr Health J 7: 935-942.

Samanek M (1992). Children with congenital heart disease: probability of natural survival. Pediatr Cardiol 13: 152-158.

Samanek M (1994). Boy: Girl ratio in children born with different forms of cardiac malformation: a population-based study. Pediatr Cardiol 15: 53-57.

Samanek M (2000). Congenital heart malformations: prevalence, severity, survival, and quality of life. Cardiol Young 10: 179-185.

Samanek M, Voriskova M (1999). Congenital heart disease among 815,569 children born between 1980 and 1990 and their 15-year survival: a prospective Bohemia survival study. Pediatr Cardiol 20: 411-417.

Samanek M, Slavik Z, Krejcir M (1991). Seasonal differences in the incidence of congenital heart defects. Czech Medicine 14: 146-155.

Samanek M, Slavik Z, Zborilova B, Hrobonova V, Voriskova M, Skovranek J (1989). Prevalence, treatment, and outcome of heart disease in live-born children: a prospective analysis of 91,823 live-born children. Pediatr Cardiol 10: 205-211.

Sampson A, de Crespigny LC (1992). Vanishing twins: the frequency of spontaneous fetal reduction of a twin pregnancy. Ultrasound Obstet Gynecol 2: 107-9.

Sanderson M, Williams MA, White E, Daling JR, Holt VL, Malone KF, Self SG, Moore DE (1998). Validity and reliability of subject and mother reporting of perinatal factors. Am J Epi 147: 136-40.

Sandridge AL (2002). Risk factors for congenital heart disease in Saudi Arabian children. Non-communicable diseases, LSHTM, Upgrading document.

Sandridge AL (2005). The consanguinity question: What, How and Why? Research Seminar, Weill Cornell Medical College, Sept, Doha, Qatar.

Sandridge AL (2000). Collecting pedigree information in an epidemiological context. Statistica – Anno LX – 2000, 4:745-751.

Sandridge AL, Greer W, Al-Menieir M, Al Rowais A (2006). The impact of altitude on the burden of congenital heart defects in Saudi Arabia. Submitted to: Int J Cardiol, August 2006.

Savitz DA, Schwingl PJ, Keels MA (1991). Influence of Paternal Age, Smoking, and Alcohol Consumption on Congenital Anomalies. Teratology 44: 429-440.

Sawardekar KP (2005). Profile of major congenital malformations at Nizwa Hospital, Oman: 10-year review. J Paediatr Child Health 41: 323-330.

Scanlon KS, Ferencz C, Loffredo CA, Wilson PD, Correa-Villasenor A, Khoury MJ, Willett WC and BWIS Group (1998). Preconceptional folate intake and malformations of the cardiac outflow tract. Epi 9(1): 95-98.

Schull WJ, Neel JV (1972). The effects of parental consanguinity and inbreeding in Hirado, Japan. V. Summary and interpretation. Am J Hum Genetics 24: 425-453.

Scott DJ, Rigby ML, Miller GAH, Shinebourne EA (1984). The presentation of symptomatic heart disease in infancy based on 10 years' experience (1973-82). Br Heart J 52: 248-57.

Serenius F, Edressee AW, S. AR (1988). Characteristics of the obstetric population in a Saudi Maternity Hospital. Acta Paediatr Scand Suppl 346: 29-43.

Shafi T, Khan MR, Atiq M (2003). Congenital heart disease and associated malformations in children with cleft lip and palate in Pakistan. Br J Plastic Surgery 56: 106-9.

Shami SA, Grant JC, Bittles AH (1994). Consanguinity marriage within social/occupational class boundaries in Pakistan. J Biosoc Sci 26: 91-96.

Shami SA, Qaisar R, Bittles AH (1991). Consanguinity and adult morbidity in Pakistan. Lancet 338:954

Shami SA, Schmitt LH, Bittles AH (1989). Consanguinity related prenatal and postnatal mortality of the populations of seven Pakistani Punjab cities. J Med Genetics 26: 267-271.

Sheiner E, Shoham-Vardi I, Sheiner EK, Mazor M, Katz M, Carmi R (1999). Maternal factors associated with severity of birth defects. Int J Gynecol Obstetrics 64: 227-232.

Singh, G. (2006). Aortic stenosis, supravalvar (http://www.emedicine.com/ped/topic2178.htm last accessed August 7, 2007).

Stein Z, Belmont L, Durkin M (1987). Mild mental retardation and severe mental retardation compared: experiences in eight less developed countries. Upsala J Med Sci Suppl 44: 89-96.

Stein Z, Susser M (1976). Maternal starvation and birth defects. Birth defects: risks and consequences. S. Kelly, Hook EB, Janerich DT, Porter IH: 205-220.

Stephensen SS, Sigfusson G, Eiriksson H, Sverrisson JT, Torfason B, Haraldsson A, Helgason H (2004). Congenital cardiac malformations in Iceland from 1990 through 1999. Cardiol Young 14: 396-401.

Stocker FP (2003). The European Paediatric Cardiac Code: where do we stand? Cardiol Young 13: 111-112.

Stoll C, Alembik Y, Dott B, Roth MP (1998). Study of Down Syndrome in 238,942 Consecutive Births. Ann Genet 41(1): 44-51.

Stoll C, Alembik Y, Roth MP, Dott B (1999). Parental consanguinity as a cause for increased incidence of births defects in a study of 238,942 consecutive births. Ann Genet 42(3): 133-139.

Stoll C, Alembik Y, Roth MP, Dott B, De Geeter B (1989). Risk factors in congenital heart disease. Eur J Epi 5(3): 382-391.

Stoltenberg C, Magnus P, Lie RT, Daltveit AK, Irgens LM (1997). Birth defects and parental consanguinity in Norway. Am J Epi 145(5): 439-448.

Stoltenberg C, Magnus P, Skrondal A, Lie RT (1999). Consanguinity and recurrence risk of stillbirth and infant death. Am J Public Health 89(4): 517-523.

Storch TG, Mannick EE (1992). Epidemiology of Congenital Heart Disease in Louisiana: An Association between Race and Sex and the Prevalence of Specific Cardiac Malformations. Teratology 46: 271-276.

Strandberg TE, Jarvenpaa A-L, Vanhanen H, McKeigue PM (2001). Birth outcome in relation to licorice consumption during pregnancy. Am J Epi 153(11): 1085-8.

Stumpflen I, Stumpflen A, Wimmer M, Bernaschek G (1996). Effect of detailed fetal echocardiography as part of routine prenatal ultrasonographic screening on detection of congenital heart disease. Lancet 348: 854-57.

Subramanyan R, Joy J, Venugopalan P, Sapru A, Al Khusaiby SM (2000). Incidence and spectrum of congenital heart disease in Oman. Ann Trop Paed 20: 337-341.

Sung RYT, So LY, Ng HK, Ho JKS, Fok TF (1991). Echocardiography as a tool for determining the incidence of congenital heart disease in newborn babies: a pilot study in Hong Kong. Int J Cardiol 30: 43-47.

Tamim H, Khogali M, Beydoun H, Melki I, Yunis K and the National Collaborative Perinatal Neonatal Network (2003). Consanguinity and apnea of prematurity. Am J Epi 158(10): 942-946.

The Heart Institute for Children (2006). (http://www.childrenheartinstitute.org/educate/heartwrk/hearthse.htm last accessed July 6, 2006). Fairfax, Virginia.

Tikkanen J and Heinonen OP (1994). Risk factors for hypoplastic left heart syndrome. Teratology 50: 112-117.

Tikkanen J and Heinonen OP (1993). Risk factors for coarctation of the aorta. Teratology 47: 565-572.

Tikkanen J, Heinonen OP (1992). Risk factors for atrial septal defect. Eur J Epi 8(4): 509-515.

Tikkanen J, Heinonen OP (1991). Maternal exposure to chemical and physical factors during pregnancy and cardiovascular malformations in the offspring. Teratology 43: 591-600.

Tikkanen J, Heinonen OP (1990). Risk factors for cardiovascular malformations in Finland. Eur J Epi 6(4): 348-356.

Tikkanen J, Heinonen OP, Kurppa K, Rantala K (1990). Cardiovascular malformations and maternal exposure to video display terminals during pregnancy. Eur J Epi 6(1): 61-66.

Tikkanen J, Kurppa K, Timonen H, Holmberg PC, Kuosma E, Rantala K (1988). Cardiovascular malformations, work attendance, and occupational exposures during pregnancy in Finland. Am J Industrial Med 14: 197-204.

Tynan MJ, Becker AE, Macartney FJ, Jimenez MQ, Shinebourne EA, Anderson RH (1979). Nomenclature and classification of congenital heart disease. Br Heart J 41:544-553.

US Department of Health and Human Services Public Health Service, HCFA. (1980). ICD-9 CM: The international classification of diseases, 9th revision, clinical modification, 2nd ed. Washington, DC: US GPO. (DHHS publication no. (PHS) 80-1260).

Wahab A, Ahmad M, Shah SA (2005). Migration as a determinant of marriage pattern: preliminary report on consanguinity among Afghans. J Biosoc Sci 00: 1-11.

Warsy AS, El-Hazmi MAF (1999). Diabetes mellitus, hypertension and obesity - common multifactorial disorders in Saudis. East Mediterr Health J 5: 1236-1242.

Watkins ML, Botto LD (2001). Maternal pre-pregnancy weight and congenital heart defects in the offspring. Epi 11(4): 439-446.

Whittemore R, Wells JA, Castellsague X, (1994). A second-generation study of 427 probands with congenital heart defects and their 837 children. J Am Coll Cardiol 23(6): 1459-67.

Wiseman RA, Dodds-Smith IC (1984). Cardiovascular birth defects and antenatal exposure to female sex hormones: a reevaluation of some base data. Teratology 30: 359-370.

WHO (1993). Polycholorinated biphenyls and terphenyls: environmental health criteria 140. Geneva, Switzerland, World Health Organization. Div Environmental Health, p. 185.

Wright L (2006). The looming tower: Al Qaeda and the road to 9/11. Knopf, New York.

Zakzouk S (2002). Consanguinity and hearing impairment in developing countries: a custom to be discouraged. J Laryngology Otology 116: 811-816.

Zakzouk S, El-Sayed Y, Bafaqeeh SA (1993). Consanguinity and hereditary hearing impairment among Saudi population. Ann Saudi Med 13: 447-450.

Zhan SY, Lian ZH, Zheng DZ, Gao L (1991). Effect of fathers' age and birth order on occurrence of congenital heart disease. J Epi Comm Health 45: 299-301.

Zhang J, Savitz DA, Schwingl PJ, Cai W (1992). A case-control study of paternal smoking and birth defects. Int J Epi 21(2): 273-278.

Zhu JL, Vestergaard M, Hjollund NH, Olsen J (2006). Pregnancy outcomes among female hairdressers who participated in the Danish National Birth Cohort. Scand J Work Environ Health 32: 61-6.

Zierler S, Theodore M, Cohen A, Rothman KJ (1988). Chemical quality of maternal drinking water and congenital heart disease. Int J Epi 17(3): 589-594.

Zlotogora J (1997). Genetic disorders among Palestinian Arabs: 1. Effects of consanguinity. Am J Med Genetics 68: 472-475.

Appendices

Appendix 1A – ICD-9, ISC and EPC coding systems compared for endocardial cushion defect and single ventricle

	ICD 9	ISC	EPC
Endocardial cushion defect	745.6 Endocardial cushion defects 745.60 Endocardial cushion defect, unspecified type 745.61 Ostium primum defect Persistent ostium primum 745.69 Other Absence of atrial septum Atrioventricular canal type ventricular septal defect Common atrioventricular canal Common atrium	202 Partial type (any or all of the following) 204 -characteristic ventricular septal defect 205 - defect in lowermost portion of atrial septum (ostium primum defect) 206 - cleft in anterior cusp of mitral valve 207 - absent or rudimentary septal cusp of tricuspid valve 202 unspecified 208 Complete type (common AV canal) (all of the following) -single atrioventricular valve -defect in the lowermost portion of atrial septum -ventricular septal defect*	06.06.00 Atrioventricular septal defect (unspecified) 06.06.01 AVSD with isolated atrial component (primum ASD) 06.06.08 AVSD with isolated ventricular component 06.06.09 AVSD with atrial & ventricular components (complete) 06.05.01 AVSD AV valvar abnormality (unspecified) 06.05.06 AVSD AV valvar regurgitation (unspecified). 01.01.20 AV septal defect and TOF
Single ventricle (Common ventricle)	745.3 Cor trilocare biatriatum Single ventricle	520 Single ventricle (unspecified) 522 with normally related great arteries 523 with transposition of the great arteries** 524 "D" loop 524 "L" loop 530 Single ventricle – aplasia of right ventricular sinus (double inlet left ventricle) 533 with transposition of great arteries 534 "D" loop 535 "L" loop 540 Single ventricle – aplasia of left ventricular sinus (double inlet right ventricle) 543 with transposition of great arteries 544 "D" loop 545 "L" loop 550 Single ventricle – absence of recognizable right and left ventricular sinuses and ventricular septum 553 with transposition of great arteries 554 "D" loop 555 "L" loop	01.04.04 Double inlet LV

*WHO code associated with this defect is not current (746.6 and 746.5).
**WHO code associated with this defect is not current (746.3)

Appendix 1B: Literature Review of CHD Risk Factors

	Risk Factor	Defect Studied	Authors (Year)	Study Design	Findings	Limitations	Notes	Evidence Level
1	Consanguinity	All CHD	Stoll et al. 1999	Case control	No association found	Accepted as consanguineous non-consanguinous (ie more distantly related than 2cd cousin) couples in controls.	NFBDM[1]	Fair
2		All CHD without chromosomal abnormalities	Hassan, Haleem, Bhutta, 1997	Case control	No association found. Unadjusted OR 0.97 (CI_{95}=0.69-1.36)	Chart review. Method of collection of consanguinity not defined. Degree of consanguinity not defined.		Poor
3		All CHD	Gev, Roguin, Freundlich 1986	Cohort	OR of 2.59 associated with first cousin consanguinity (OR calculated by ALS. CI not reported.)	N=1,546. Oddly, no cases of diabetes were found in the population and no case of CHD in the parents. No sibling CHD. Only one Down syndrome. Found CHD incidence of 18 per 1000. Found no multiple defects. Only mention first and second degree relatives (misclassification of exposure?).		Poor
4		All CHD	Becker et al. 2001	Case series compared to national data	Significant association between first cousin consanguinity and defects such as ASD, VSD, AVSD, PS and PA	Used 'predominant lesion' method of categorizing multiple defects. Misclassifying of exposure probable.		Poor
5		Visible Congenital malformations	Hashmi 1997	Descriptive case series	40% of related parents had CM versus 26% of unrelated (p=< 0.01).	No comparison group.		Poor
6		Prenatal and post natal loses	Al Husain, Al Bunyan 1997	Cohort	No difference between consanguineous and non-consanguineous offspring.	Consanguinity included those more distant than second cousin. Possible misclassification of exposure as no half or multiple relationships described.		Poor
7		All CHD	Bassili et al. 2000	Case control	Adj OR 2.38 (CI_{95}1.92-2.96)	Consanguinity included those cousins less closely related than 2cd cousins. 894 cases birth to 15 years of age. Possible recall bias. Most likely not incident cases.		Poor
8	Familial history of noncardiac anomalies	Type B with DGS	Loffredo et al. 2000	Case control	7.2 (1.5-39.2)		BWIS	Good
9		Atrial septal defect	Tikkanen, Heinonen 1992	Cohort	CM in the father 10 (1.6-61) CM in the mother's mother 5.0 (1.6- 16) CM in mother's sister or brother 2.5 (1.1, 5.9)	Used embryological method for classifying multiple diagnoses in one child. Uncorrected results		Good

[1] Northeastern France Birth Defects Monitoring System

	Risk Factor	Defect Studied	Authors (Year)	Study Design	Findings	Limitations	Notes	Evidence Level
10	Race	All CHD	Correa-Villasenor et al. 1991	Case control	Ebstein's 3.7 (1.1-12.5) AS* 3.6 (1.7-7.6) PA 2.5 (1.0-6.1) COA 2.2 (1.4-3.5) dTGA 1.6 (1.1-2.5) AVSD 1.4 (1.0-1.9) but with AS there was also interaction between race and SES PS 0.6 (0.4-0.8) Heterotaxia 0.4 (0.3-0.8)		BWIS	Good
11	Sex	All CHD	Rothman, Fyler 1976	Descriptive	PDA more common in girls 115 of 179 (63%, $CI_{90\%}$ = 30-42). AS (78%, $CI_{90\%}$ = 66-87); COA (59%, $CI_{90\%}$ = 53-66); and TGA (66%, $CI_{90\%}$ = 61-70). more common in boys.	Predominant lesion method for classifying multiple CHD within the same child	NERICP Registry	Fair
12		Atrial septal defect	Tikkanen, Heinonen 1992	Case control	Did not find an increase of males 0.8, $CI_{95\%}$ =0.5, 1.4.	Used embryological method for classifying multiple diagnoses in one child.	Finish Registers[2]	Good
13		All CHD	Gensburg, Marshall, Druschel 1993	Descriptive	Ratio of female to male was 0.3 in diagnostic group I, 0.4 for diagnotic groups IIA and II B and III but closer to 0.50 for IIC, IV and V. Differences for race also noticed.	Used an embryological criteria for categorization. Closely modeled on BWIS work.	Upstate New York[3]	Good
14		All CHD	Samanek, 1994	Cohort	A higher proportion of boys was found with DORV, HLHS, TGA, aortic stenosis, pulmonary atresia, tricuspid atresia, COA, and CTGA. There were signficantly more girls than boys with PDA, Ebstein's anomaly, Truncus, AVSD and TOF.		Bohemia	Good
15		All CHD	Rose, Hewitt, Milner.1972	Case series	Stronger correlation for males than for females between rubella exposure and PDA. Year to year changes in the percentage of males for CHD as a whole.			

[2] Finnish Register of Malformations and Children's Cardiac Register.
[3] Congenital Malformation Registry

	Risk Factor	Defect Studied	Authors (Year)	Study Design	Findings	Limitations	Notes	Evidence Level
16	Twin birth	L-TGA	Kuehl, Loffredo 2003	Case control	1.5, $CI_{95\%}$ = 1.0-19.4 increased in strength after removing Ivemark syndrome infants to OR=5.8 $CI_{95\%}$ = 1.3-26.1.		BWIS	Good
17		Looping and conotruncal defects	Berg et al., 1989	Case control	Findings allowed speculation that "the twinning process may be related or contributory to the development of CCVM. This process would not be expe3cted to affect both members of a twin pair equally. This may account for the large proportion of discordant twin paris." Howeverm mechanistic group indicated concordance!	From Ferencz et al. (1993) bias by disproportionately greater fetal loss among multiple gestations.	BWIS	Good
18		Atrial septal defect	Tikkanen, Heinonen 1992	Case control	7.8 (1.4, 44)	Used embryological method for classifying multiple diagnoses in one child.	Finish Registers	Good
19	Gestation ≤ 37 weeks				2.0 (1.3, 6.5)			Good
20	Birthweight < 2 500 g				8.0 (3.1, 21)			Good
21	Placental weight < 600g				2.7 (1.5, 4.9)			Good
22	Low birthweight for gestational age	dTGA TOF Endocardial cushion HLHS PS COA severe VSD minor VSD ASD	Rosenthal et al. 1991	Case control	NS 4.4 (2-9.6) 4.5 (1.3-16.1) 4.7 (2.1-10.6) 2.2 (1.1-4.4) NS 3.3 (1.6-6.8) NS NS		BWIS	Good
23	Birth rank	All CHD	MacMahon 1952		No association found	Very early study. Did not report the nosology used or the method of classifying multiple diagnoses within the same child.		Poor
24		All CHD	Heinonen 1976		First born 1.4	No confidence limit reported. Very early study. Nosology not reported. Isolated/Multiple method of classifying multiple CHD within the same child.		Poor

	Risk Factor	Defect Studied	Authors (Year)	Study Design	Findings	Limitations	Notes	Evidence Level
25	Birth rank (continued)	All CHD	Zhan et al. 1991	Case control study	Birth order > 2 increases risk for CHD. 3.3 (2.4-4.5)	Took cases up to 5 years of age Did not address issue of multiple CHD		Fair
26		All CHD	Rothman, Fyler 1976	Descriptive	TGA increasing risk with increased birth order. PDA was associated with a decrease in risk with increasing birth order. ASD was associated with being first born. For PS those born first born had a lower risk.	See above	NERICP	Fair
27		All CHD	Bassili et al. 2000	Matched Case control	Greater than 5th Adj OR 0.84 (0.58-1.21)	Included cases and controls up to 15 years of age. Grouped into ≤ 10 and > 10. Possible recall bias. Matched on age and sex but not time since birth.	Removed non-cardiac associated anomalies from risk factor analyses	Good
28	Maternal Age	All CHD	MacMahon 1952		No association found	See above.		Poor
29		All CHD	Rothman, Fyler 1976	Descriptive	TGV associated with increasing maternal age after having controlled for Down Syndrome.	See above.	NERICP	Fair
30		All isolated CHD Isolated CHD with non-cardiac malformations Recognized syndromes VSD ASD	Stoll et al. 1989	Cross-sectional	No association found 801 cases of 105,374 births. Incidence of 7.6/1000. Mean maternal age was 26.5 for all and with Down syndrome excluded 26.1. Mean control maternal age was 26.0.	No indication as to whether the VSD and ASD categories are isolated or coupled with other cardiac diagnoses.	NFBDM	Fair
31		Atrial septal defect	Tikkanen, Heinonen 1992	Case control	≥ 30 Uncorrected OR= 1.8 (1.0, 3.2) Adjusted Or = 1.2 (0.6, 2.4)	Used embryological method for classifying multiple diagnoses in one child.		Good
32		All CHD without genetic factors	Correa-Villasenor, et al. 1993	Case control	Multivariate analysis of cases with genetic risk factors adjusted OR = 1.35 ($CI_{95\%}$ = (1.2-1.5) for 20-29 and adjusted OR = 1.83 ($CI_{95\%}$ = (1.5-2.3) for 30-39.	This result looks like it must be an error. Reference group has changed without explanation from 20-29 to < 20.	BWIS	Poor

	Risk Factor	Defect Studied	Authors (Year)	Study Design	Findings	Limitations	Notes	Evidence Level
33	Fetal-pelvic disproportion	9 sub-groups: see above	Pradat 1992b	Case control	OR= 1.4 ($CI_{95\%}$ = 1.1-1.9)			Good
34	Hydramnios	9 sub-groups: see above	Pradat 1992b	Case control	OR = 8.0 ($CI_{95\%}$ = 3.8-17.0)			Good
35	Paternal age (continues on next page)	All CHD	Lian, Zack, Erickson 1986	Case control	Increased risk for TGA for fathers > 45 (OR > 3.63)	No CI presented Repeated mesaures data Surveillance data.	MACDP VV Study	Fair
36		All CHD	Zhan et al. 1991	Case control study	Birth order > 2 increases risk for CHD OR=3.3 (2.4-4.5) adj for paternal age Paternal age < 25 associated with increased risk 2.77 (2.21-3.47) adj for birth order	Took cases up to 5 years of age Did not address issue of multiple CHD	Hospital based	Fair
37		All CHD	Stoll et al. 1989	Cross-sectional	No association found Mean case paternal age was 29.5. Control paternal age was 29.2	Surveillance data. Most data collected from chart review and/or neonatalogists.		Good
38	Paternal age (continued from previous page)	All CHD	Olshan, Schnitzer, Baird 1994		ASD 45-49 2.7 (1.3-5.8) PS 35-39 2.0 (1.0-4.0)	Repeated measures data	BCHSR	Fair
39		All CHD	Pradat, 1992c	Case control	No effect observed.	Same study as previously reported.		
40		All CHD	Bassili et al. 2000	Case control	Adj OR > 40 1.97 (1.43-2.70) 23% versus 16%	894 cases birth to 15 years of age. Possible recall bias. Most likely not incident cases.		Poor
41	Paternal age, smoking and alcohol consumption	All CHD	Savitz, Schwingl, Keels 1991	Case control	PS 30-34 - 4.3 (1.1-16.1) Adj 35-39 - 7.5 (1.6-36.3) Adj No association with paternal smoking or paternal alcohol consumption.	May have misclassification bias of cases as each case was assigned, in an unspecified way, to one of 10 congenital categories. Low prevalence compared to high prevalence	CHDS Adjusted for mother's age, race, education and smoking	Poor
42	Paternal smoking	Birth defects	Zhang et al. 1992	Case control	OR 1.21 ($CI_{95\%}$ =1.0, 1.5) overall birth defects.	Cases were all birth defects. Only considered 28 weeks gestation to 1 week postpartum. Paternal smoking reported by proxy (the mother).		Fair

	Risk Factor	Defect Studied	Authors (Year)	Study Design	Findings	Limitations	Notes	Evidence Level
43	Pregnancy resulting from IVF	CVM	Anthony et al., 2002	Case control	increased risk (OR=1.6, $CI_{95\%}$ = 1.1-2.2)	Only had about 53% power. Possible multiple testing issues. Hawthorne effect due to the increased surveillance for IVF conceptions.		Fair
44	Involuntary Childlessness	All CHD	Pradat 1992b	Case control	None between involuntary childlessness and CHD (OR = 1.1. $CI_{95\%}$ = 0.8-1.5) or a time to pregnancy time of 6 months and CHD (OR=0.4, $CI_{95\%}$ = 0.2-1.1).			
45		All CHD	Cedergren et al. , 2002	Case control				
46	Previous stillbirths/spontaenous abortion	IAA type B without DGS	Loffredo et al. 2000	Case control	9.4 (1.3-53.1)		BWIS	Good
47		9 sub-groups: see above Truncus	Pradat 1992	Case control	No association found 3.88 (1.97-7.64)			Good
48		Atrial septal defect	Tikkanen, Heinonen 1992	Case control	265 (34, 546)		Used embryological method for classifying multiple diagnoses .	Good
49	Previous perinatal death	9 sub-groups: see above	Pradat 1992	Case control	1.89 (1.20-2.99)			Good
50	Birth at high altitude	ASD and PDA	Miao et al. 1988a Miao et al. 1988b	Cohort	Prevalence Sea level 0.28% 2,260 meters 1.5 % 3,000 meters 3.5 % 4.500 meters 4.0 % OR of 4.6 for high altitudes.	No stratifiction by age, no information on births in the area Small numbers of cases Unusual that only ASD, PDA, pulmonary anoamlies, BAV and arterial anomalies were identified.		Poor
51			Alzamora et al. 1953	Descriptive	PDA and ASD more likely to be found in patients born at high altitudes.			
52			Penaloza et al. 1964		PDA .72% compared to .04% at sealevel>3500 meters			

	Risk Factor	Defect Studied	Authors (Year)	Study Design	Findings	Limitations	Notes	Evidence Level
53	Maternal bleeding during pregnancy	IAA type B without DGS[4]	Loffredo et al. 2000	Case control	3.7 (1.4-11.4)		BWIS	Good
54		Atrial septal defect	Tikkanen, Heinonen 1992	Case control	1.9 (1.3, 2.8)	Uncorrected results	Used embryological method for classifying multiple diagnoses in one child.	Good
55	Non cardiac malformations	All CHD	Eskedal et al.2004	Registry	13% had an extra-cardiac anomaly excluding DS. 7% had Down syndrome alone. 3% had DS and at least one other extra-cardiac anomaly.	3257 infants registered from 1990-99 CHD only CHD and Down syndrome onely CHD and a non-cardiac malformation other than Down syndrome with or without Down syndrome		Good
56		All CHD	Kramer et al. 1987	Descriptive	4% had DS. 4% had another syndrome. TOF had significantly more ECM's than any other CHD.	June 1981-August 1982. 1016 German children up to 16 years. Non-incident cases. CHD only CHD and a major ECM CHD and a minor ECM CHD and a chromososomal syndrome CHD and a non-chromosomal syndrome		Fair
57		All CHD	Ferencz et al. 1989	Case control	27 % had a non cardiac anomaly.			
58	Maternal exposure to hormones	TGA	Levy, Cohen, Fraser 1973		7 of 76 cases were exposed to sex-hormones during pregnancy. 0 of 76 controls were such exposed.		Controls were mothers with a child with a Mendelian disorder to control against recall bias.	Good
59		Conotruncal	Nora, Nora 1973		20 of 224 CHD cases versus 4 of 262 controls ($p<0.001$)	No details on methods		Fair

[4] IAA Type B with DiGeorge Syndrome

	Risk Factor	Defect Studied	Authors (Year)	Study Design	Findings	Limitations	Notes	Evidence Level
60	Maternal exposure to hormones (continued)	VACTERL patients	Nora, Nora 1975		9 of 15 cases versus 2 of 15	Small study size	Controls were chromosomal anomalies excluding Down or functional murmers	Good
61		Heart disease	Harlap, Prywes, Davies 1975		Cases:5 observed versus 2.6 expected Controls: 63 versus 65.4	Minimal detail on methods		Fair
		All CHD	Heinonen et al. 1977b		18/1000 versus 8/1000. Crude RR=2.3. Adj RR by type of hormone were NS.	Small number of defects. Low power. *Wiseman and Dodds-Smith (1984) proved that this study suffered from misclassification bias of cases.*	CPP	Poor
62		Conotruncal	Ferencz et al. 1980		No association found.	Matched on 10 characteristics.		Good
63		All CHD	Bassili et al. 2000	Case control	Adj OR 1.66 ($CI_{95\%}$=1.1-2.6)	894 cases birth to 15 years of age. Possible recall bias. Most likely not incident cases.	Exposure to the 8th week gestation	Good
64	Maternal starvation	Central Nervous System	Stein, Susser 1976		Found relationship between starvation in the first trimester and development of the. (RR=2.0)	Ecologic study		Fair
65	Maternal obesity pre-pregnancy	Any CHD	Mikhail, Walker, Mittendorf 2002	Case control	Isolated cardiac malformations from African – American women 6.5 (1.2, 34.9)	Excluded possible confounding exposures. Imprecise estimate – small sample size (7 cases and 144 controls) Unable to control for additional confounders Inadequate description of measurement of risk factor (how was pre-pregnancy weight assessed?).	Perinatal database and the clinical genetics records, Dept of Obstetrics and GynecologyUniversity of Chicago.	Poor

	Risk Factor	Defect Studied	Authors (Year)	Study Design	Findings	Limitations	Notes	Evidence Level
66	Maternal obesity pre-pregnancy (continued)	Isolated defects CHD	Watkins, Botto 2001	Case control.	Protective effect found with underweight prepregnancy BMI < 16.5 Adj OR 0.64 (0.43-0.97) BMI = 16.5 to 19.8. Adj OR 1.53 (Isolated VSD or ASD) (1.04,2.25) Adj OR 1.57 (VSD) (1.04, 2.36) Adj OR 1.40 (Isolated plus multiple cardiac defects) (1.01-1.95)	To increase the etiologic homogeneity of the case group, excluded cases of known etiology (syndromes). Contradictory results (Low weight has more risk for All CHD but higher weight has more risk for specific types of CHD.) Abstract discusses non-significant findings and ignores significant ones. Accepted self-reported weight. May have included unrecognized diabetics in exposure group.	MACDP ABDCCS Hierarchically classified	Poor Good
67		All CHD	Cedergren et al. 2002	Case control	For BMI $\geq$ 29OR =1.5, $CI_{95\%}$ = 1.1-1.9.			Good
68	Maternal diabetes	All CHD	Ferencz et al. 1990	Case control	Found a three fold increase in overt diabetes as compared to controls. Overt 3.1 (1.3-7.8) Gestational 1.5 (.9, 2.2) DORV 21.3(3.3, 136.3) Truncus 12.8 (1.4, 114.6) TOF 6.2 (1.4, 27.4) VSD 3.5 (1, 11.3)	Very difficult to do the definitive study because of the rarity of diabetes and the rarity of CHD especially by subgroup.		Good
69		Early Cardiac defects (Hierarchical Groups 1-3) versus Obstructive and shunting (4-6) versus Cardiomyopathy (Group 7)	Loffredo, Wilson, Ferencz 2001	Case control	Early CVM 4.7 (2.8-7.9) Laterality (1) 10.0 (3.7-27.0) Outflow with TGA 3.0 (1.1-8.7) Outflow without TGA 6.6 (3.2-13.3) complete AVSD 22.8 (7.4-70.5) Cardiomyopathy 15.1 (5.5-41.3)			Good
70		9 sub-groups: see above Truncus	Pradat 1992b	Case control	2.67 (1.43-4.99) 3.7 (1.86-7.35)			Good

	Risk Factor	Defect Studied	Authors (Year)	Study Design	Findings	Limitations	Notes	Evidence Level
71	Maternal diabetes (continued)	Serious or major congenital malformations from the MACDP dataset	Becerra et al. 1990		**NIDDM (n=28)** Truncus 17.9 (2.4, 132.6) TGV (27.2 (3.5, 208.5) VSD (3.8, 108.1) Dextrocardia 56.9 (4.1, 794.1) PDA 9.8 (1.3, 72.5) Pulm artery atresia 61.1 (4.7, 791.3) **Gestational Diabetes (n=12)** Truncus 76.0 (6.8, 843.9) TGV 57.1 (5.4, 598.9) VSD 32.6 (2.5, 434.4) PDA 48.9 (4.5, 532.3)	Multiple response approach to CHD diagnosis. Case control study therefore exposure definition is retrospective and subjects may be misclassified. Did not review the medical charts of all the mothers who did not report a history of diabetes mellitus (DM). Too low prevalence of gestational DM. Possibly mothers of case children may have been better screened for gestational DM. Wide confidence limits. Did not measure metabolic control during the first trimester of pregnancy.	Very strong point estimates with lower bounds strongly indicative of a risk. Stable point estimates within organ systems.	Good
72		All CHD	Stoll et al. 1989	Cross-sectional	No association found			Good
73		All CHD	Cedergren et al., 2002	Case control	OR=2.4, $CI_{95\%}$ = 1.4-4.2.			
74	Maternal Diet	Any CHD	Pitt, Samson 1961		Control infants had more grams of protein (72 as compared with 59) in the maternal diet than CHD children, more calories (2453 compared with 1989), more iron (10.7 compared with 8.6), more Vitamin C (86 compared to 57) and more niacin (11.5 compared to 9.0).	Eleven CHD cases of a total 99 congenital malformations: sample size very small	One of the earliest studies in investigating diet and the incidence of congenital defects as a whole.	Fair
75	Maternal exposure to caffeine-containing beverages	Any CHD	Rosenberg et al., 1982	Case control	No association found	Controls were other malformed infants. Used 'use of caffeine-containing drugs' as a confounder instead of added to estimate of risk.		
76	Maternal exposure to folic acid antagonists	Neural Tube Defects	Hernandez-Diaz et al. 2001		2.8 (1.7, 4.6) for any folic acid antagonist. 6.9 (1.9, 25.7) for carbamazepine 4.8 (1.5, 16.1) for trimethoprim	Did not control for diet	SEUBDS[5]	Fair

[5] Slone Epidemiology Unit Birth Defects Study

	Risk Factor	Defect Studied	Authors (Year)	Study Design	Findings	Limitations	Notes	Evidence Level
77	Maternal derangement of homocysteine metabolism	All CHD	Kapusta et al. 1999	Case control	Fasting hyperhomocysteinemia present in 46% of study group 3-6 months after delivery compared with 14% of controls. OR=5.1 (1.8-14.4).	Small study but could be related to stress from being a parent of a CHD child. Better to have had blood level before knowledge by the mother of CHD status of infant.		Good
78		VSD	Rosenquist, Ratashak, Selhub 1996	Clinical trial	23% of embryos sufered VSD after an exposure to a teratogenic dose of homocysteine.	Animal study Avian study showed that 4/18 embryos exposed to an excess amount of homo cysteine developed VSD.		Intriguing
79	Maternal exposure to glycyrrhizin (licorice)	Low birth weight	Strandberg et al. 2001	Cohort with Case control analysis	Elevated OR for earlier delivery was associated with a high intake of glycrrhizin 2.5 (1.1, 5.5; p=0.03).	Didn't control for glyccrhizin in the alcohol which these Finnish women likely consumed. Preliminary design.		Poor
80	Maternal exposure to high vitamin A intake	Pulmonary stenosis	Mastroiacov o et al. 1999		1 case of 311 births exposed to 10,000-300,000 IU per day of vitamin A prescribed for dermatologic conditions or breast fibrocystic disease.	Exposed persons only from Teratology Information Service. Assessment of cases from doctors or mothers. Sample size of small and statistical power low		Good
81	Maternal multivitamin use	Any CHD hierarchically defined	Botto et al. 2000		Reduced OR for all heart defects, outflow, TGA, VSD.	How to control for 'good diet' and no vitimin use versus 'bad diet' and no vitamin use?		Good
82		Conotruncal	Botto et al. 1996		Found decreased risk with peri-conceptional multivitaimn use for Isolated Conotruncal as a group and TGV. Timing of use essential. Only peri and early use is protective.	No diet information. No genetic information.	Compared conotruncal defects against infants without congenital anomalies and with affected controls.	Good
83		Outflow tract	Scanlon et al. 1997		NS	Controlled for adequate diet	BWIS	Good

	Risk Factor	Defect Studied	Authors (Year)	Study Design	Findings	Limitations	Notes	Evidence Level
84	Maternal nausea during pregnancy	Nonsyndromic CHD	Boneva et al. 1999		Women with early onset, daily frequency, long-lasting NP had lower OR for CHD (0.81 (0.67-0.99)). Women with any nausea who took any medications or Bendectin were found to be protected against CHD All 0.77 (0.61-0.97) Bendectin 0.67 (0.50-0.92). Women with Level 1 nausea and all medications 0.74 (0.56-0.97) Women with Level 2 nausea who took Bendectin 0.14 (0.00-0.86) For specific defects found that with ASD			Good
85	Maternal exposure to chemical hair treatments	Preterm delivery and low birth wt	Blackmore-Prince et al. 1999		No relationship between use of chemcial hair treatments and outcome	Low participation rate (65%). High prevalence of exposure in both groups and low power.		Poor
86		I-TGA	Kuehl, Loffredo 2003	Case control	OR for L=TGA of 3.7, $CI_{95\%}$ = 1.6-8.5 after syndromeic cases removed 5.6, $CI_{95\%}$ = 2.3-13.7.		BWIS	Good
87	Maternal gestational hyperthermia (environmental or due to febrile episode)	Limb defects	Martinez-Frias et al., 2001	Case series	No risk assessment			NA
88	Maternal exposure to influenza	TGA	Ferencz et al. 1997	Case control	For the whole group no association. However for the intact ventricular septum group (n=106) 2.1 (1.2-3.6) found. Other sub=types reported		BWIS	Good
89		Circulatory system malformations	Hakosalo, Saxen 1971		No association found	Used only "affected" controls.		Fair
90	Maternal illness	All CHD	Stoll et al. 1989	Cross-sectional	Small, protective associations found			Good
91		All nonsyndromic CHD and subtypes	Botto, Lynberg, Erickson, 2001	Case control	Respiratory infections with fever 1.9 (1.4, 2.6) Tricuspid atresia 5.2 (1.3, 20.2) Aortic stenosis 6.9 (1.0, 14.8) Aortic coarctation 2.7 (1.2, 6.0) VSD 1.8 (1.1, 2.9)		Respiratory infections which are febrile ABDCCS	

	Risk Factor	Defect Studied	Authors (Year)	Study Design	Findings	Limitations	Notes	Evidence Level
92	Maternal epilepsy	All CHD	Stoll et al. 1989		No association found			Good
93		9 sub-groups: Truncus Septuma anomalies Mitral anomalies Tricuspid anomalies HLHS Endocardial cushion Artery malformations COA	Pradat 1992	Case control	(3.95 - upper limit not available because 0 controls with epileptic mothers)		RCM and CCR[6]	Good
94		All CHD	Cedergren et al., 2002	Case control	3 of 269 cases having exposure and 0 of 524.	OR not calcuable.		Good
95	Maternal thyroid disease	Described in other paper 9 sub-groups	Pradat 1992b	Case control	No association found			Good
96			Cedergren et al. 2002	Case control	Suggestion of elevated risk. 3 of 269 cases and 2 of 524 controls. OR = 2.94 (CI_{95}= 0.3-35.4)			
97	Seasonality of birth	All CHD	Feldt et al. 1971		7.2/1000 Dec-Feb 6.4/1000 Mar-May 5.2/1000 June-Aug 4.3/1000 Sept-Nov	Early study. Excluded isolated right aortic arch, anomolies of aortic arch branching, isolated anomalies of systemic venous return, BAV. Did not control for confounding when looked at seasonality. Did not report nosology. Used predominant lesion method for classifying multiple CHD.	CPP	Poor
98		All CHD	Samanek, Slavik, Krejcir 1992	Cohort	Evidence that for different defects (defined haemodynamically) that there are seasonal patterns which for some may have corresponded to influenza epidemics.			Good
99		All CHD	Rose, Hewitt, Milner 1972	Case series	6 to 7% increase of CHD as a whole in the fall and winter (Oct-March) than April-September. More TGA Aug-Jan. Pulmonary valve stenosis seen more in the			

[6] Swedish Registry of Congenital Malformations and the Child Cardiology Registry

	Risk Factor	Defect Studied	Authors (Year)	Study Design	Findings	Limitations	Notes	Evidence Level
100	Influenza treated with antitussives	Defect of laterality and looping	Ferencz et al. 1997	Case control	4.6 (1.4-15.5)			
101	Maternal consumption of medication	All CHD	Stoll et al. 1989	Cross-sectional	No association found			Good
102	Maternal consumption of Benzodiazepines in utero	Malformations	Laegreid, et al. 1987		High anecdotal correlation between benzodiazepine use and malformation	No control group		Fair
103		TGV and LTGV	Ferencz et al. 1997	Case control	Adjusted: OR = 3.3 (CI_{99} = 1.3-8.2)			Good
104	Maternal consumption of Metronidazole in utero	LTGV	Ferencz et al. 1997	Case control	Adjusted: OR = 5.5 (CI_{99} = 1.1-26.8)			
105	Maternal exposure to ibuprophin/aspirin	TGA	Ferencz et al. 1997	Case control	For transposition/intact V septum group OR=2.5($CI_{95\%}$=1.2-4.5). Bicuspid aortic valve: OR=3.8 ($CI_{95\%}$ = 1.7-8.6) AVSD: OR=2.5 ($CI_{95\%}$ = 1.4-4.3) taken for menstrual pain LMP. Membranous VSD 1.5 ($CI_{95\%}$ = 1.0-2.3)		BWIS	Good
106		IAA type "B" with Digeorge syndrome	Loffredo et al., 2000	Case control	OR=3.0 ($CI_{95\%}$ = 1.4-6.5)			
107	Urinary tract infection treated with sulfonamide	Defect of laterality and looping	Ferencz et al. 1997	Case control	7.5 (2.1-26.6)			
108	Maternal exposure to x-rays	All isolated CHD Isolated CHD with ECM, Recognized syndromes, VSD ASD	Stoll et al. 1989	Cross-sectional	No association found	No indication as to whether the VSD and ASD categories are isolated or coupled with other cardiac diagnoses.	NFBDM	Fair
109		All CHD	Bassili et al. 2000	Case control	Exposure to 8th week, Adj OR 6.48 (1.38-43.96)	894 cases birth to 15 years of age. Possible recall bias. Most likely not incident cases.		Good
110	Maternal smoking	All CHD	Stoll et al. 1989	Cross-sectional	No association found			Good
111		Truncus TGA	Kallen 1999	Case control	1.23 (1.02-1.49) 1.32 (1.02-1.71)	Controlled for year of birth, maternal age, parity and educational level but not		Fair

	Risk Factor	Defect Studied	Authors (Year)	Study Design	Findings	Limitations	Notes	Evidence Level
	Maternal smoking (continued)	ASD			1.63 (1.04-2.57)	controlled for maternal diabetes, epilepsy, rubella infections and alcohol use. No dose response demonstrated.		
112		9 sub-groups: see above	Pradat 1992	Case control	No association found			Good
113	Maternal exposure to pesticides	TAPVR	Correa-Villasenor et al. 1991a	Case control	In children with family history of cardiac problems there was a dose response: Pesticides OR 2.06 ($CI_{99\%}$ = 0.82-5.15) Pesticides and familial noncardiac abnormality OR 6.3 ($CI_{99\%}$ = 2.2, -8.1) Pesticides and familial cardiac abnormality OR 19.1 ($CI_{99\%}$ = 3.6-102.0) Both OR 58.3 ($CI_{99\%}$ = 5.1-662.8)	Small sample	BWIS 99 CI	Good
114		TGA	Loffredo et al. 2001b	Case control	Significant OR for any exposure to pesticides during critical period OR=2.0 ($CI_{95\%}$ = 1.2-3.3) In multivariate analysis: herbicides OR=2.8 ($CI_{95\%}$ = 1.2-6.9) and rodenticides OR=4.7 ($CI_{95\%}$ = 1.5-14.2)	No data collection of specific solvents used by the mothers.	BWIS	Good
115	Maternal work in agricultural trades (possible proxy for pesticdes exposure)	Conotruncal heart defects	Adams et al. 1989	Case control	16 (3.05, 85.54) ($p < .10$)	Wide confidence limit		Fair
116	Maternal occupational exposures	All CHD	Stoll et al. 1989	Cross-sectional	No association found			Good
117		All CHD	Bassili et al. 2000	Case control	Adj OR 2.86 (1.26-6.52)	894 cases birth to 15 years of age. Possible recall bias. Most likely not incident cases.		Good
118	Maternal exposure to soldering (proxy for lead)	TAPVR	Correa-Villasenor et al. 1991	Case control	OR = 15.49 (99% 1.95, 122.73)	Small sample size - 37 cases.	BWIS	Good
119	Maternal exposure to paint/paint stripping (proxy for lead)	TAPVR	Correa-Villasenor et al. 1991	Case control	OR=2.96 (99% 1.12, 7.69)	Small sample size - 37 cases.	BWIS	Good

	Risk Factor	Defect Studied	Authors (Year)	Study Design	Findings	Limitations	Notes	Evidence Level
120	Maternal exposure to glycol ethers	All cardiac Endocardial cushion and septal defects Malformations of cardiac outflow HLHS Valve anomolies Other	Cordier et al. 1997	Case control	No association found.	Most likely only identified more severe cardiac anomalies as limited to identification in week 1. No direct exposure data. Repeated measures.	EUROCAT Case control study	Poor
121	Maternal exposure to organic solvents	TGA	Ferencz et al. 1997	Case control	For transposition/intact septum group OR 3.2 (1.4,7.1).		BWIS	Good
122	Maternal exposures to chemicals, dyes, lacquers and paints at work	Conal septal malformations[7]	Tikkanen and Heinonen 1990	Cohort	2.9 (1.2, 7.5)	Used embryological method for classifying multiple diagnoses in one child.	FRCM or CCR[8] Exposure in first trimester	Good
123		Atrial septal defect	Tikkanen, Heinonen 1992	Cohort	Uncorrected OR 1.9 (1.1, 3.4) Adjusted OR 1.9 (1.1, 3.4))			Good
124	Maternal use of arts/crafts paints	IAA type B without DGS	Loffredo et al. 2000	Case control	4.8 (1.3-17.4)		BWIS	Good
125	Maternal exposure to occupational anaesthetic gases	Heart and great vessels	Pharoah et al. 1977		13.8/1000 births heart and great vessel malformations reported for anaesthetists versus 3.6/1000 for other physicians and 6.6/1000 in the National Child Development Study.	Completely self-reported. No quantification of exposure. Used a reference control population. No confirmation of the malformation. Response rate was only 72%.	Respondents medically trained. Data on all pregnancies were collected.	Good
126		Congenital abnormalities	Cohen et al. 1974		9.6% versus 7.6% (p<.03) Results standaradized by age and smoking.	Inadequate response rate (51% for cases and 33% for controls). Lack of detail in results and poor control for possible confounding.		Poor
127	Paternal exposures as a fire fighter	Clark group flow lesions	Olshan, Teschke, Baird 1990		VSD 3.98 (1.31-12.16) ASD 5.72 (1.17-27.98) 281 livebirths to firemen in 21 years	Were the children independent samples? No hazardous exposure measurement. Linkage study rather than actual data collection.		Poor

[7] TOF, TGA, Truncus, DORV, Aortopulmonic window, PA

[8] Finnish Register of Congenital Malformations or Children's Cardiac Register

	Risk Factor	Defect Studied	Authors (Year)	Study Design	Findings	Limitations	Notes	Evidence Level
128	Paternal occupational exposures	All CHD	Bassili et al. 2000	Case control	Adj OR 1.23 (0.95-1.59)	894 cases birth to 15 years of age. Possible recall bias. Most likely not incident cases.		Good
129	Maternal exposure to ambient air pollution	Isolated cardiac defects Aortic artery Defects of atrium Endocardial and mitral valve Pulmonary artery and valve Conotruncal Other VSD	Ritz et al. 2002	Ecological study	Single-pollutant model: exposure to ozone in the second month at greater than 2.85 pphm found a higher rate of isolated aortic artery and valve defects (n=274): OR = 2.68 (1.19, 6.05). Dose response found for VSD in second month for exposure to carbon monoxide (n=260): 1.14-1.56 ppm (1.62 (1.05, 2.48)) 1.57-2.38 ppm (2.09 (1.19, 3.67)) >2.27 ppm (2.95 (1.44, 6.05)). In a multiple-pollutant model found in the group exposed to greater than 2.86 pphm of Ozone OR=2.94 (1.00, 8.67).	Ecological study (possible exposure misclassification) Only looked at 'isolated cardiac defects'. 'Isolated' not defined (as opposed to multiple or as opposed to cardiac plus other congenital malformation). OR adjusted for decade of birth, infant sex, maternal race, and age, single versus multiple birth, parity, prenatal care, maternal education and season of conception		Fair
130	Maternal exposure to public drinking water contamination	Major cardiac defects VSD	Bove et al. 1995	Ecological study	1,2-dichloroethane detected (2.81 (90 CI 1.26, 5.90))	No individual hazardous exposure measurement		Fair
131		All CHD	Goldberg et al. 1990	Ecological study	35% of children with CHD (n=707) had exposure to the contaminated water area versus 10% of 2 of the control groups which were the 'average household'. After the clean-up the proportion of children with CHD in those areas dropped back to the average of the entire Tucson Valley.	Did not collect data on exposures to pregnant women. No data presented on 3rd control group. Poorly written.		Poor
132	Exposure to envirnomental polluation	ALL CHD	Abushaban et al. 2004	Ecological study	Annual incidence per 10,000 live births of CHD increased from 40 pre-invasion to 103 postliberation ($p<0.001$).	Unable to distinguish from families inside Kuwait during the study period. Also, were unable to identify babies who had PDA of prematurity.		Good

	Risk Factor	Defect Studied	Authors (Year)	Study Design	Findings	Limitations	Notes	Evidence Level
133	Residence	All CHD	Bassili et al. 2000	Case control	Semiurban Adj OR 1.52 ($CI_{95\%}$=1.2-1.91) Rural 3.00 ($CI_{95\%}$=2.3-4.0)	894 cases birth to 15 years of age. Possible recall bias. Most likely not incident cases.		Poor
134		All CHD	Cedergren, Selbring, Kallen (2002)	Case control	Rural residence Adj OR 1.4 ($CI_{95\%}$=1.1-1.8) for case county. Reference county showed for City residence Adj OR = 1.3 ($CI_{95\%}$=1.1-1.5).			good

Appendix 1D: Review of the literature on consanguinity with prevalence levels

	Authors (Year)	Population	Coefficient of Inbreeding	DC	FC	FC_1	SC	DR	NC
1	Bener, Alali (2006) 1515 women	Qatar	0.02	3	35		17		45
2	Kir, Gulec, Bakir, Hosgonul, Tumerdem (2005) 387 married soldiers	Turkey	0.03 0.03	0	19	2	3	7	69
3	Wahab, Ahmad, Shah (2005) Resident population – 265 couples Refugee population – 168 couples	Afghanistan	 0.03 0.03	 0 0	 51 48	 4 1	 0 1	 20 10	 24 40
4	Gunaid, Hummad, Tamim (2004) 1050 couples	Yemen	0.02	3	30	5	7	12	43
5	Tamim, Khogali, Beydoun, Melki, NCPNN (2003) 21723 parents	Lebanon	NR	0	7		6		87
6	Roodpeyma, Kamali, Afshar, Naraghi (2002)	Iran	NR	0	16		3		71
7	Zazouk, (2002) 9540 children < 15 Zakzouk, El-Sayed, Bafaqeeh (1993) 6421 children < 12	Saudi Arabia Riyadh, KSA	NR NR	22 19			23 28		55 53
8	Khoja, Farid (2000) 8,894 women	Saudi Arabia	NR	41			11		48
9	Basilli, Mokhtar, Dabous, Zaher, Mokhtar, Zaki (2000)	Egypt	0.01	0	17	2	3	3	75
10	Radovanovic , Shah, Behbehani (1999) Kuwait City, Kuwait 263 mainly Urban origin households Jahra, Kuwait 242 mainly Bedouin origin households	Kuwait	 NR NR	 4 6	 13 26	 0 0	 5.7 10.4	 2.5 17.5	 75 40
11	Al-Abdulkareem, Ballal, (1998)	Dammam, KSA	0.03	13	20	8	3	9	48
12	Al Husain, Al Bunyan (1997)	Riyadh, KSA	0.02	1	27	11	2	10	49
13	Al-Gazali, Bener, Abdulrazzaq, Micallef, Al-Khayat, Gaber (1997) Al Ain, UAE Dubai, UAE	UAE	0.02 0.02 0.02	4 5 1	26 28 21	3 3 4	3 2 7	15 17 8	49 46 60
14	El-Hazmi, Al-Swailem, Warsy, Al-Swailem, Sulaimani, Al-Meshari, (1995)	Saudi Arabia Central Northern N western S western East	0.02 0.03 0.02 0.03 0.02 0.03		26 30 18 27 26 41		15 13 17 21 12 9	16 18 17 20 12 9	57 61 52 68 54 59
15	Badaruddoza, Afzal, Akhtaruzzaman (1994)	India	.02	0	17	12	14	0	57
16	Shami, Grant, Bittles (1994)	Pakistan	.03	1	41	3	1	38	16
17	Al-Salem, Rawashdeh (1993)	Jordan	.03	3	34	7	6	13	36
18	Khoury, Massad (1992)	Jordan	.02	1	32	3	3	11	50
19	Jaber, Merlob, Bu, Rotter, Shohat (1992)	Arab Israel	0.04-0.16	28			11		61
20	Saedi-Wong, Al-Frayh, Wong (1989)	Saudi Arabia	NR	0	31		23		46
21	Shami, Schmitt, Bittles (1989)	Pakistan	0.02-0.03	2	60	4	1	33	
22	Basaran, Sayli, Basaran, Solak, Artan, Stevenson (1988)	Turkey	< .01	< 1	7	4	4	6	79
23	Serenius, Edressee, Swailem (1988)	Riyadh, KSA	NR		52		3	11	34
24	Chaleby and Tuma 143 schizophrenic patients and their companions	Saudi Arabia	NR		16 12		09 07	22 10	52 71
25	Gev, Roguin, Freundlich (1986)	Arab Israel	NR		24		8	68	
26	Al-Awadi, Naguib, Moussa, Farag, Teebi, El-Khalifa (1986) n=5007	Kuwait	0.02	2	30	1	1	20	46
27	Freundlich, Hino (1984) Druze 550 women interviewed. Muslim Christian	Israel	NR	<1 2 0	34 26 18	8 4 6	6 8 5	52 60 71	
28	Govinda Reddy (1983)	India	NR	19*	22		5		54
29	Bashi (1977)	Arab Israel		4					
30	Schull, Neel (1972)	Japan	NR	0	16		17**		67
31	Cook, Hanslip (1966)	Jordan	NR	0	32	21		48	

*Uncle-niece marriages which are equivalent in inbreeding coefficient to double first cousin

**Reported as one or the other or both parents could be shown to be the product of a consanguineous marriage

In all examples, if the data comes from a case control study then it is the background population which is reported. DC=Double first cousin, FC=First cousin, FC_1=First cousin once removed, SC=Second cousin, DR=Distant Relation, NC=Non-Consanguineous.

If DC or FC_1 were not mentioned they were assumed to be 0.

NR=Not reported

Appendix 1E: Review of the literature on consanguinity as a risk factor with assessed evidence level

	Authors (Year)	*Methods* Study type, N, When, Where Population (hospital / population)	*Outcome measure*	*Findings for increased risk for consanguineous unions*	*Limitations*	*Exposure data collection*	*Evidence Level*[1]
1	Bener, El Hakeem, Abdulhadi 2005	Cross-sectional, 2277 newborns screened in 2003. Hospital based. Doha, Qatar.	Hearing loss	Overall HL prevalence of 5.2%. 61% of HL cases were consanguineous versus 25% of non HL ($p < 0.00$)	Population not well defined. Ethnically mixed. HL not subdivided into hereditary and environmental. Results not stratified by bilateral unilateral deafness.	Not defined	Poor
2	Tamim, Khogali, Beydoun, Melki, NCPNN 2003	Cross-sectional, 597 newborns < 37 weeks of gestation admitted to ICU with no congenital malformations, sepsis or neurologic disorders 1998-2001 Greater Beirut, Lebanon	Apnea of prematurity	In multiple gestations OR reported for FC 4.41 (1.4-14.1)	Controls were not from the general population.	FC versus NC and DR. Collection method not described.	Good
3	Queisser-Luft, Stolz, Wiesel, Schlaefer, 2002	Population based birth cohort, Mainz, Germany, 1990-98, all conceptions > 15th week gestation and all induced abortions. N= 30,940 newborn infants and fetuses.	All major malformations: including chromosomal	OR 2.6 (1.7-4.0) for "consanguinity" (not defined) adjusted for other factors for any major malformation.	Very thorough and active surveillance however details on N of consanguineous families and collection of consanguineous data not provided.	Not defined	Strong
4	Roodpeyma, Kamali, Afshar, Naraghi 2002	Case-control, 346 cases of CHD and 346 controls 1995-2000 Tehran, Iran	Congenital heart defect	No association found. Remarkably low rate of DM in mothers (<0.01)	No statement that multiple probands were excluded from analysis.	Not defined	Poor
5	Becker, Al-Halees, Molina, Paterson 2001	Cohort of 891 CHD patients compared to population survey of 3212 controls. Saudi Arabia Jan-August 1998.	Congenital heart defect	Significant association between rate of consanguinity in CHD population versus background population: 40% versus 28 % (p , 0.001).	Used 'predominant lesion' method of categorizing multiple defects. Misclassification of exposure probable. Used prevalent as well as incident data (survivor bias).	Not defined.	Poor
6	Hussain, Bittles, Sullivan 2001	Cross-sectional from 2 population surveys. Indian data: 1992-93, 5447 infants; Pakistani data: 1990-91, 3993 infants	Under 5 mortality	Increased risk in consanguineous unions for early mortality with control for death clustering using logistic regression. India: 1.2 (1.0-1.4) $p < 0.05$ Pakistan: 1.3 (1.2-1.6) $p < 0.01$	Offspring of women married only once, singletons, only analyzed FC.	Not defined	Strong, but clinically small increased risk.
7	Khoury and Massad 2000	Cross-sectional, 2007 couples randomly selected from entire Jordanian population in 1980.	Reproductive wastage: fertility, stillbirth, infant mortality	Stillbirth more frequent in consanguineous couples (controlled for years of marriage) 11//1000 LB v. 6/1000 LB ($p < 0.05$). Reported congenital malformations 17.5/1000 LB v. 9.8/1000 LB ($p < 0.01$). Infant mortality (FC) 71/1000 LB v. 49/1000 LB ($p < 0.01$). Female infant mortality (FC) 67/1000 v. DR and NC 58/1000 ($p < 0.01$).	None.	Consanguinity data well collected and well defined.	Strong

[1] *Evidence Level* assessed by the Investigator on a 4 point scale of Strong, Good, Fair or Poor.

	Authors (Year)	Methods Study type, N, When, Where Population (hospital / population)	Outcome measure	Findings for increased risk for consanguineous unions	Limitations	Exposure data collection	Evidence Level[1]
8	Durkin, Khan, Davidson, Huq, Munir, Rasul, Zaman, 2000	Cross-sectional, national household survey of childhood disability, Bangladesh, 1987-88	Serious cognitive and mild cognitive disability.	Unadjusted OR serious cognitive disability: Urban 1.1 (0.4-3.1) Adjusted OR serious cognitive disability: Rural 15.1 (3.1-74.3) Prevalence of 6/1000 compared to 19/1000 found in previous study.	Possible misclassification bias. Reports uncle-niece marriages. 93% of infants had homebirths. Unable to identify known risk factors and other known variables such as multiple births or traumatic brain injuries.	FC or UN Data collection method not defined.	Poor
9	Bassili, Mokhtar, Dabous, Zaher, Mokhtar, Zaki 2000	Frequency matched case control study	Congenital heart diseases	All CHD- Adj OR 2.4 (1.9-3.0) VSD – Adj OR 2.7 (2.0-3.5) ASD – Adj OR 2.4 (1.6-3.5)	Well powered. Collected phylograms.	Data collection defined.	Strong
10	Stoltenberg, Magnus, Skrondal, Terje Lie 1999	Cross-sectional, using Norwegian Registry data. 629 888 births occurring between 1967 and 1994 to unrelated parents and 3466 births to related parents.	Recurrent stillbirth and infant death	For parents who were first cousins with a previous infant death compared to non-first cousins with no previous infant death the stillbirth adj risk (sibling number, maternal age, mother and father's educational level, year of birth) was 1 (-20-22) and the infant adj risk was 68 (13, 122).	Restricted analysis to first cousins consanguinity.	FC only. Data collection method not defined	Strong
11	Stoll, Alembik, Roth, Dott 1999	North-Eastern France Case control study from 238,942 consecutive births	B irth defects	Exclusing known Mendelian conditions, 1.21% in cases and 0.27 in controls.	Accepted as consanguineous non-consanguineous (ie more distantly related than 2cd cousin) couples in controls.		Fair
12	Radovanovic Z, Shah N, Behbehani B 1999 (1998)	Cross-sectional sample of 25% of all households of Kuwaiti nationals from Kuwait City and Jahra. 1407 individuals with 959 current or previous marriages	Prevalence of Consanguinity	Bedouin ethnicity and year of marriage associated with consanguineous marriage.	Did not define "Bedouin". Lack of independence. "Marriages" analyzed. Consanguineous marriage may be associated with individual.	Very well collected	
13	Dorsten, Hotchkiss, King 1999	1777 singletons born from 1917 to 1988 to Amish families in Pennsylvania, USA.	Perinatal mortality Neonatal mortality Post-neonatal mortality	The more consanguineous the marriage, the greater the chances of dying during the first year for infants who survive the first week following birth.		Very well collected	Strong
14	Becker, Al Halees 1999	949 Saudi Arabian hospital patients with CHD compared to rates from published data on 3212 families	Prevalence of consanguinity in the two groups		Possible misclassification of exposure. No half or multiple relationships described. Background population statistics collected using different methods.	Data collection method not defined.	Poor
15	Al-Abdulkareem, Ballal 1998	Cross-sectional study, Ever-married Saudis. 944 females, 363 males.	Reproductive wastage	No difference between consanguineous and non-consanguineous offspring.	Statistical analysis not well described.	Data collection method not defined.	Poor
16	Al Husain, Al Bunyan 1997	Cross-sectional study of 2001 married Saudis living in Riyadh. 1365 women and 636 men aged 20 to 45 years, in 1993.	Prenatal and Postnatal mortality	No difference between consanguineous and non-consanguineous offspring.	Consanguinity included those more distant than second cousin. Possible misclassification of exposure as no half or multiple relationships described.	Data collection method not defined.	Good

Appendix 1E: Review of the literature on consanguinity as a risk factor with assessed evidence level

	Authors (Year)	Methods Study type, N, When, Where Population (hospital / population)	Outcome measure	Findings for increased risk for consanguineous unions	Limitations	Exposure data collection	Evidence Level[1]
17	Stoltenberg, Magnus, Lie, Daltveit, Irgens 1997	Cross-sectional survey of all births between 1967-1993 in Norway considering a population of Pakistani origin (n=7494).	Birth defects	Elevated risk for children of 2 Pakistani parents Adjusted OR = 1.4 (1.2-1.6)		Consanguinity question hard-coded. FC or closer, other, NC	Strong
18	Hassan, Haleem, Bhutta 1997	Case control study, 8331 births between 1987 and 1992. 34 cases of CHD. Hospital based. Pakistan.	Congenital heart diseases	No association found between consanguinity and CHD.	Methods for capture of consanguinity not described. Categories not described.		Poor
19	Narchi, Kulaylat, 1997 Al-Hasa, Saudi Arabia	Cross-sectional, 18,146 live deliveries 1987-1992	Congenital malformations	No association found between CHD and congenital malformations	Rates found in population compared to published rates. (I.e., could have analysed using RR.)	Data collection method not defined.	Poor
20	Abulrazzaq, Bener, Al-Gazali, Al-Khayat, Micallef, Gaber, 1997	Cross-sectional, 2033 UAE married parous residents in Dubai and Al Ain, 15+, Oct 94-March 95		Congenital abnormalities 1.7 (1.5-1.9) Leukemias 1.2 (1.4-2.0) Other neoplasms 1.5 (1.1-2.1) Chronic liver disease 1.7 (1.3-2.1) Mental retardation 1.5 (1.2, 1.9) Eye disease 0.6 (0.4-0.9)	Data not clearly independent (multiple outcomes per family unit analyzed)	Data collection method not defined.	Good
21	Al-Gazali, Dawodu, Sabarinathan, Varghese, 1995	16,419 consecutive live and stillbirths over 500 birth at three main hospitals in Al Ain, UAE 1992-1994.	Multiple congenital abnormalities suspected or diagnosed up to 1 week.	1.7 (1.3-2.2) 10.5 /1000 births	Data not clearly independent (multiple outcomes per family unit analyzed).	Data collection method not defined.	Good
22	Abu-Rezq, Al-Tarkait, Husien, Qasrawi, Radovanovic, 1995	Case control study of 212 Kuwaitis aged 4 to > 43, matched by age, area of residence, sex and Kuwaiti versus bedouin	Multiple handicaps Cases had more handicapped siblings	1.9 7.0	Data not independent. Multiple children from same consanguineous pair included.	Data collection method not defined.	Poor
23	Badaruddoza, Afzal, Akhtaruzzaman , 1994	Cross-sectional study of 1721 infants in Aligarh, North India.	Congenital heart defects	37 cases of whom 1.2% NC and 3.4 C. RR=2.8	95% CI not presented. Extremely high prevalence of disease (21/1000 screened).	Geneologically traced to establish degree of consanguinity	Good
24	Zakazouk, El-Sayed, Bafaqeeh, 1993	Random sample of 6421 Saudis < 12 years of age, Riyadh, Saudi Arabia, May 1988-September 1990.	Sensorineural hearing impairment	RR=2.0	95% CI not presented. Data not independent. Multiple children from same consanguineous pair included.	Data collection method not defined. Missing categories.	Poor
25	Jain, Nalini, Chandra, Srinivasan, 1993	Hospital based case control study, Pondicherry, India. 18 months 1988-89. 400 cases; 1000 controls	Congenital malformations, Reproductive wastage	RR=2.0	95% CI not presented. Data not independent. Multiple children from same consanguineous pair included.	Data collection method not defined. Ambiguous categories.	Poor

Appendix 1E: Review of the literature on consanguinity as a risk factor with assessed evidence level

	Authors (Year)	Methods Study type, N, When, Where Population (hospital / population)	Outcome measure	Findings for increased risk for consanguineous unions	Limitations	Exposure data collection	Evidence Level[1]
26	Bundey, Alam, 1993	Prospective study of 4934 children in Paksistan.	Postneonatal mortality and childhood morbidity including autosomal recessive diseases	1.86% of consanguineous Pakistanis had postneonatal deaths as compared to 0.34 % non-consanguineous Pakistanis, 0.54% Europeans and 1.12% Afro-Caribbean. Serious malformation rates were 1.83% for Consanguineous Pakistani, 1.01 for non-consanguineous Pakistani, 0.49 for European. Authors note that CHD was not associated with consanguinity in this study.	Some results discussed were not shown. Risk analysis of consanguinity as a risk factor not shown.	Data collection method defined.	Poor
27	Bittles, Grant, Shami 1993	Cross-sectional, 9250 families 1979-85 Punjab, Pakistan	Reproductive wastage	Stillbirths ranged from 9% DFC; 4% FC; 3% FC_R, 4% SC, 3% NC. Greater fertility?	DFC, FC, FC_R, SC, NC		Good
28	Jaber, Merlob, Bu, Rotter, Shohat 1992	Cross-sectional, 610 Arab families within one village. 1988-1989. Israel	Major malformations	FC 15.8% DR 15.1 Near inter-village marriages 8.3 Far inter-village marriages 4.1 Between classes p<0.01.	Not generalizable: specific to this extended family descended from < 20 original families who at the time of study all carried the same last name.	FC, DR (2cnd or 3rd), DF, DV	Good
29	Shami, Qaisar, Bittles 1991	825 outpatients from the Pakistan Institute of Medical Sciences for Nuclear Oncology, Islamabad, Pakistan, 1987-1988.	Diseases	Mentally retarded infants (f=0.04), people with cancer (f=0.04), and deaf/mute (f=0.04)) babies had higher co-efficient of inbreeding than the general population (f=0.02).	Small study. Mixed diseases.		Poor
30	Naguib, Al-Awadi, Moussa, Farag, Teebi 1989	401 patients with numerical chromosomal aberrations, Kuwait, 1980-1983. 403 controls.	Nondisjunction	OR = 1.8 for FC. 1.8 for < FC. No CI presented. Log-linear analysis found that the ordered by significance, maternal age, paternal age and consanguinity were the strongest fators.	Not all patients accounted for (n=362).	Data collection method not defined.	
31	Shami, Schmitt, Bittles 1989	3329 interviews door to door or during labour & delivery. 7 cities, Punjab region, Pakistan 1980-83.	Prenatal and postnatal mortality	Using a regression equation authors were able to show that mortality under random mating was lower than death ascribed to inbreeding measured as lethal equivalents per gamete (p<0.001).	Unable to control for SES and there was noticeable variation between the 7 cities studied. Analysis method unusual.		Poor
32	Chitty, Winter 1989	63 442 births 1980-1985 at four hospitals in the North West Thames region, UK. 803 perinatal deaths.		Pakistanis had a perinatal mortality rate of 1.39 (1.05-1.82) p < 0.05)	Borderline significance. Not controlled for consanguinity or SES.	Incomplete ascertainment	Poor
33	Balarajan, Soni Raleigh, Botting 1989	England and Wales, 1982-85, 9077 to women born in the UK and 1295 to women born overseas.	SIDS	Post-neonatal mortality per 1000 live births Pakistani mothers: 6.4/1000 Caribbean mothers 4.5/1000 UK and Irish mothers 4.1/1000 Indian mothers 3.9/1000 African mothers 3.0/1000 Bangladeshi mothers 2.8/1000	Mother's ethnicity classified by country of birth.	Does not deal with consanguinity as a variable.	Poor
34	Afzal 1988	566 randomly selected healthy 9-12 year old children, from Bhagalpur, India via door to door survey. Independence of measurement. Took only 1st or 2nd born. Excluded if parents were themselves from	Cognitive behaviour using Weschler's Intelligence Scale for Children (WISC)	Consanguinity (p<0.001) and locality (p<0.001) independently affect IQ scores and locality interacts with consanguinity (p<0.05).	IQ of parents not tested. Hard to imagine that the authors were able to find so many families where the parents met the study criteria of being the first recently consanguineous couple.	Only considered equivalent to FC consang.	Good

Appendix 1E: Review of the literature on consanguinity as a risk factor with assessed evidence level

	Authors (Year)	Methods Study type, N, When, Where Population (hospital / population)	Outcome measure	Findings for increased risk for consanguineous unions	Limitations	Exposure data collection	Evidence Level[1]
		consanguineous families. 748 outbred and 566 inbred children.					
35	Khoury, Cohen, Diamond, Chase, McKusick 1987	Case control study of 211 cases of ascertained between 1969 and 1980 to Amish families in Pennsylvania, USA.	Pre-reproductive death	Adjusted results showed that 1. Offspring closer than 2nd cousin are 2.35 times more likely to have a birth defect recorded at birth. 2. Inbred offspring are 1.49 times more likely to a + family history of siblings dying in the pre-reproductive period. 3. Inbred offspring are at a higher risk of IGR (2.31)	Confidence limits not included.		Good
36	Chaleby, Tuma 1987	143 randomly selected schizophrenic patients Saudi Arabia	Schizophrenia	NS	Control group not tested to be free from disease. Underpowered.	3 levels of consang. FC, SC, DR	Poor
37	Gev, Roguin, Freundlich 1986	Cross-sectional survey of 1546 children in Israel of Arab and Druze origin.	Congenital heart defects	FC 3.2; SC 1.6; NC 1.24 % $p < 0.05$. Authors did not calculate RR. Self-calculated =2.59 with CI provided.	Oddly, no cases of diabetes were found in the population and no case of CHD in the parents. No sibling CHD. Only one Down syndrome. Found CHD incidence of 18 per 1000. Found no multiple defects. Only studied first and second degree relatives. Druze included. All Arabs included.	Phylogram	Poor
38	Al-Awadi, Naguib, Moussa, Farag, Teebi, El-Khalifa 1986	Cross-sectional, 5007 females randomly selected in 1983. Kuwait	Reproductive wastage	N.S.			
39	Agawal, Sinha, Jensen 1984	186 male 13-15 year old, secondary school students, 86 FC 100 NC India	Raven matrices IQ test	Mean adjusted for age and SES: FC 28; NC 34 ($p<0.001$) with more variance in FC group ($p<0.01$)			
40	Govinda Reddy 1983 India	Three castes of high, middle and low SES in Andhra Pradesh. 2524 couples surveyed in 1978-1979	Fertility and survival to age 21	Mean number of pregnancies: Consanguineous 7.2. Non-consanguineous 5.6 ($p< 0.05$). Mean number of live births Consanguineous =6.8 Non-consanguineous 5.3. ($p< 0.05$). Mean number of surviving offspring: Consanguineous = 3.9 Non-consanguineous 3.9. (p=NS).	Did not control for years of marriage. Did they control for SES in the way they think they did?	Phylogram used with inter-rater reliability establishing reliability of the data.	Good
41	Alfi, Chang, Azen 1980	11,614 singleton births, 107- Kuwait	Down syndrome	1.7/1000 Down syndrome babies identified. Consanguinity sig associated with Down syndrome after controlling for maternal age RR 4.1 & 5.0 (CI not shown) ($p<0.005$).	FC, FC_R, SC, NC		
42	Bashi 1977	Cross-sectional, 3203 Arab children from grades 4 and 6 in Israel	Cognitive performance	12 year olds from DC showed higher variance in general intelligence tests, Arabic, Hebrew and Science. Outbred children achieved the highest performance and offspring of DC achieved the lowest.	DFC, FC, NC		

Appendix 1E: Review of the literature on consanguinity as a risk factor with assessed evidence level

	Authors (Year)	Methods Study type, N, When, Where Population (hospital / population)	Outcome measure	Findings for increased risk for consanguineous unions	Limitations	Exposure data collection	Evidence Level[1]
43	Schull, Neel 1972	Infants from 10,530 marriages collected in 1964 Japan	Various measures (see findings)	Fetal loss and non-accidental death prior to 21 were 4% more in consanguineous children than NC. Higher fertility and birthrate in consanguineous versus NC. Five % consanguineous childlessness versus 10% in NC. Tapping rate was lower in adults from consanguineous families. Not significant: fetal death, physical development, Sys & dis blood pressure, disease of eye and ear, visual accommodation & acuity, auditory acuity, IQ, school performance.			
44	El-Alfi, Shaker, Shaath, Salam 1968	Cross-sectional, 4625 live births in 1967, hospital based, Kuwait	Malformations	54% in consanguineous parents; 46% in non-consanguineous.	Not controlled for maternal illness		Fair
45	Cook, Hanslip 1966 Jordan	1963-64, North-east Jordan, 1097 women interviewed attending clinics.	All child mortality Infant mortality	FC = 252/1000 FC_R and SC 240/1000 DR and NC 222/1000 P = NS FC = 203/1000 FC_R and SC 178/1000 DR and NC 152/1000 P < 0.01		Hard coded	Good

CC: case control
MRA: Medical Records Abstraction

Month	MRN	Instructions	Appointment Date for Interview	Interview Complete	Date of Birth
December	788189				
2004	792241				
	785587				
November	810533			1	
2004	798511			1	
	808413	App after 1 year			4/20/2004
	799594	App after 1 year			10/13/2004
	808466	App after 1 year			10/17/2004
October	773508	No appointment			7/8/2004
2004	794971			1	
	808118			1	
	793344			1	
	799582			1	
September	763031			1	
2004	792053			1	
	785669			1	5/1/2004
	769400			1	
	790972			1	
	783527			1	
	790603			1	
	788489			1	
	795547			1	
	791148			1	
August					
2004	750352			1	
	765497			1	
	763698			1	
	790432			1	
	790435			1	
	760879			1	
	777231		No appointment		4/23/2004
	785492			1	
	757135		No Appointment		11/20/2003
	790833			1	
	784331			1	
	792591			1	
July					
2004					
	785557			1	
	780270			1	
	784151			1	6/1/2004
	763441			1	
	785699			1	
	786735			1	
June					
2004					
	777789			1	
	780376			1	
	781360			1	
	757605			1	
	512163			1	
	480906	Too Old			11/13/2000
	776084			1	
	782875			1	

Month	MRN	Instructions	Appointment Date for Interview	Interview Complete	Date of Birth
	778721			1	
	732777			1	
	777023			1	
	784486			1	
	778296			1	
	783029			1	
	758926			1	
	784045			1	
May 2004					
	775469			1	
	774998			1	
	773328			1	
	764435			1	
	763507	This is brother of 763506	No appointment		1/12/2004
	763506	Refused"she doesn't want	only one to be registered		
	777909			1	
	776587			1	
	771039			1	
	775614			1	
April 2004					
	775168			1	
	772976			1	
	762987			1	
	768846	Too Old			28/9/2000
	767773			1	
	769156			1	
	769101			1	
	739474			1	not shown
	769903			1	
	767157			1	2/15/2004
	772396			1	
	764424			1	
March 2004					
	768947	Deceased			
	757463			1	
	763322			1	
	769807			1	
	760363			1	
	764842			1	
	771434			1	
	747979	Deceased			
February 2004					
	763559			1	
	763987			1	
	756573			1	
	765897			1	
	764722			1	
	766068			1	
	760668			1	
	531132			1	
	765966			1	
	762758			1	
	765899			1	
	767791			1	

Month	MRN	Instructions	Appointment Date for Interview	Interview Complete	Date of Birth
January 2004					
	754198		No appointments scheduled		11/14/2002
	761153			1	
	756024			1	
	757966			1	
	761758			1	9/8/2003
	730324			1	
	760588			1	
	761155			1	
	764702			1	9/3/2003
	763897			1	
	757292			1	
December 2003					
	750546			1	
	756358			1	
	742860	sister already interviewed	516880		28/7/2003
	753618			1	
	754580	call/ (Not abstracted)	No appointments scheduled		2/21/2002
	735486			1	
	743139			1	
November 2003	748516	PDA			
	738099			1	13/7/2002
	732281		No appointments scheduled		4/5/2003
	749498			1	
	751183			1	
	756634			1	
	756426			1	
	756495	Call (Not abstracted)	No appointments scheduled		5/23/2003
	750815	Mitral valve			
	473849			1	
	750985			1	
October 2003	750332	PDA			
	738902			1	
	720877			1	
	741103			1	
	752189			1	
	752592			1	
	733418			1	
	711558	Father divorced mother & refuse	Alderea,Maha(Oct 26/04 at 9:15)		22/10/2002
	749046		27/11/04 at 10:30		26/8/2003
	749497	Born in 1994			
	743854	Call			3/8/2003
	745340	Too old to be interviewed			4/29/2000
	752716	Born in 1995			
	744701	Nurse pediatric(Not abstra	16/10 9:15 (didn't arrive for the app.)		6/12/2003
	742254	PDA			
	752891			1	
	746617			1	
	749496			1	

Month	MRN	Instructions	Appointment Date for Interview	Interview Complete	Date of Birth
September					
2003	737846	PDA			
	721905	PDA			
	747437			1	
	746234			1	
	483942	CHB, PDA			
	748280			1	
	748834				
	742334	Deceased			
	748375			1	
	515120	Call	No appointments scheduled		1/8/2001
	527359	Call	No appointments scheduled		18/1/2002
	734679	Nurse Pediatric + Ped Car	06/12/2004 09:05:00 13:40		23/5/2003
	744347			1	
	743084	Call	No appointments scheduled		2/7/2002
	527199	Call	No appointments scheduled		5/9/2002
August					
2003	737661			1	
	744344			1	
	740675			1	
	744593			1	
	741519			1	
	532027	Call		1/2 done	25/7/2001
	745892	Isolated (HCM)			
	746804			1	
	740200			1	
	740642	Deceased (Registered in July, 2003)			
	743345			1	
July					
2003	734403			1	
	733944			1	
	738265	PDA			
	740725			1	
	734724			1	
	732940			1	
	739669			1	
	516751			1	
	742363			1	
	719164	Deceased			
	513632	Deceased			
	729211	DCM	Deceased		
	527339			1	
	521759			1	
	517537			1	25/11/2001
	56582			1	
June					
2003	724405			1	
	728404	call	No appointments scheduled		28/9/2002
	725445			1	
	735471			1	
	734888	Deceased			
	720312			1	
	736510			1	
	737956			1	
	539845			1	
	736647			1	
	735157			1	
	731990			1	
	733134			1	
	513351	Deceased			

Month	MRN	Instructions	Appointment Date for Interview	Interview Complete	Date of Birth
May	730088			1	
2003	730079	Abdullah to call. Next appt	24/7/05		10/8/2001
	731052			1	
	728615	CHB			
	733464			1	
	728837			1	
	527272			1	
	733144			1	
	734502			1	
	731346			1	
	484269			1	
	735017	refused			
	730055			1	
	720573			1	
	722074			1	
April	719183			1	
2003	728002			1	
	720710			1	
	504267			1	
	727315			1	
	728904			1	
	726712			1	
	517625			1	
	714699			1	
	729034	call/ PDA	No appointments scheduled		19/10/2002
					1/11/2002
March	516880			1	
2003	720396			1	
	720246			1	
	723395			1	
	530879			1	
	539656			1	
	726536			1	
	723853			1	
	727039		by Phone		7/20/2001
	726931			1	
February	718738	call	No appointments scheduled		12/14/2001
2003	721383			1	
	721124			1	
	723219	DCM PFO			
	715849			1	
	721774	Isolated PDA			
	721909			1	
	503380			1	
	717167			1	
January	71900			1	
2003	720200			1	
	720403			1	
	520207			1	
	719007			1	
	715711			1	
	530915	Prolapsed QT. No need to interview.			
	718720			1	
	721327			1	
	521729	call	No appointments scheduled		3/17/2002
	520630			1	
	520232			1	

Month	MRN	Instructions	Appointment Date for Interview	Interview Complete	Date of Birth
	530934			1	
	539946			1	
	529855			1	
	505360			1	
	714764			1	
	720164	REFUSED			
	710171			1	
	59081			1	
December	714404			1	
2002	540509	Telephone only, generally mothe	No appointments scheduled		4/24/2002
	715728			1	
	527533			1	
	529836			1	
	715073			1	
	716090			1	
	513397			1	
	531297	Deceased			
	712501			1	
November	712503			1	
2002	712106			1	
	712109	call	No appointments scheduled		7/12/2001
	712622	Deceased			
	69336	ISOLATED PDA			
	712249			1	
	69351			1	
	712656	Began interview but refuse	Refused		
	531996			1	
October	710043			1	
2002	528747			1	
	539854			1	
	528591	Isolated PDA			
	528592			1	
	528594	Deceased			
September	531208			1	
2002	528622	Too old now			9/19/1999
	520237	PFO			
	529651			1	
	516658	PFO			
	531764		No appointments scheduled		1/1/2001
	539864			1	
	539766			1	
	69377			1	
	531894	Isolated PDA			
August	529809			1	
2002	530916			1	
	519457	Refused			
	527566	Ped Pre Caths	12/19/2004 8:30		7/10/2002
	530970			1	
	519882			1	
	502793			1	
	517595			1	
	520296			1	
	527598	Isolated PFO			

Month	MRN	Instructions	Appointment Date for Interview	Interview Complete	Date of Birth
July	529703	Apointment after 1 year			7/6/2002
2002	69305			1	
	527407	call	No appointments scheduled		6/2/2002
	527322			1	
	528727			1	
	528730			1	
	506841			1	
	515145			1	
	515157			1	
	515158	call	No appointments scheduled		7/5/2001
	528685			1	
	527193	Drs.Hajjar/Frayha //Fa	12/29/2004 13.30 Call		5/14/2002
June	515203	Call	No appointments scheduled		4/1/2001
2002	484827			1	
	527329	Deceased			
	527231			1	
	515231			1	
	520146	PFO, SVT			
	485576			1	
	515197	PDA			
February	516751			1	
2002					
September					
2000	471076			1	
				247	

28 September 2003/2 Shaban 1424

	Deliver in	If normal gestation	Conceived in
1	Muharram		4 (Rabia Al Thani)
2	Safar		5 (Jumada Al Awal)
3	Rabia Al Awal		6 (Jumada Al Thani)
4	Rabia Al Thani		7 (Rajab)
5	Jumada Al Awal		8 (Shaban)
6	Jumada Al Thani		9 (Ramadan)
7	Rajab		10 (Shawwal)
8	Shaban		11 (Dhu Al Qada)
9	Ramadan		12 (Dhu Al Hijjah)
10	Shawwal		1 (Muharram)
11	Dhu Al Qada		2 (Safar)
12	Dhu Al Hijjah		3 (Rabia Al Awal)

RAC#991 031 KACST approved Military and KFSHRC
Risk Factors for CHD in Saudi Infants

TERATOLOGY 65:78–87 (2002)
DOI 10.1002/tera.10016

Design and Development of an Internet Registry for Congenital Heart Defects

WAJEEH MITRI, AMY L. SANDRIDGE, SHAZIA SUBHANI, AND WILLIAM GREER*
Biostatistics, Epidemiology and Scientific Computing Department, King Faisal Specialist Hospital and Research Centre, Riyadh 11211, Saudi Arabia

ABSTRACT

Background: Congenital Heart Defects (CHD) are conditions that encompass more than 50 diagnoses and are due to developmental abnormalities early in fetal life. The King Faisal Specialist Hospital and Research Centre in the Kingdom of Saudi Arabia treats approximately 100 new cases per month. We recently developed a new CHD Registry that captures, stores and processes our data via the Internet.

Methods: The Registry was developed using Hypertext Markup Language (HTML), Microsoft Active Server Pages and Microsoft Structured Query Language (SQL).

Results: Details of CHD cases are captured in a World Wide Web (WWW) Registry, permitting any browser-enabled PC or Mac to participate fully in all registry functions, including data-entry, viewing, editing, searching, reporting, validating, charting, and exporting data subsets to statistics packages. It includes "administrative" features and an active security system. The paper forms have been designed to reflect the "look and feel" of the Web pages. Automatic validation procedures are also included.

Conclusions: Our Registry has been in operation for 3 years. It serves 10 PCs and contains more than 3,000 registered cases of CHD. It is the first CHD Registry to be fully functional on the Internet. It is also the first *dedicated* CHD registry, and the first to routinely report on the full spectrum of CHD diagnoses. The WWW offers several logistical advantages to disease registries, especially those that represent large regions. It also offers the possibility of sharing resources between registries, facilitating the aggregation and analysis of disease data on a world-wide scale. This is useful for rare diseases such as CHD (see http://rc.kfshrc.edu.sa/chdr/demo/).

Teratology 65:78–87, 2002.

INTRODUCTION

The Internet has developed exponentially since its inception in the 1980s. In particular, the World Wide Web (WWW) has outgrown its original objective of simply allowing the same document to be shared from different locations (Marine et al., '93), and has reached the stage where new categories of application are being developed almost on a daily basis. We have already seen the successful application of the WWW to both medical research and routine clinical problems. Two clear examples are the Human Genome Initiative (Bishop, '99) and Evidence Based Medicine (Jadad et al., '00). One area, however, which has been slow to take advantage of these opportunities, is the field of clinical or disease registries.

A disease registry is an ongoing, systematic, and inclusive listing of all individuals with an identified disease from a defined population (MacLennan, '78). Although the range of information held in a registry may be limited, its power lies in its comprehensive coverage of the patient population it serves. Disease registries are an important resource in epidemiological surveillance (Wilson et al., '93; Schulman et al., '93), and are being used increasingly as management tools by hospital administrators and health-care planners (van Bemmel and Musan, '97). A good disease registry can also be a vital resource for clinical researchers because it provides an efficient way to identify particular subsets of patients for research studies and clinical trials (Timmreck, '94). Coupled with computer technology, modern disease registries can be powerful software tools; they can easily model complicated data-structures (such as *hierarchical* pedigree relationships), and they allow complex database searches to be performed on a routine basis.

The Internet now offers registries additional logistical advantages. A WWW registry can be accessed from anywhere, using a regular Web browser, allowing "universal" data-entry, searching, and analysis. Furthermore, because WWW software is largely independent of scale, a single solution can often be applied in a variety of circumstances. Registry content can also benefit from the standard WWW language (Hypertext Markup Language; HTML) that, for example, inherently distinguishes between nominal and continuous variables.

The King Faisal Specialist Hospital and Research Centre (KFSH&RC) is a tertiary care institution committed to providing state-of-the-art medical care, and

*Correspondence to: William Greer, Biostatistics, Epidemiology, and Scientific Computing Department, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia. E-mail: greer@kfshrc.edu.sa

Received 12 December 2000; Accepted 19 September 2001

has already developed several successful disease registries, including a well-published Tumor Registry, which offer a means to identify local risk factors and document the changing patterns of diseases in the Kingdom, a phenomenon driven by the rapid pace of demographic and cultural change that Saudi Arabia has experienced during the last 20 years.

Since our Cardiology Unit opened in 1977, a large number of Congenital Heart Defect (CHD) cases have been treated, leading to the creation of a CHD Registry in 1997 based on a Microsoft Access database (Becker and Al-Halees, '00). A similar PC solution was also recently adopted by Grech and Pace ('99) with their dBASE IV Pediatric Heart Disease Registry. It quickly became clear, however, that a more sophisticated approach was required, partly because of the complex nature of the disease. CHD is due to developmental abnormalities in the first 5 to 8 weeks of fetal life, encompassing over 50 diagnoses (World Health Organization, '77), and this can make particularly stringent demands on registry structure and contents.

In 1999, the stand-alone CHD registry at KFSH&RC was replaced by a completely new system. In addition to making substantial modifications to its data-structure and reporting facilities, we also took this opportunity to re-examine the design requirements from a wider perspective. We wanted to establish a registry that would be accessible from any location in the Kingdom via a comprehensive WWW user-interface. Our primary motivation for an Internet approach was that we foresaw the need to expand our hospital-based registry to a nation-wide system, probably within the next few years.

The transition from a *standalone* database to a WWW design inevitably raised fundamental questions of data security and posed several programming and organizational problems that may be characteristic of registries. Our purpose here is to describe the software solution that we ultimately developed, the KFSH&RC WWW CHD Registry, and to highlight the principal advantages of Internet Disease Registries, especially in the context of rare diseases.

DATABASE DESIGN AND SECURITY

The database component of the WWW Registry was designed to store the contents of the paper forms used by the original KFSH&RC registry, but was substantially modified to take advantage of the new WWW features, such as radio buttons. The first page of the paper form was designed for patient registration (Fig. 1) and was split across 3 separate WWW pages: demography, anatomy, and diagnosis. The second (treatment) and third (follow-up) pages of the paper form were each assigned a single WWW page. Each WWW page was then associated with its own underlying database table, culminating in five tables. A registration number was assigned to every new CHD patient and was used as the primary key for database access. To improve the speed and accuracy of the data-entry process, and to promote internal standards, the coding schemes for categorical registry variables (such as diagnosis and consanguinity) were stored in their own "look-up" tables. The overall database structure is depicted in Figure 2.

Data security is an important issue that is tightly controlled by the CHD Registrar and the KFSH&RC CHD steering committee. Security is especially important when connections to the Internet are considered, and several security levels were therefore implemented within the CHD Registry software. The fundamental level of security simply restricts user access to a limited set of TCP/IP addresses. Under no circumstances is a user allowed to communicate with the Registry if the workstation TCP/IP address is not in the security list. Currently only internal (Intranet) IP addresses are allowed access, but this can be modified by the Webmaster.

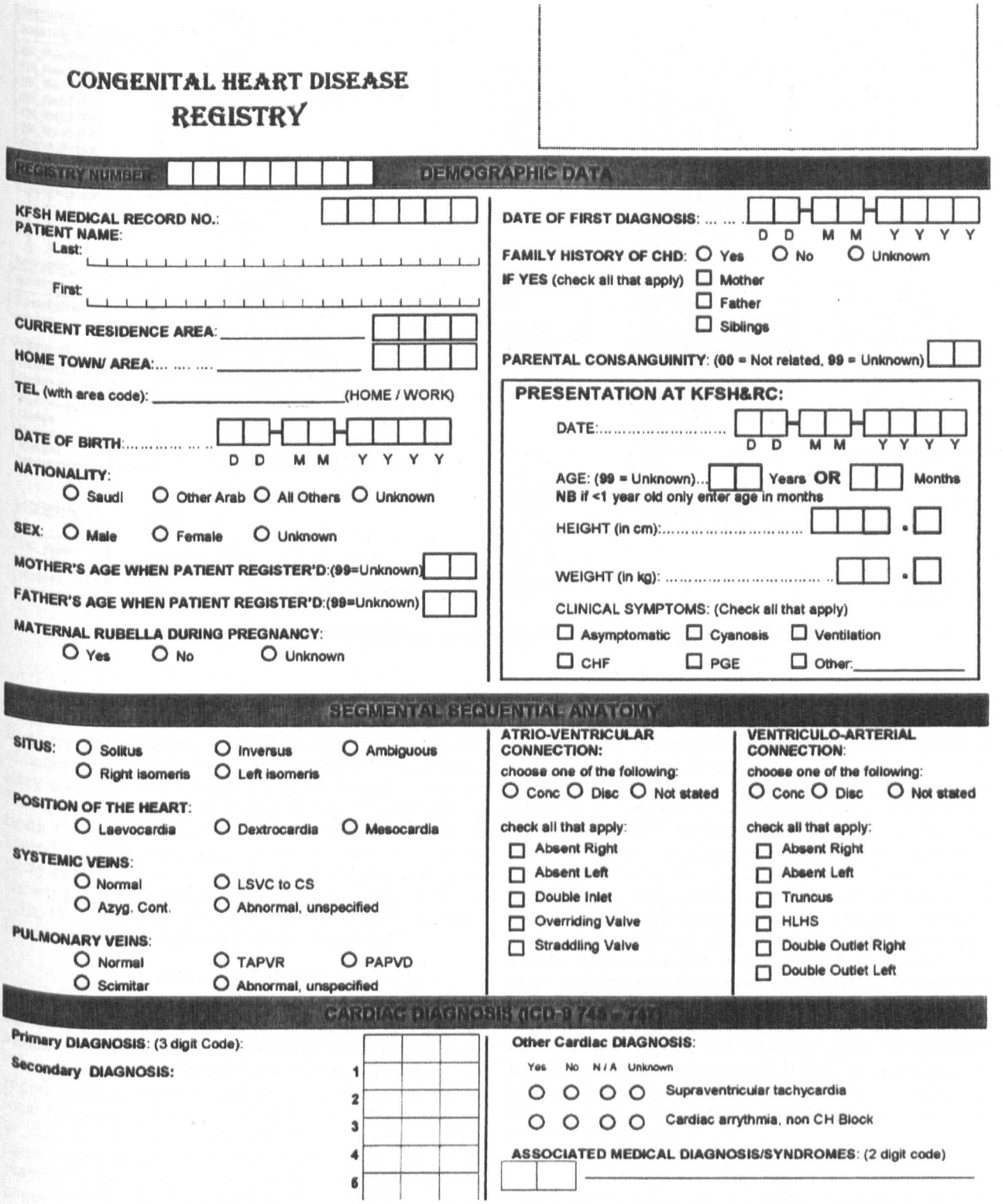
There are three levels of purpose-built "active" security software:

1. The first is based on the *cookie* concept. A cookie is a small file that must be downloaded to the user's own workstation before any access to CHD data can occur. This download is conducted interactively via a dedicated KFSH&RC CHD Registry Web-page, and requires a special cookie password to be supplied to the user by the Registrar. The downloaded cookie is date-stamped with a 1-month expiration date; a new cookie must be obtained before then, and that requires a new password.
2. The Registry Login page provides the second level of security, via the traditional "User-ID/password" that the user must supply in order to proceed. No access to the CHD Registry is possible if these cannot be authenticated by the Web and SQL Servers. After successful authentication, a user is given a set of permissions based on their predefined level of authority; several session parameters are defined on the server at this point, and are used for subsequent user-verification. These are defined for this specific session only, and expire after a pre-specified period of inactivity (currently 60 min).
3. One of these session parameters contains a code that changes daily. This is used as a third level of security by confirming that the user of this session has indeed successfully passed through the authentication process.

A number of passive security measures have also been implemented, such as the constant monitoring of all system access and the provision of regular reports to the CHD Registrar.

USING THE CHD REGISTRY

The CHD Registry program comprises instructions contained in Microsoft Active Server Pages (ASP) files. Their order of execution defines the path followed by the program and therefore the sequence of Web-pages



CONGENITAL HEART DISEASE REGISTRY

REGISTRY NUMBER:

DEMOGRAPHIC DATA

KFSH MEDICAL RECORD NO.:

PATIENT NAME:
Last:
First:

CURRENT RESIDENCE AREA:

HOME TOWN/ AREA:

TEL (with area code): (HOME / WORK)

DATE OF BIRTH: D D M M Y Y Y Y

NATIONALITY:
O Saudi O Other Arab O All Others O Unknown

SEX: O Male O Female O Unknown

MOTHER'S AGE WHEN PATIENT REGISTER'D:(99=Unknown)

FATHER'S AGE WHEN PATIENT REGISTER'D:(99=Unknown)

MATERNAL RUBELLA DURING PREGNANCY:
O Yes O No O Unknown

DATE OF FIRST DIAGNOSIS: D D M M Y Y Y Y

FAMILY HISTORY OF CHD: O Yes O No O Unknown

IF YES (check all that apply)
☐ Mother
☐ Father
☐ Siblings

PARENTAL CONSANGUINITY: (00 = Not related, 99 = Unknown)

PRESENTATION AT KFSH&RC:

DATE: D D M M Y Y Y Y

AGE: (99 = Unknown) Years OR Months
NB if <1 year old only enter age in months

HEIGHT (in cm): .

WEIGHT (in kg): .

CLINICAL SYMPTOMS: (Check all that apply)
☐ Asymptomatic ☐ Cyanosis ☐ Ventilation
☐ CHF ☐ PGE ☐ Other:

SEGMENTAL SEQUENTIAL ANATOMY

SITUS: O Solitus O Inversus O Ambiguous
O Right isomeris O Left isomeris

POSITION OF THE HEART:
O Laevocardia O Dextrocardia O Mesocardia

SYSTEMIC VEINS:
O Normal O LSVC to CS
O Azyg. Cont. O Abnormal, unspecified

PULMONARY VEINS:
O Normal O TAPVR O PAPVD
O Scimitar O Abnormal, unspecified

ATRIO-VENTRICULAR CONNECTION:
choose one of the following:
O Conc O Disc O Not stated

check all that apply:
☐ Absent Right
☐ Absent Left
☐ Double Inlet
☐ Overriding Valve
☐ Straddling Valve

VENTRICULO-ARTERIAL CONNECTION:
choose one of the following:
O Conc O Disc O Not stated

check all that apply:
☐ Absent Right
☐ Absent Left
☐ Truncus
☐ HLHS
☐ Double Outlet Right
☐ Double Outlet Left

CARDIAC DIAGNOSIS (ICD-9 745 - 747)

Primary DIAGNOSIS: (3 digit Code):

Secondary DIAGNOSIS:
1
2
3
4
5

Other Cardiac DIAGNOSIS:

Yes	No	N / A	Unknown	
O	O	O	O	Supraventricular tachycardia
O	O	O	O	Cardiac arrythmia, non CH Block

ASSOCIATED MEDICAL DIAGNOSIS/SYNDROMES: (2 digit code)

Fig. 1. Registration form for the KFSH&RC CHD Registry. This paper form is subdivided into three separate Web-Pages for data-entry.

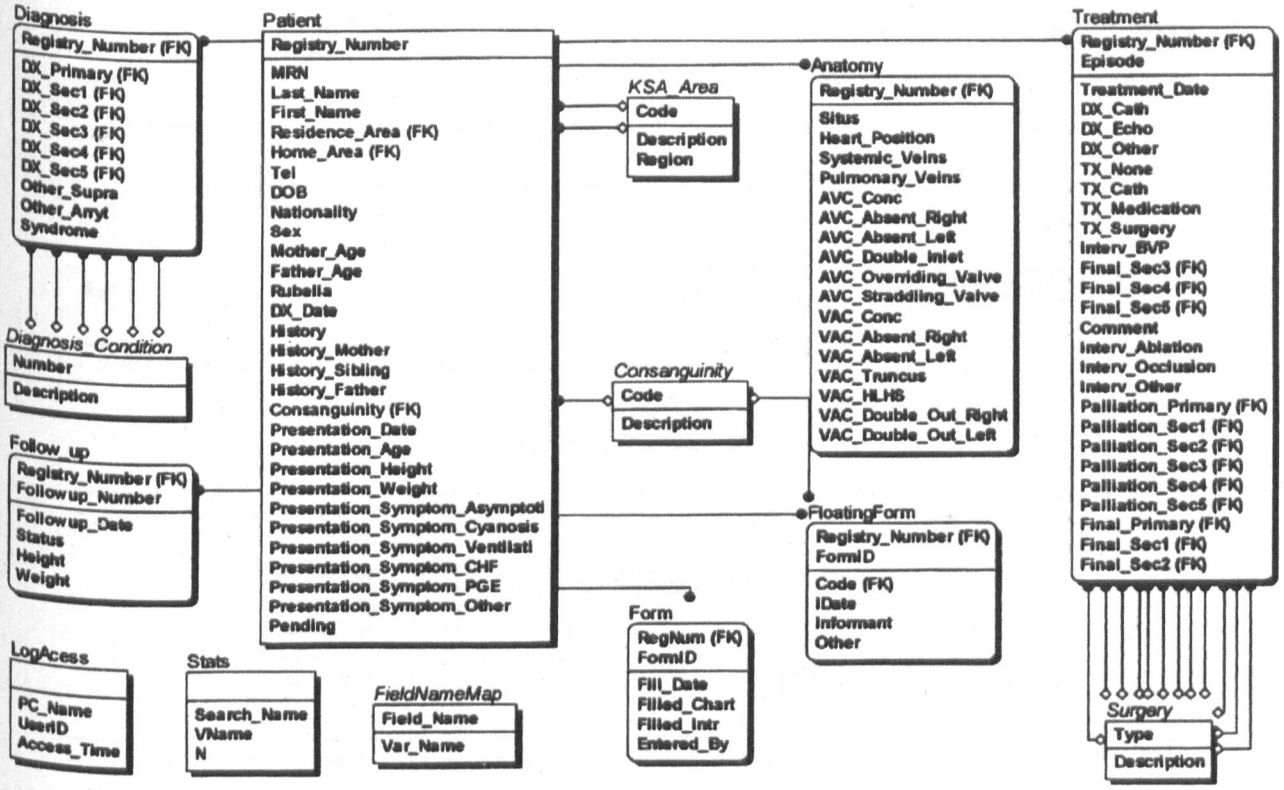


Fig. 2. The database structure of the KFSH&RC CHD Registry.

displayed to the user. In practice, to access the CHD Registry a user selects its HTTP address from the list of bookmarks within their regular WWW browser (registry operation is routinely tested with both Netscape Navigator and Microsoft Explorer at 800 × 600 resolution). On the first page the user is obliged to enter a User-ID and Password which are checked for authenticity before the main CHD menu is displayed (Fig. 3) showing the five Registry options: (1) Add, View or Edit, (2) Search, (3) Chart, (4) Report, and (5) Administration (administrator privileges required).

Add, view or edit

A valid registry accession number is required in order to add a new patient to the database. The system validates the format of the number, checks for duplicates and opens the demographics page; this begins the registration process. A registry accession number (or local hospital medical record number) is also required to view or edit an existing record; the patient record page is presented to the user, containing a menu displaying links to each of the five main database WWW pages and to any "floating forms" currently in use. A floating form is a temporary extension to the registry and is intended to facilitate certain types of studies without compromising the routine structure of the database. Empty linked pages are indicated by red dots next to the links, which change to green after data-entry. A user can select specific treatment or follow-up episodes to view or edit.

Data-entry errors are handled precisely; data can be added or changed only when the user selects the "save" or "save changes" options. When this occurs, the data from the current Web page are processed by an ASP file that cross-checks the validity of all the data items. If there are no errors, the data are saved and the user is automatically redirected back to the patient data page. If an item does not pass the check, an appropriate HTML string is added to a list of "Warnings and Errors" and an error flag is set. Eventually the error flag is tested: if it has been set, the user is presented with a page showing the list of warnings and errors. If the list contains any errors, the mistake must be corrected before the data can be saved. If the list contains only warnings, any newly-entered data may be edited, or the error-checking may be overridden and the data saved in its current form.

Search

The Registry includes an option to search for records that satisfy certain user-specified conditions. Text fields can contain wild card characters (e.g., "%" indicates "any") and radio buttons include a choice of "all" that is translated as "*do not search on this field*". The

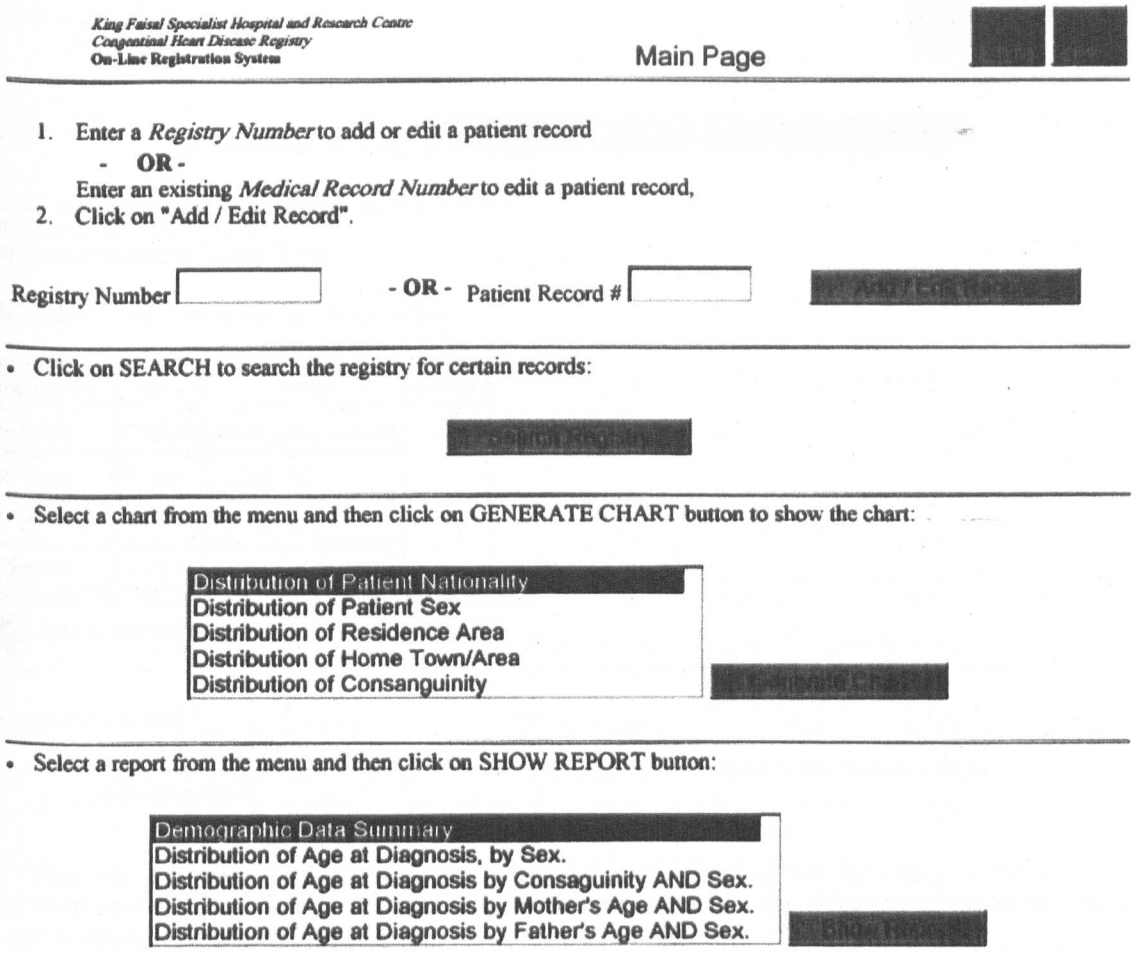


Fig. 3. The CHD Registry main Web-page, showing the available options.

query is submitted to the database and the results of this search generate a new HTML page (Fig. 4) that shows the query in a simplified natural language format along with all matching records. Records may then be accessed individually by clicking on their accession number.

Chart and report

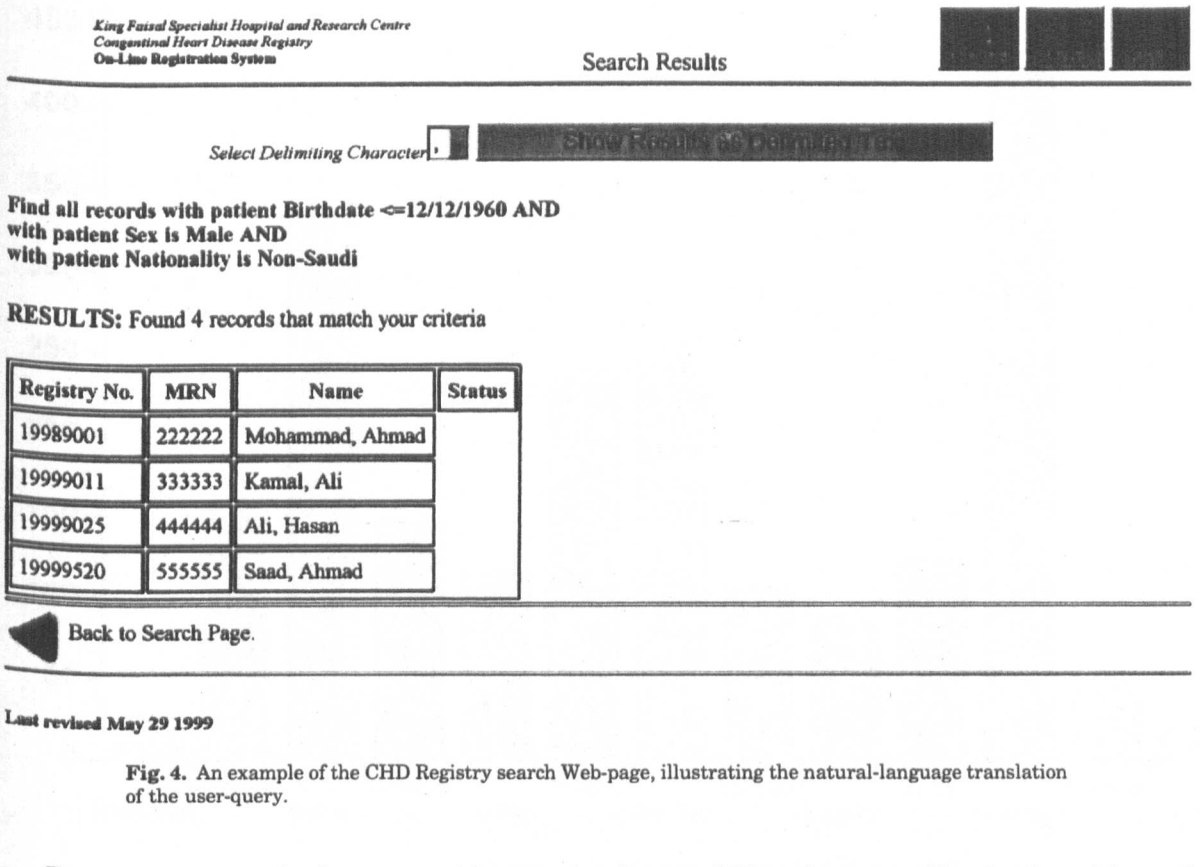
These options include a facility to generate various predefined charts and reports from the registry data. Charts can be further manipulated within the browser of the local workstation and saved to disk for later use with other applications such as Word or Powerpoint.

ADMINISTRATIVE FUNCTIONS

Each CHD Registry user is classified as *data-entry, registrar* or *administrator* staff. Users in the last two categories have special privileges that permit them to access the Administrator page from the main CHD menu. This allows the registrar or an administrator to produce specific predefined reports or to export the data for use within classical statistics packages.

There are currently five predefined administrative reports: 1) a detailed list of users who have accessed the system over a specified period; 2) a list of records (identified by registry accession number and name) that do not have an entry in either the anatomy or the diagnosis table; 3) a list of records awaiting validation by the CHD Registrar; 4) a list of records and fields containing null values; and 5) a list of null values for the follow-up table only.

An *export* page allows the user to select specific tables or individual fields for export as comma-delimited text files. Javascript code is built into the page to help the user select which fields or tables to export. The exported file can be viewed by clicking on a link that shows the file in a separate window. The first line in the text file is a comma-delimited list of exported field



King Faisal Specialist Hospital and Research Centre
Congenital Heart Disease Registry
On-Line Registration System

Search Results

Select Delimiting Character ,

Find all records with patient Birthdate <=12/12/1960 AND
with patient Sex is Male AND
with patient Nationality is Non-Saudi

RESULTS: Found 4 records that match your criteria

Registry No.	MRN	Name	Status
19989001	222222	Mohammad, Ahmad	
19999011	333333	Kamal, Ali	
19999025	444444	Ali, Hasan	
19999520	555555	Saad, Ahmad	

Back to Search Page.

Last revised May 29 1999

Fig. 4. An example of the CHD Registry search Web-page, illustrating the natural-language translation of the user-query.

names. These are not exactly the same as the corresponding field names in the database because the exported file is targeted at the major statistical analysis packages (such as SAS and SPSS) that impose limitations on the structure and content of variable names. These name transformations are achieved via an additional lookup table within the database.

Two annual reports have already been produced using this Registry (KFSH&RC, '99; Molina and Sandridge, '00) and are in the public domain (copies can be obtained from the CHD Registrar, MBC03, KFSH&RC, P.O. Box 3354, Riyadh 11211, Saudi Arabia). The production of a third report for 1998–2000 is currently underway.

Several aspects of CHD in the Kingdom are becoming clear. Only 60% of the diagnoses are made before the patient's first year of age (Fig. 5), although some registries (Rothman and Fyler, '76; Stierman, '94; Pershyn-Kisor et al., '00) and studies (e.g., Ferencz et al., '93) have excluded patients outside this age group. To date our oldest registered patient is over 40 years old and has Ebstein anomaly.

Until recently, *date of birth* has not been routinely recorded in Saudi Arabia (culturally it has never been considered important), therefore the age-profiles (at the child's birth) of older parents tend to exhibit characteristic uncertainty. Nevertheless, we can see (Fig. 6) that CHD births continue to occur into the fifth decade for mothers and the ninth decade for fathers, raising the possibility of an age-effect in the etiology of the disease within the Kingdom (Stoll et al., '89; Zhan et al., '91; Olshan et al., '94).

The most important item recorded by the registry is diagnosis (Table 1). We use the ICD-9 coding system (within the 745.0–747.49 range, there are 54 individual CHD diagnoses) because of its compatibility with other reporting sources, although this strategy is currently being re-examined. We also code additional diagnoses that our cardiologists consider important. A complete list (including all observed diagnostic *patterns*) can be found in the Annual Report (Molina and Sandridge, '00).

DISCUSSION

We have successfully developed and implemented an Internet Registry for Congenital Heart Defects at KFSH&RC. For almost the last 3 years it has served 10 concurrent workstations throughout the hospital campus. More than 3,000 cases have already been registered, and the current accrual rate is approximately 100 new cases and 300 follow-up visits per month. A demonstration version of our software can be viewed at http://rc.kfshrc.edu.sa/chdr/demo/.

This is the first registry to regularly report on the full spectrum of CHD diagnoses (isolated diagnoses are in Table 1). World-wide, there are over 25 regional and international registries for congenital malformations.

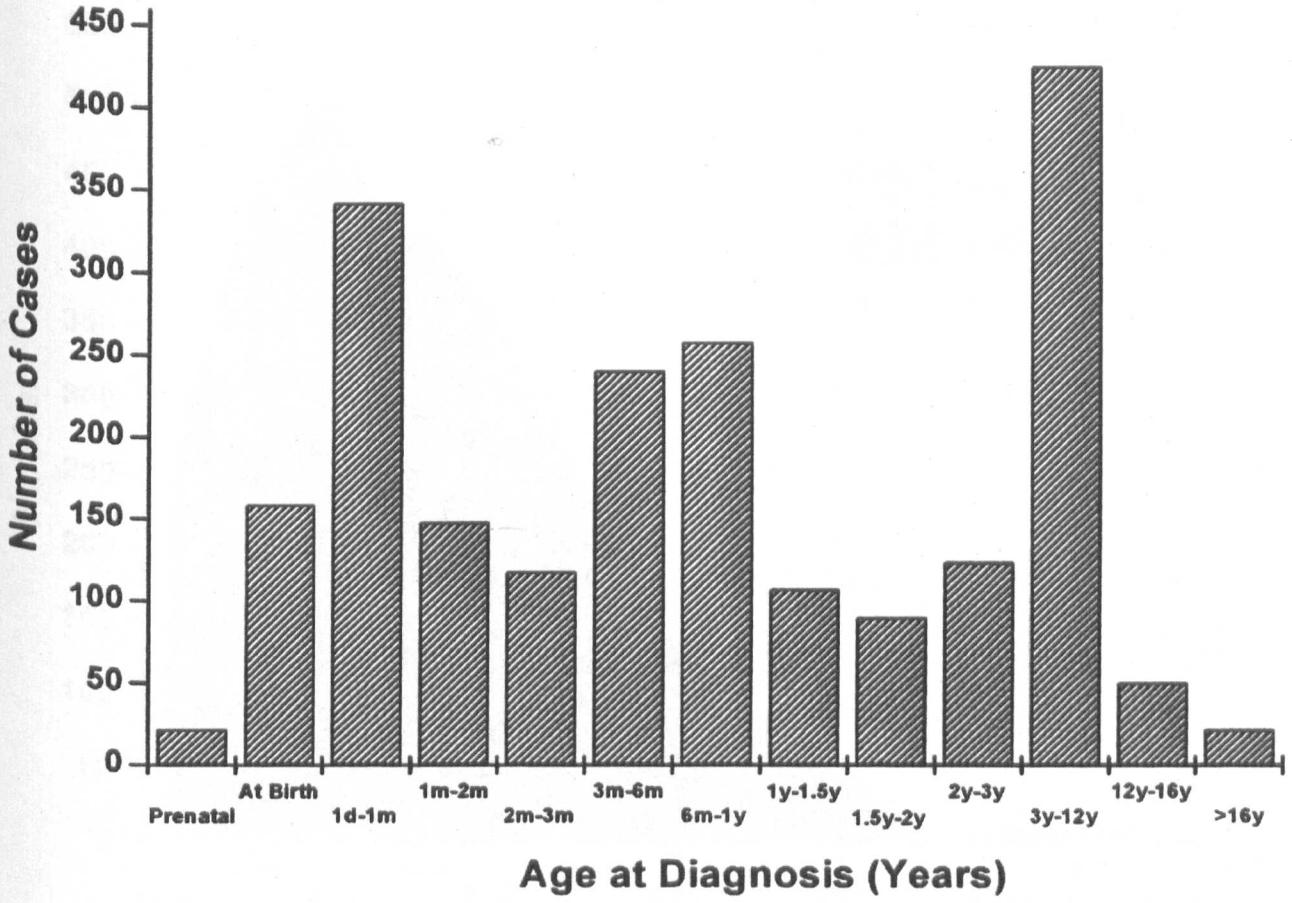


Fig. 5. The distribution of the age of the CHD patients at diagnosis.

Many participate in the WHO's International Clearinghouse for Birth Defects Monitoring System (ICBD, '00) and in the EUROCAT system (Lechat and Dolk, '92; EUROCAT, '01). Congenital heart defects fall under the rubric of birth defects, but data has been reported by the Clearinghouse on only two diagnoses, although some regions such as California (Stierman, '94), Southern (Annual Report of the South Australian Birth Defects Register, '96) and Western (Bower et al., '98) Australia regularly report up to nine.

This is also the first registry to specialise in CHD. The New England Regional Infant Cardiac Program (Talner, '98) focuses on contributing to larger efforts (Moller et al., '95) rather than disease surveillance, and although the widely published Baltimore Washington Infant Study Group (Ferencz et al., '97) conducted a series of CHD-only case-control studies between 1981 and 1989, they did not institute a formal registry. By contrast, ours is intended to develop into something resembling EUROCAT.

This is certainly the first CHD Registry to be fully functional on the Internet. The WHO guidelines for monitoring birth defects (World Health Organization, '93) were unfortunately just published before the WWW became available as a practical scientific resource, and focus on the data structure itself, rather than the technique of information delivery. Since then, the gap between the data and the technique has effectively diminished, so that an ideal registry design should now consider both aspects simultaneously.

KFSH&RC is one of the principal referral hospitals for heart defects in the Kingdom of Saudi Arabia (KSA). The CHD Registry currently serves only the patient population attending KFSH&RC, but in the near future this will be extended to include other geographical locations, probably doubling the monthly accrual rate and the number of workstations. Eventually, a more representative National CHD Registry is expected to emerge, with a correspondingly larger throughput and a much wider user base. Under these circumstances, one clear advantage of the WWW-orientated approach is that little or no software modifications would be required; indeed, the processing power of the current WWW server may even be sufficient to support the extra load.

In developing the CHD Registry software, our primary design objectives were to achieve a secure system with easy database access, scalable to a large number of workstations at different geographical locations (within the hospital and throughout KSA), perhaps

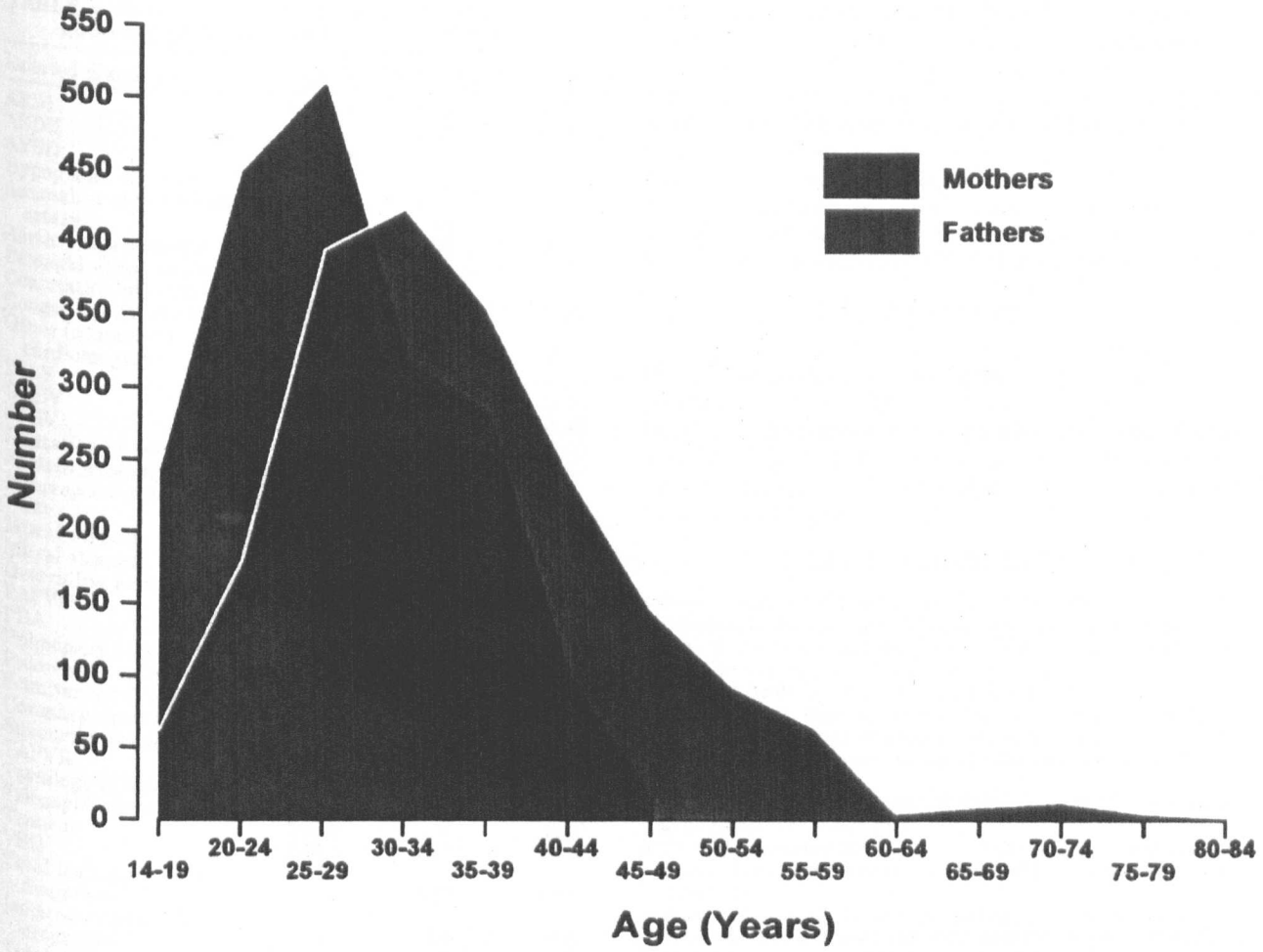


Fig. 6. The distribution of the ages (at birth) of the mothers and fathers of the CHD patients.

using different types of computers. Secondary objectives were to clarify the structure of the data items being stored in the registry, and to develop the necessary data-validation procedures suitable for CHD data. Special emphasis was placed on ease-of-use and the generation of regular customised reports.

Our final design was based on seven simple concepts: 1) each patient should be identifiable by a unique registry number; 2) the paper form should remain the primary data source; 3) the computer screen should appear identical to this form; 4) all data should be flagged as "pending" until approved by the registrar; 5) data validation should be possible in "batch mode"; 6) non-core data-items should remain in separate "floating forms"; and 7) the user-interface should be simple and easy to use.

Security was our largest single concern (Chapman and Zwicky, '95), reflecting a similar worry among the general research community. The popular misconception, however, that a computer connected to the Internet runs a high risk of being penetrated by hostile users is an improbable scenario for most institutions with a reasonable Internet strategy. Nonetheless, in the context of a patient registry, our task was to reduce this low probability even further.

Unexpected problems arose in several areas. We rediscovered the usual dilemma of registry content, because excessive use of scroll bars in a WWW context can make the user-interface particularly unwieldy. It also became clear that some of the new WWW features (usually regarded as positive aids to data-entry) were actually slowing down the entry of CHD data and causing confusion due to excessive switching between the computer mouse and keyboard. The implementation of missing values became more critical, because the HTML code that implements a radio button, for example, does not permit a default value to be stored. We also found that attempting data-validation across the WWW caused several logistical problems, given the batch-orientated nature of registry procedures.

From a wider perspective, we see the Internet bringing new opportunities for all disease registries. The ability to share registry resources, both data and programs, across the Internet means that a large degree of

TABLE 1. Frequency table of isolated CHD diagnoses observed at KFSH and RC from 1998–1999*

Isolated diagnosis	ICD-9	Number	Percentage
ASDI	745.61	2	0.20
ASDII	745.5	125	12.40
AVSD	745.69	41	4.10
Hypoplasia of aorta	747.22	3	0.30
Anomalies of pulmonary artery	747.3	13	1.30
Aortic valve stenosis	746.3	33	3.30
Bicuspid aortic valve	746.4	6	0.60
Coarctation of aorta	747.1	21	2.10
Congenital heart block	746.86	7	0.70
Other (congenital cardiomegaly)	746.89	43	4.30
DILV	745.3	2	0.20
DORV	745.11	1	0.10
dTGV	745.1	5	0.50
Dilatation of aorta	747.29	10	1.00
Ebstein anomaly	746.2	3	0.30
Interrupted inferior vena cava	747.40	1	0.10
Mitral atresia	746.6	11	1.10
Mitral stenosis	746.5	6	0.60
Overriding aorta/RA arch	747.21	1	0.10
PAPVD	747.42	2	0.20
PDA	747.0	140	13.90
Pulmonary atresia	746.01	1	0.10
Pulmonary valve stenosis	746.02	130	12.90
Scimitar syndrome	747.49	2	0.20
Coronary artery anomaly	746.85	3	0.30
Subaortic stenosis	746.81	26	2.60
TAPVR	747.41	1	0.10
Tetralogy of fallot	745.2	123	12.20
Tricuspid atresia/stenosis	746.1	1	0.10
Truncus	745.0	6	0.60
VSD	745.4	211	20.90
Total isolated ICD-9 diagnoses	—	980	97.40
Isolated non-ICD-9 diagnoses	—	29	2.90
Total isolated diagnoses	—	1,009	100.00

*45% of the registered patients have an isolated diagnosis; the remaining 55% have two or more diagnosis and are not included in this table. A detailed diagnostic breakdown can be found in the Annual Reports of the KFSH and RC CHD Registry.

commonality can be established between different registries for the same disease, no matter where they are physically located in the world. With suitable WWW and database designs in place, data that are stored in a "local" registry can also simultaneously participate in an "international" registry, subject to any constraints imposed by the local authorities. Coding of data, often a practical barrier to routine collaboration, can also be standardized, and in many cases an identical data-entry form can be used at different locations. The WWW therefore offers a very straightforward route for the transformation of local disease registries into regional databases, and the integration of regional or countrywide data into true International Disease Registries.

In particular, the ability of Internet registries to span continents offers for the first time a practical, reliable and ongoing framework for the investigation of rare diseases, such as CHD, which have hitherto been constrained by small sample-sizes or confounded by mismatches in the coding schemes between different registries. With sufficient international effort, this could lead in the near future to a substantial increase in the patient count for the less common CHD diagnoses. We would be willing to respond quickly to provide the necessary practical co-ordination, should there be any interest among the research community in forming an "International" CHD Registry at this stage.

ACKNOWLEDGMENTS

The authors would like to thank Mr. R. Paterson and Dr. C. Molina for developing the original CHD Access database, and the KFSH&RC CHD Registry Committee (Dr. Z. Al Halees, Dr. F. Al Mohanna, Dr. O. Galal and Dr. E. De Vol) for reviewing this manuscript. This project was approved by the Research Advisory Council (RAC No. 991026).

LITERATURE CITED

Annual Report of the South Australian Birth Defects Register. 1996. Adelaide, South Australia: Women's and Children's Hospital.

Becker S, Al-Halees Z. 1999. First cousin matings and congenital heart disease in Saudi Arabia. Comm Genet 2:69–73.

Bishop MJ. 1999. Genetics databases. London: Academic Press.

Bower C, Ryan A, Rudy E, Grace L. 1998. Report on the Birth Defects Registry of Western Australia 1980–1997. SUBIACO. Western Australia: King Edward Memorial Hospital Centre for Women's Health.

Chapman DB, Zwicky ED. 1995. Building internet firewalls. California: O'Reilly and Associates.

EUROCAT. (accessed 2001 May 31). European Registration of Congenital Anomalies [Internet site]. Available: www.iph.fgov.be/eurocat/41.htm.

Ferencz C, Rubin JD, Loffredo C, Magee CA. 1993. Epidemiology of congenital heart disease: the Baltimore-Washington Infant Study, 1981–1989. Mt. Kisco, NY: Futura Publishing Co., Inc.

Ferencz C, Loffredo CA, Correa-Villasenor A, David Wilson PD. 1997. Genetic and environmental risk factors of major cardiovascular malformations. The Baltimore-Washington Infant Study, 1981–1989. Mt. Kisco, NY: Futura Publishing Co., Inc.

Grech V, Pace J. 1999. Automation of follow-up and data analysis of paediatric heart disease in Malta. Int J Cardiol 68:145–149.

International Centre for Birth Defects, Italy. 2000. Annual Report 2000 with data for 1998. Rome: International Centre for Birth Defects.

Jadad AR, Haynes RB, Hunt D, Browman GP. 2000. The Internet and evidence-based decision-making: a needed synergy for efficient knowledge management in health care. CMAJ 162:362–365.

King Faisal Specialist Hospital and Research Centre Congenital Heart Disease Registry: Annual Report. 1999. Riyadh, Saudi Arabia: KFSH&RC.

Lechat MF, Dolk H. 1992. Registries of congenital abnormalities: the EUROCAT experience: a concerted action of the E.C. International Workshop Impact of the Environment in Reproductive Health. Copenhagen (30 Sept.–4 Oct. 1991).

MacLennan R, Muir C, Steinitz R, Winkler A. 1978. Cancer registration and its techniques. Lyon: International Agency for Research on Cancer.

Marine A, Kirkpatrick S, Neou V. 1993. Chapter 9. INTERNET: getting started. New Jersey: Prentice Hall.

Molina C, Sandridge AL. 2000. King Faisal Specialist Hospital and Research Centre, Congenital Heart Disease Registry: Second Annual Report. Riyadh, Saudi Arabia: KFSH&RC.

Moller JH, Moodie DS, Blees M, Norton JB, Nouri S. 1995. Symptomatic heart disease in infants: comparison of three studies performed during 1969–1987. Pediatr Cardiol 16:216–222.

Olshan AF, Schnitzer PG, Baird PA. 1994. Paternal age and the risk of congenital heart defects. Teratology 50:80–84.
Pershyn-Kisor MA, Bush RA, Smith TC, Honner WK, Gray GC. 2000. Department of Defense Birth Defects Registry Report for the period: January 1, 1999 through June 30, 1999. Dept. of Defense Center for Deployment Health Research. San Diego, California: Naval Health Research Center.
Rothman KJ, Fyler DC. 1976. Sex, birth order, and maternal age characteristics of infants with congenital heart defects. Am J Epidemiol 104:527–534.
Schulman J, Edmonds LD, McClearn AB, Jensvold N, Shaw GM. 1993. Surveillance for and comparison of birth defect prevalences in two geographic areas—United States, 1983–1988. Mor Mort Wkly Rep CDC Surveill Summ 42:1–7.
Stierman L. 1994. Birth defects in California: 1983–1990 Sacramento, California: California Birth Defects Monitoring Program.
Stoll C, Alembik Y, Roth MP, Dott B, De Geeter B. 1989. Risk factors in congenital heart disease. Eur J Epidemiol 5:382–391.
Talner NS. 1998. Report of the New England Regional Infant Cardiac Program, by Donald C. Fyler, MD, Pediatrics 65(Suppl):375–461. Pediatrics 102:258–259.
Timmreck C. 1994. An introduction to epidemiology. Boston: Jones & Bartlett.
van Bemmel JH, Musan MA. 1997. Ch. 20. Hospital information systems: clinical use. In: Handbook of Medical Informatics. Bohn: Springer.
Wilson PD, Correa-Villasenor A, Loffredo CA, Ferencz C. 1993. Temporal trends in prevalence of cardiovascular malformations in Maryland and the District of Columbia, 1981–1988. The Baltimore-Washington Infant Study Group. Epidemiology 4:259–265.
World Health Organization. 1977. Manual of the international classification of disease, injuries, and causes of death (based on the recommendations of Ninth Revision Conference, 1975). Geneva: World Health Organization.
World Health Organization. 1993. Guidelines for the development of national programmes for monitoring birth defects (prepared by the International Centre for Birth Defects of the International Clearinghouse for Birth Defects Monitoring Systems, Rome). Geneva: World Health Organization.
Zhan SY, Lian ZH, Zheng DZ, Gao L. 1991. Effect of fathers' age and birth order on occurrence of congenital heart disease. J Epidemiol Community Health 45:299–301.

APPENDIX: DEVELOPMENT SOFTWARE

The CHD Web pages were developed in Hypertext Markup Language (HTML) using Active Server Pages and ActiveX Data Objects (Microsoft Corp). The database was created with SQL Server (Version 7, Microsoft Corp.). ODBC Administrator (Version 3.5, Microsoft Corp.) was used to create logical connections between the database and the Web-server. File Manager (Version 3.1, Software Artisans Inc.) was used for file-management operations which involve exporting data. Chart FX Internet (Version 3.0, Software FX Inc.) was used to generate interactive on-line charts. The CHD Registry is served using Microsoft's Internet Information Server (IIS).

```
      PROGRAM CHDPRG
C     ==============

C     May 17, 2005, Written by William Greer, PhD

C     Program to process ASCII file of CHD pregnancy data.
C     Each record in the file records data for an individual baby.

      CHARACTER*40 FNAME1, FNAME2
      CHARACTER*1 Z

C     -----------
C     Housekeeping
C     -----------

C     Initialize Filenames
      FNAME1(1:40)='                '//
     +     '                '
      FNAME2(1:40)='                '//
     +     '                '

C     Store Horizontal Tab
      Z(1:1)=ACHAR(9)

C     Get input datafile name
190   CONTINUE
      WRITE(6,150)
150   FORMAT(/, 1H+' Datafile Name ? ',$)
      READ(5,200,ERR=190) FNAME1
200   FORMAT(A)

C     Get actual length of input datafile filename
      LNAME1=LENN(FNAME1)

C     Construct output datafile name. Assume 3-character
C     extension on input filename.
      LNAME2=LNAME1
      FNAME2(1:LNAME2)=FNAME1(1:(LNAME1-3))//'PRO'

C     Open input and output datafiles
      OPEN(UNIT=21,FILE=FNAME1(1:LNAME1))
      OPEN(UNIT=22,FILE=FNAME2(1:LNAME2))

C     Write Output Datafile header
C     WRITE(22,330) FNAME1(1:LNAME1)
330   FORMAT(/,' Processed Results from File: ',A,/)

      WRITE(22,331) Z,Z,Z,Z,Z,Z,Z,Z,Z,Z,Z,Z,Z,Z,Z
331   FORMAT('CASEID',A,' PAR',A,'GRAV',
     +     A,'LIVE',A,'STIL',A,'MISS',A,' ECT',A,'CURR',
     +     A,'LOSS',A,' NEO',A,' INF',
     +     A,'ABNO',A,'PPRO',A,'MPRO',
     +     A,'DEAD',A,' MAJ')

C     Move down the screen 1 line.
      WRITE(6,20)
```

```
20      FORMAT(//)

C       Initialise total input record counter.
        NREC=0

C       Initialize Previous ID Holder
C       IDPREV=0

C       Initialize New-Woman Flag
C       0=> Same Woman, 1=> New Woman
        IWOMAN=0

C       Initialise Pregnancy Counter (per woman)
        NPREG=0


C       Initialise Data Counters
        NPAR=0
        GRAV=0.0
        NLIVE=0
        NSTILL=0
        NMISS=0
        NECTOP=0
        NCURR=0
        NLOSS=0
        NNEO=0
        NINF=0
        NABNOR=0
        NPP=0
        NMAT=0
        NTDEAD=0
        NMAJOR=0
        NHMOM=0

C       ----------------------------
C       Read Data and Do Calculations
C       ----------------------------

C       Primary Loop
300     CONTINUE

C         ---------------
C         Read Next Record
C         ---------------

C         Read the data in free-format datafile.
C         Assume input datafile has 15 variables.
          READ(21,*,ERR=310,END=320) ID,   IPREG,  ICASE,  ISTUDY,
     +                    IOUTC, IMGEST, IALIVE, IABNOR,
     +                    IDAGE, IABNSP, IPPROB, IPROB,
     +                    IBREST,IBLEED, IHEAL,  IEHSP,
     +                    IMAJOR,IHMOM

C         Correct unknown designation for multiple gestation.
          IF(IMGEST.EQ.9) IMGEST=1
```

```
C       Update record counter.
        NREC=NREC+1

        WRITE(6,40) NREC
40      FORMAT(1H+,'Processing Record: ',I6)

C       ---------------------------------
C       Set Woman Flag and Pregnancy Counter
C       ---------------------------------

        IF(ID.NE.IDPREV) THEN

C         New Woman
          IWOMAN=1

C         Write out the results from the previous woman.
          IF(IDPREV.NE.0) THEN
               NGRAV=(IFIX(10.0*GRAV))/10
            MPRO=NMAT+NHMOM
            WRITE(22,400)  IDPREV,Z,
     +                NPAR,Z,NGRAV,Z,
     +              NLIVE,Z,NSTILL,Z,NMISS,Z,
     +              NECTOP,Z,NCURR,Z,
     +              NLOSS,Z,NNEO,Z,NINF,Z,
     +              NABNOR,Z,NPP,Z,MPRO,Z,NTDEAD,Z,
     +              NMAJOR
400         FORMAT(I10,15(A,I4))
          ENDIF

C         Initialise Data Counters
          NPAR=0
          GRAV=0.0
          NLIVE=0
          NSTILL=0
          NMISS=0
          NECTOP=0
          NCURR=0
          NLOSS=0
          NNEO=0
          NINF=0
          NABNOR=0
          NPP=0
          NMAT=0
          NTDEAD=0
          NMAJOR=0
          NHMOM=0

C         Initialise Pregnancy Counter
          NPREG=1

C         Update Previous ID Holder
          IDPREV=ID

        ELSE

C         Same Woman
```

```
      IWOMAN=0

C     Increment Pregnancy Counter
      NPREG=NPREG+1

      ENDIF

C     ----------
C     Do Calculations
C     ----------

C     1. PARITY (Number of babies born alive)
      IF(IWOMAN.EQ.1.AND.IOUTC.EQ.1)      NPAR=1
      IF(IWOMAN.EQ.0.AND.IOUTC.EQ.1)      NPAR=NPAR+1

C     2. GRAVIDITY (Number of pregnancies, complete or incomplete)
      GEST=FLOAT(IMGEST)
      GSHARE=1.0/GEST
      IF(IWOMAN.EQ.1)                     GRAV=GSHARE
      IF(IWOMAN.EQ.0)                     GRAV=GRAV+GSHARE

C     3. Detailed Gravidity:

C           (i)  Number of Livebirths
               IF(IWOMAN.EQ.1.AND.IOUTC.EQ.1)  NLIVE=1
               IF(IWOMAN.EQ.0.AND.IOUTC.EQ.1)  NLIVE=NLIVE+1

C           (ii) Number of Stillbirths
               IF(IWOMAN.EQ.1.AND.IOUTC.EQ.2)  NSTILL=1
               IF(IWOMAN.EQ.0.AND.IOUTC.EQ.2)  NSTILL=NSTILL+1

C           (iii) Number of Misscarriages/Abortions
               IF(IWOMAN.EQ.1.AND.IOUTC.EQ.3)  NMISS=1
               IF(IWOMAN.EQ.0.AND.IOUTC.EQ.3)  NMISS=NMISS+1

C           (iv) Number of Ectopic/Molar Pregnancies
               IF(IWOMAN.EQ.1.AND.IOUTC.EQ.4)  NECTOP=1
               IF(IWOMAN.EQ.0.AND.IOUTC.EQ.4)  NECTOP=NECTOP+1

C           (v)  Number of Current Pregnancies
               IF(IWOMAN.EQ.1.AND.IOUTC.EQ.9)  NCURR=1
               IF(IWOMAN.EQ.0.AND.IOUTC.EQ.9)  NCURR=NCURR+1

C     4. Pregnancy Wastage Per Mother

C           (i)  Pregnancy Loss (Stillbirth+Miscarriage+Ectopic)
               NLOSS=NSTILL+NMISS+NECTOP

C           (ii) Neonatal Death ( < 1 month)
               IF(IWOMAN.EQ.1.AND.IDAGE.LE.30) THEN
                    IF(IDAGE.GE.0.AND.IOUTC.EQ.1) NNEO=1
               ENDIF
               IF(IWOMAN.EQ.0.AND.IDAGE.LE.30) THEN
                    IF(IDAGE.GE.0.AND.IOUTC.EQ.1) NNEO=NNEO+1
               ENDIF
```

```
C               (iii) Infant Death ( < 1 year)
                   IF(IWOMAN.EQ.1.AND.(IDAGE.LE.365.AND.IDAGE.GT.30)) THEN
                        IF(IDAGE.GE.0.AND.IOUTC.EQ.1) NINF=1
                   ENDIF
                   IF(IWOMAN.EQ.0.AND.(IDAGE.LE.365.AND.IDAGE.GT.30)) THEN
                        IF(IDAGE.GE.0.AND.IOUTC.EQ.1) NINF=NINF+1
                   ENDIF

C          5. Pregnancies with an abnormality.
                   IF(IWOMAN.EQ.1.AND.IABNOR.EQ.1)  NABNOR=1
                   IF(IWOMAN.EQ.0.AND.IABNOR.EQ.1)  NABNOR=NABNOR+1

C          6. Pregnancies with a pregnancy problem.
                   IF(IWOMAN.EQ.1.AND.IPPROB.EQ.1)  NPP=1
                   IF(IWOMAN.EQ.0.AND.IPPROB.EQ.1)  NPP=NPP+1

C          7. Pregnancies with a maternal health problem.
                   IF(IWOMAN.EQ.1.AND.IHEAL.EQ.1)   NMAT=1
                   IF(IWOMAN.EQ.0.AND.IHEAL.EQ.1)   NMAT=NMAT+1

C          8. Total Number of Deaths per Woman.
                   IF(IWOMAN.EQ.1.AND.(IOUTC.EQ.1.AND.IALIVE.EQ.2))
     +                        NTDEAD=1
                   IF(IWOMAN.EQ.0.AND.(IOUTC.EQ.1.AND.IALIVE.EQ.2))
     +                        NTDEAD=NTDEAD+1

C          9. Total Number of Pregnancies Associated with a Major Illness per Woman.
                   IF(IWOMAN.EQ.1.AND.IMAJOR.EQ.1)  NMAJOR=1
                   IF(IWOMAN.EQ.0.AND.IMAJOR.EQ.1)  NMAJOR=NMAJOR+1

C          10. Number of Pregnancies with mother who has CHD.
                   IF(IWOMAN.EQ.1.AND.IHMOM.EQ.1) NHMOM=1
                   IF(IWOMAN.EQ.0.AND.IHMOM.EQ.1) NHMOM=NHMOM+1

C          ----------
C          End Calculations
C          ----------

           GOTO 300

310        CONTINUE
C          Read error.
           WRITE(6,315) (NREC+1)
315        FORMAT(/,' Error reading input record #',I6,/)
           STOP

C          End of input data
320        CONTINUE

C          Write out results for last woman
           NGRAV=(IFIX(10.0*GRAV))/10
           MPRO=NMAT+NHMOM
           IF(IDPREV.NE.0) THEN
             WRITE(22,400)  IDPREV,Z,
     +                NPAR,Z,NGRAV,Z,
     +              NLIVE,Z,NSTILL,Z,NMISS,Z,
```

```
     +          NECTOP,Z,NCURR,Z,
     +          NLOSS,Z,NNEO,Z,NINF,Z,
     +          NABNOR,Z,NPP,Z,MPRO,Z,NTDEAD,Z,
     +          NMAJOR
          ENDIF

          WRITE(6,500) NREC
500       FORMAT(//,' Processed ',I6,' Records in Total: ',//)

C         Close datafiles
          CLOSE(UNIT=21)
          CLOSE(UNIT=22)

C         Stop program
          STOP

C         End compilation
          END

      FUNCTION LENN(STRING)
C     ═══════════════════════

C         Function to determine the actual (useful) length of a character
C         string.

          CHARACTER*(*) STRING

C         Get the conceptual length.
          LN=LEN(STRING)

C         Loop round the string, backwards, testing for the first non-blank and
C         non-null.
          DO 100 I=LN,1,-1

C           Get the Ascii-Decimal-Equivalent of the character (A.D.E.).
            IADE=ICHAR(STRING(I:I))

C           Test it for space or null.
            IF(IADE.NE.0.AND.IADE.NE.32) THEN
C             We must have hit a character. Take this value of I as
C             the actual length of the character string.
              LENN=I
              RETURN
            ENDIF

100       CONTINUE

C         If we reach here, then we must be on the first character,
C         or have an empty string. Set length to 1 to avoid output errors.
          LENN=1

          RETURN

          END
```

Appendix 4A BWIS Classification of defects included in case control study

	N	%	N	%
Laterality and Looping			11	4.7
Dextrocardia, AVSD,	1	9.1		
Dextrocardia, ASD II with or without PDA	2	18.2		
Dextrocardia, ASD II, VSD	1	9.1		
Dextrocardia, VSD muscular	1	9.1		
Dextrocardia, TOF	2	18.2		
Dextrocardia, ASVD, TAPVR, DORV, VSD,	1	9.1		
Dextrocardia, TGV, AVSD, TAPVR, Pulmonary atresia, Right aortic arch,	1	9.1		
Dextrocardia, TGV, DILV, Pulmonary valve stenosis, Hypoplastic right heart syndrome, PDA	1	9.1		
Dextrocardia, DORV, Pulmonary valve stenosis, PAPVD, VSD	1	9.1		
DVOAT, Mesenchymal cell			22	9.4
Isolated **TOF**	4	18.2		
TOF, Pulmonary valve stenosis	1	4.5		
TOF, Pulmonary valve atresia	1	4.5		
TOF, Pulmonary valve atresia, VSD, PDA	2	9.1		
TOF, ASD II, Pulmonary artery hypoplasia, PFO	1	4.5		
DORV, TGV	1	4.5		
DORV, VSD	1	4.5		
DORV, ASDI, PDA	1	4.5		
DORV, VSD, perimembranous, PFO	2	9.1		
DORV, ASD I, VSD, Pulmonary valve stenosis, PFO, PDA	1	4.5		
DORV, VSD, Pulmonary valve stenosis	1	4.5		
DORV, VSD, COA, PFO, PDA	1	4.5		
DORV, VSD sub-aortic, ASD II large	1	4.5		
DORV, PAPVD, DILV, PFO	1	4.5		
Truncus, Interrupted aortic arch, COA, PDA	1	4.5		
Truncus, VSD, PFO, PDA	1	4.5		
Truncus, VSD	1	4.5		
DVOAT, Complete Transposition			25	10.6
TGV, PDA	5	20.0		
TGV, ASD II with or without PDA	3	20.0		
TGV, ASD II, Bicuspid pulmonary valve, PDA	1	4.0		
TGV, VSD muscular, PDA	5	20.0		
TGV, VSD muscular, ASD II, PDA	4	16.0		
TGV, DILV, VSD	1	4.0		
TGV, DILV, Pulmonary valve stenosis	1	4.0		
TGV, COA, Tricuspid valve atresia, Hypoplastic aortic arch, DILV	1	4.0		
TGV, Tricuspid valve atresia, PDA	1	4.0		
TGV, COA, VSD, PFO	1	4.0		

	N	%	N	%
Extracellular Matrix Defects			20	8.5
Isolated **AVSD**	4	20.0		
AVSD, PDA with or without PFO	7	35.0		
AVSD, ASD II with or without PDA	4	20.0		
AVSD, ASD I, PDA	1	5.0		
AVSD, ASD II, VSD perimembranous, PDA	1	5.0		
AVSD, VSD, PDA	1	5.0		
AVSD, COA, Hypoplasia of aortic arch, PDA	1	5.0		
Isolated **ASDI**	1	5.0		
Targeted Growth Defects			8	3.4
TAPVR, ASD II, PFO, PDA	1	12.5		
TAPVR, ASD large sinus, PDA	2	25.0		
TAPVR, HLHS,	1	12.5		
PAPVR, PFO	1	12.5		
PAPVR, ASD I,	1	12.5		
PAPVR, ASDII, VSD, PFO, PDA	1	12.5		
Other anomalies of great veins	1	12.5		
Cell Death Defects			17	7.2
Isolated **VSD muscular** (one or multiple)	2	11.8		
VSD muscular, with PDA and / or PFO	4	29.4		
VSD muscular, ASD II, with or without PDA	5	29.4		
VSD muscular, ASD II, Bicuspid aortic valve, PDA	1	5.9		
VSD muscular, ASD II, Interruption of aortic arch, PDA	1	5.9		
VSD muscular, ASD II , Pulmonary valve atresia, PDA	1	5.9		
Tricuspid valve atresia, VSD, ASD II, Pulmonary valve atresia	1	5.9		
Ebstein's Anomaly, PFO	1	5.9		
Hemodynamic Defects, Right-sided flow lesions			19	8.1
Isolated **Pulmonary valve stenosis**	1	5.3		
Pulmonary valve stenosis, with PDA and/ or PFO	3	15.8		
Pulmonary valve stenosis, ASD II with or without PDA	3	15.8		
Pulmonary valve stenosis, ASD II, Hypoplasia pulmonary artery	1	5.3		
Pulmonary valve stenosis , VSD perimembranous, with PDA and / or PFO	2	10.6		
Isolated **Pulmonary artery stenosis**	1	5.3		
Pulmonary artery stenosis, ASD II	2	10.5		
Pulmonary artery stenosis, VSD perimembranous, PFO	1	5.3		
Pulmonary artery stenosis, VSD perimembranous, PDA	1	5.3		
Pulmonary valve atresia, PFO, PDA	1	5.3		
Pulmonary valve atresia, Hypoplastic right heart syndrome	1	5.3		
Pulmonary valve atresia, VSD perimembranous, PDA	2	10.5		

	N	%	N	%
Hemodynamic Defects, Left-sided flow lesions			28	11.9
ASD II, **Bicuspid aortic valve**	1	3.6		
VSD perimembranous, **Bicuspid aortic valve**, PFO	1	3.6		
VSD perimembranous, **Interuption aortic arch**, Hypoplasia aortic arch, PDA	1	3.6		
COA, PDA	2	7.1		
COA, Hypoplasia aortic arch, PDA	3	10.7		
COA, ASD II, Hypoplasia of aortic arch , PDA and / or PFO	2	7.2		
COA, VSD perimembranous with or without PDA	3	10.8		
COA, Aortic valve stenosis	1	3.6		
Isolated **HLHS**	4	14.3		
HLHS, ASDII, VSD, Hypoplasia aortic arch & pulmonary artery	1	3.6		
Isolated **Aortic valve stenosis**	1	3.6		
Aortic valve stenosis, Bicuspid aortic valve	3	10.7		
Aortic valve stenosis, Subaortic stenosis	2	7.1		
Aortic valve stenosis, PFO	1	3.6		
Aortic valve stenosis, VSD	1	3.6		
Subaortic stenosis, Hypoplasia aortic arch	1	3.6		
Hemodynamic Defects, Septal Defects			85	36.2
Isolated **ASD II**	24	28.2		
Isolated **ASD II**, PDA with or without PFO	12	13.0		
ASD II, VSD perimembraneous with or without PDA and /or PFO	16			
ASD II, VSD perimembranous, mitral stenosis	1	1.2		
ASD II, Hypoplasia of pulmonary artery	1	1.2		
ASD II, SVT, PDA	1	1.2		
Isolated **VSD perimembraneous** with or without PDA and / or PFO	30			
Total			235	100.0

Notes:
1: PFO, patent formen ovale, a mild form of ASD II
2: The defect which determined the embryological placement of the defect in the category is bolded

EUROCAT Documentation

From EUROCAT Guide 1.3 and reference documents. Instructions for the Registration and Surveillance of Congenital Anomalies, September 2005.

From Chapter 3.3
Coding of EUROCAT subgroups of Congenital Anomalies

	ICD10-BPA	ICD9-BPA	Comments
Congenital heart disease	Q20-Q26	745, 746, 7470-7474	Exclude isolated PDA with gestational age < 37 weeks
Common arterial truncus	Q200	74500	
Aortic Septal Defect		74501	
Transposition of great vessels	Q203	74510	
Single ventricle	Q204	7453	
VSD	Q210	7454	
ASD	Q211	7455	
AVSD	Q212	7456	
Tetralogy of Fallot	Q213	7452	
Triscuspid atresia and stenosis	Q224	7461	
Ebstein's anomaly	Q225	7462	
Pulmonary valve stenosis	Q221	74601	
Polmonary valve atresia	Q220	74600	
Aortic valve atresia/stenosis	Q230	7463	No code for atresia
Hypoplastic left heart	Q234	7467	
Hypoplastic right heart	Q226		No code
Coarctation of aorta	Q251	7471	
Total anomalous pulmonary venous return	Q262	74742	

Notes:

1. Cases with more than one anomaly are only counted once in the "All Anomalies" subgroup.
2. Minor anomalies for exclusion Chapter 3.2 are only excluded when isolated. For cardiac these include
    a. Absence of hypoplasia of umbilical artery, single umbilical artery
    b. Functional or unspecified cardiac murmur
    c. PDA if less than gestational age < 37 weeks
    d. Peripheral pulmonary artery stenosis
3. In EUROCAT Prevalence calculations, a baby/fetus with several anomalies is counted once within each class of anomaly. The number in different classes cannot be added to reach a total number of babies/fetuses. A baby is counted once only in any given prevalence rate.

"All prevalence rates and counts for subgroups are based on cases, not malformations. Thus a baby with VSD and valve stenosis will be counted ONCE in "all anomalies", ONCE in "cardiac", ONCE in "VSD", ONCE in "valve stenosis"." p. 95

Use ICD10 codes only. ICD 9 codes are only used for retrospectively making subgroups for the earlier years of EUROCAT.

Appendix 4C: KFSH&RC Regsitry Data 1998-2003 Categorized using the EUROCAT Lesion Method

	1998		1999		2000		2001		2002		2003		Total	
Malformations of cardiac septa (ICD-9 745.01, 745.2, 745.4, 745.5, 745.6, 745.8, 745.9)	1566	41.4	1232	45.4	868	45.5	589	45.5	522	42.8	680	41.7	5457	43.5
Malformations of great arteries and veins (ICD-9 747.0-747.4)	959	25.3	644	23.7	470	24.6	380	29.4	330	27.0	464	28.4	3247	25.9
Malformations of valves (ICD-9 746.0-746.7)	840	22.2	558	20.6	394	20.6	215	16.6	251	20.6	342	21.0	2600	20.7
Anomalies of cardiac chambers and connections (ICD-9 745.00, 745.1, 745.3, 745.7)	420	11.1	280	10.3	177	9.3	110	8.5	117	9.6	146	8.9	1250	10.0
Total defects	3785	100.0	2714	100.0	1909	100.0	1294	100.0	1220	100.0	1632	100.0	12554	100.0
Total people	2206		1781		1225		818		721		963		7714	
Transposition of great vessels (745.1)	201	16.2	135	16.4	72	13.4	29	8.6	50	15.7	81	17.5	711	3.8
AVSD (745.6)	187	15.1	129	15.6	142	26.4	77	22.8	67	21.1	109	23.6	649	3.5
Coaractation of aorta (747.1)	215	17.4	156	18.9	79	14.7	57	16.9	55	17.3	87	18.8	235	1.3
Tetrology of Fallot (745.2)	246	19.9	175	21.2	122	22.7	72	21.4	49	15.4	64	13.9	99	0.5
Hypoplastic left heart syndrome(746.7)	5	0.4	3	0.4	0	0.0	2	0.6	4	1.3	20	4.3	34	0.2
Hypoplastic right heart syndrome (746.9)	91	7.4	47	5.7	27	5.0	23	6.8	17	5.3	14	3.0	219	1.2
Truncus 745.0	36	2.9	22	2.7	13	2.4	5	1.5	9	2.8	19	4.1	50	0.3
Dextrocardia (746.87)	90	7.3	55	6.7	26	4.8	24	7.1	21	6.6	19	4.1	320	1.7
Double chambered right ventricle (746.83)	39	3.2	27	3.3	8	1.5	6	1.8	12	3.8	7	1.5	568	3.1
Sub-aortic stenosis (746.81)	101	8.2	72	8.7	46	8.6	37	11.0	28	8.8	36	7.8	728	3.9
Mitral atresia ((746.89)	26	2.1	4	0.5	3	0.6	5	1.5	6	1.9	6	1.3	104	0.6
Total	1237	100.0	825	100.0	538	100.0	337	100.0	318	100.0	462	100.0	3717	20.0

NB: Premature PDA's have been removed
Shaded area was used in calculations for Table 4.6 and Figure 4.4

Appendix 5B: Detailed and collapsed consanguinity coding CHD case control study

	SANGCOD2	Detailed description	N	%	Cumulative Percent		N	%
1	0a	First, Cross; Father's parents Matrilateral	1	0.21	90.11			
2	0a	First, Double	2	0.41	38.02			
3	0a	First, Matrilateral; Third once removed, Patrilateral; Fourth, Pa	1	0.21	88.97	Closer than	22	4.56
4	0a	First, Matrilateral or Cross; Second Patrilateral	2	0.41	47.91	First		
5	0a	First, Matrilateral; Double great grand-parents	1	0.21	94.30	Cousin		
6	0a	First, Matrilateral; Second (half) once removed, Matrilateral	1	0.21	92.40			
7	0a	First, Matrilateral; Second Cross	1	0.21	88.59			
8	0a	First, Matrilateral; Third Patrilateral	1	0.21	92.02			
9	0a	First, Matrilateral; Third, Patrilateral; Mother's parents Cross	1	0.21	90.87			
10	0a	First, Patrilaterallateral; Father's parents Second, Patrilateral	1	0.21	92.78			
11	0a	First, Patrilateral; Mother's parents First Patrilateral	8	1.66	87.07			
12	0a	First, Patrilateral; Second Patrilateral	1	0.21	75.29			
13	0a	First, Patrilateral; Second Patrilateral; Second (half) Patrilatera	1	0.21	91.63			
14	1a	First, Cross	32	6.64	37.26			
15	1a	First, Matrilateral	23	4.77	8.75	First	98	20.33
16	1a	First, Patrilateral	43	8.92	25.10	Cousin		
17	2a	First (half both sides), Double	1	0.21	87.45			
18	2a	First (half) Cross; Second (half) Cross	1	0.21	87.83	Closer than	4	0.83
19	2a	First (half) Cross; Second Patrilateral	1	0.21	88.21	First		
20	2a	First (half) Patrilateral; Second, Patrilateral	1	0.21	93.54	half Cousin		
21	2b	First (half) Cross	10	2.07	81.37	First half	13	2.70
22	2b	First (half) Matrilateral	3	0.62	82.89	Cousin		
23	3a	First once removed, Cross; Second, Cross	1	0.21	95.06			
24	3a	First once removed, Matri; Second Matri; Fourth Patri	1	0.21	94.68			
25	3a	First once removed, Patrilateral; First once removed, Cross	1	0.21	90.49	First Cousin	33	6.85
26	3b	First once removed, Cross	10	2.07	63.88	Once		
27	3b	First once removed, Matrilateral	5	1.04	66.92	Removed		
28	3b	First once removed, Patrilateral	15	3.11	60.08			
29	4a	First (half) once removed, Patrilateral	16	3.32	74.14	First Cousin	18	3.73
30	4a	First twice removed, Patrilateral	2	0.41	74.90	Other		
31	5a	Second Patrilateral (x2); Mother's parents First, Patrilateral	1	0.21	75.67			
32	5a	Second, Matrilateral	3	0.62	68.06	Second	38	7.88
33	5a	Second, Patrilateral	24	4.98	47.15	Cousin +		
34	5b	Second, Cross	7	1.45	54.37			
35	5b	Second, Matrilateral; Mother's parents First Patrilateral	1	0.21	89.73			
36	5b	Second, Patrilateral; Second Cross	1	0.21	91.25			
37	6a	Second (half) Matrilateral; Third Patrilateral	1	0.21	89.35			
38	6b	Second (half) Patrilateral	5	1.04	77.57			
						Second	12	2.49
39	7a	Second once removed, Cross	2	0.41	83.65	Cousin		
40	7a	Second once removed, Matrilateral	1	0.21	84.03	Other		
41	7a	Second once removed, Patrilateral	4	0.83	49.43			
42	8a	Third, Patrilateral	6	1.24	51.71	Third	7	1.45
43	8a	Third, Matrilateral	1	0.21	81.75	Cousins		
						Only		
44	9a	Third once removed, Patrilateral	1	0.21	93.16			
						Less close	18	3.53
45	9b	Fourth Patrilateral	3	0.62	65.02	than		
						Third		
46	9b	Fourth, Patrilateral; Father's parents First, Patri	1	0.21	93.92	Cousin		
		Juma'a	12	2.49	99.62			
		Unable to describe well enough to code	1	0.21	100.00			
		Total	263	54.56				
	Missing	System Missing	219	45.44				
		Total	219	45.44				
	Total		482	100.00				

Selected correlations for the Analysis of ALL Sampled N=482

Variables considered for correlations	Correlation	p-value	Test
Parity with Gravidity	0.9564	0.0000	P
Ethnicity of mother with Ethnicity of father	0.8866	<0.0001	SR
Mother's age with Father's age	0.7923	0.0000	P
Mother's origin with Father's origin	0.7442	<0.0001	KT
Mother's age with parity	0.7389	<0.0001	SR
Childhood deaths with Infant deaths	0.5996	0.0000	KT
Childhood deaths with Neonatal deaths	0.5982	0.0000	KT
Infant's weight with Gestational age	0.4491	0.0000	P
Gravidity with Pregnancy losses	0.4424	<0.0001	SR
Hair dye with Peroxide	0.4356	0.0000	KT
Level of mother's education with Level of father's education	0.3980	0.0000	KT
Vitamin use with Folic acid use	0.3937	0.0000	KT
Medications with Illness	0.3735	<0.0001	SR
Pregnancies with bleeding with number of pregnancy losses	0.3732	<0.0001	KT
Nogd use with Kohl use	0.3145	<0.0000	KT
Folic acid use with Level of mother's education	-0.2846	<0.0001	KT
Ethnicity of mother with Where mother lived until 12 years	-0.2344	0.0000	SR
Level of mother's education with Gravidity	-0.2300	<0.0001	KT
Mother's age with Mother's weight	0.2289	0.0000	SR
Vitamin use with Kohl use	-0.2133	<0.0001	KT
Where mother lived until 12 years with Net income	-0.2130	<0.0001	KT
Major maternal illness during index pregnancy with Maternal health previous pregnancy MAJ with HEALTH	-0.2113	<0.0001	KT
Folic acid use with Level of father's education	-0.2050	<0.0001	KT
Level of mother's education with Mother's ethnicity	0.2000	<0.0001	KT

Selected non-correlations for the Analysis of ALL Sampled N=482

Variables considered for correlations	Correlation	p-value	Test
Vitamin use with Ethnicity of mother	-0.1987	<.0001	SR
Pregnancies with maternal health problem with pregnancy loss	0.1969	0.1705	KT
Vitamin use with Level of mother's education	-0.1967	<0.0001	KT
Nausea with Heartburn	0.1840	<0.0001	KT
Henna use with Vitamin use	-0.1741	0.0000	KT
Major maternal illness with Neonatal death MAJ NEO	0.1709	0.0002	KT
Medications with Fever	0.1685	0.0198	SR
Multiple gestation with Gestational age	-0.1572	0.0006	P
Pesticide use in the home with Rodenticide use in the home	0.1337	0.0037	SR
Ethnicity of mother with Consanguinity PEDIGRE1	0.1226	0.0070	SR
Use of IVF with Any abnormality in pregnancy	0.1118	0.0144	SR
Pesticide use in the home with Peroxide use	0.1027	0.0262	SR
Ethnicity of mother with Consanguinity SANGCOD3	0.0983	0.0310	SR

P=Pearson product-moment correlation. KT=Kendal's Tau. SR=Spearman's Rank

Descriptive statistics for cases and controls where father's age was missing

Descriptive statistics for the 44 examples where father's age was missing are presented below. It is surprising to see that the mother's who did not know this information were neither the youngest nor the oldest. The percentage consanguineous who did not know was higher in the controls (78%) versus in the cases (50%). In terms of education, only 1 case mother who did not know her husband's age was illiterate. The other 11 (for whom this information was recorded) ranged in education from primary school education to four with university degrees. The husbands of two of the four mothers with university educations also had university educations. For the control mothers two were illiterate and one was literate although she had never been to school. There were five university graduate (22%) control mothers who did not know the age of their husbands.

Descriptive statistics for cases and controls where father's age was missing	Missing Father's age	
	Cases	Controls
N (%) missing father's age	16 (7%)	28 (11%)
N missing father's age and mother's age	4	5
Mean (median) year of mother's birth	1973 (1970)	1976 (1977)
Range of mother's year of birth	1964-1985	1963-1985
Percent consanguineous	50	78
Percent with university educations	33	22
Ethnicity	Couples: 6 Bedouin 4 Urban 2 Mixed	Couples: 6 Bedouin 17 Urban

Report on initial efforts to develop a social economic status indicator for Saudi Arabia

by Amy L. Sandridge

Problems with identifying residence and measuring SES

Residence in Riyadh was a requirement for case inclusion. Because ALS was aware from previous research projects that translating the concept of "residence" to this culture might be problematic this variable was considered carefully. Details are described in a report found in Appendix 6A. Over 99 percent of mothers were married to the father of the case or control infant. This was fortunate as there are *Shari'a* laws regarding divorce and the residence of offspring that might have complicated interviews with the mother further.

SES Measurement

As mentioned previously, there is no established method of assessing SES in the Saudi Arabian framework. The question "Location of House" and *hiy'* of residence (data not presented) were more problematic than expected during the data coding phase of the project. Women not only do not drive in Saudi Arabia but also they do not travel much on their own. There had been an intention to locate the families of cases and controls on the map of Riyadh to understand the nature of the sample and to determine if they were randomly distributed around the city by use of the *hiy'* or administrative code. Women gave a name and then this name was compared to the official list obtained from the local government. Transliteration was required. When a name was not on the list ALS consulted a Saudi Arabian colleague (Abdulrahman bin Muammer) who rationalized the *hiy'* names. His explanation for the names not being on the list were that 1.) some *hiy'* have an official name as well as a colloquial name; (2) some *hiy'* have been given new names by the local government and the mother had used the old name.

At the time of the study there had been no recorded voter registration, no property taxes required and local women do not routinely work outside the home (in this sample, only 27% of cases and 14% of controls had ever done so). It is not unexpected therefore, given this sheltered environment that the correct administrative unit of the residence would not

be known. Investigating the *hiy'* data we found that participants came from 96 of 164 *hiy'* in the Riyadh region. We interviewed cases from 76 (46%) *hiy'* for cases and controls from 61 (37%) *hiy'*. There was an overlap of 41 *hiy'* (data not shown (Appendix 6A)). It is difficult to understand the import of this result not knowing the city well (despite ALS having lived there since 1992) and not knowing the proximity of the *hiy'* to one another. Nonetheless, there was a spread of the cases and controls throughout the city. On the other hand, we found congregation of controls in 8 particular neighbourhoods (Appendix 6A) which could raise concerns regarding generalizability. Also, we had hoped that comparability of residence would indicate comparability of SES and so far this *hiy'* residence data does not completely convince us that the SES (as defined by residence) of cases and controls was comparable. Having said that, in a developing economy like Saudi Arabia's palaces and tent homes may co-exist in the same *hiy'*. The supposed terrorist enclave of the 2002-2003 period of bombings was in Al Swaidi, in the south of Riyadh. Despite it being known as a poor area, wealthy families reside there as well. Additionally, even if a family lived in a palace they might not have access to wealth, as such, but instead might be the poor relations living on the succour of the Prince. It is disappointing nevertheless that the *hiy'* of Al Swaidi contributed 14 cases and no controls. Still, without further investigation into socio-economic status (and Bedouin ethnicity) we fear that all we can do is present these results without making conclusions about them.

Another problematic issue is the concept of "house". Families in Saudi do not follow the same nuclear pattern that we generally have in the UK. A mother and her children might live one week with her family and then live with her husband's family for another week or out in a tent in the desert for awhile. Habits change for the month of Ramadan or when there is a birth or death in the extended family. Bedouins who have left the desert in compliance with the governmental efforts may not have a fixed place of abode. Possessions are limited. Wealth is aggregated in gold. Therefore, the concept of a physical base, a house or home, may be a foreign concept with which Saudi Arabians only pretend to comply. Further research by sociologists needs to be done in this area.

CHD case and control data by village of residence hiy' of Riyadh, Saudi Arabia

City, town or village name	Cases		Controls	
	N	%	N	%
Al Aflaj	2	0.9		
Al Aqeeq	3	1.3	1	0.4
Al Areja	7	3	20	8.1
Al Artawiyah	1	0.4		
Al Aziziyah	8	3.4	5	2
Al Badiah	13	5.6	10	4
Al Basitah	1	0.4		
Al Batha			2	0.8
Al Dar Baidha a			3	1.2
Al Deriyah	2	0.9		
Al Duwadmi	4	1.7		
Al Eskan	2	0.9	4	1.6
Al Faihaa	1	0.4	2	0.8
Al Falah	1	0.4		
Al Garradiyah (Jaradeya)			1	0.4
Al Ghadeer			1	0.4
Al Ghat	1	0.4		
Al Hamadia	1	0.4		
Al Hayir	1	0.4		
Al Hazm	1	0.4		
Al Hota (Hawtat Sadayr)	4	1.7		
Al Huda wa Rabi	1	0.4		
Al Izdihar	1	0.4		
Al Jaradi	1	0.4	2	0.8
Al Khaldiyah (Khaldia or Khaledya)			2	0.8
Al Khaleej	1	0.4	4	1.6
Al Kharj	4	1.7	3	1.2
Al Ma athar	1	0.4	4	1.6
Al Maazar	2	0.9		
Al Majma ah	4	1.7		
Al Malaz	4	1.7	3	1.2
Al Malik Fahd	2	0.9	1	0.4
Al Manar			1	0.4
Al Mansoorah			1	0.4
Al Maseef	3	1.3	2	0.8
Al Moghrezat	1	0.4		
Al Mohammadiyah	3	1.3		
Al Morooj	4	1.7		
Al Murabba a			1	0.4
Al Mursalat	3	1.3	1	0.4
Al Muzahmiyyah	1	0.4		
Al Nada	1	0.4		
Al Nafl	1	0.4		
Al Nahdhah	4	1.7	3	1.2
Al Nakheel			1	0.4
Al Naseem	18	7.7	29	11.7
Al Nozhah/Nusha	1	0.4		
Al Olaiyah (Olaya or Olia)	2	0.9	2	0.8
Al Oud	2	0.9	1	0.4
Al Quds	2	0.9	3	1.2

City, town or village name	Cases		Controls	
	N	%	N	%
Al Quwayiyah	3	1.3		
Al Ra eid	1	0.4		
Al Rabwah	1	0.4	4	1.6
Al Rawabi	1	0.4	2	0.8
Al Rawdah	12	5.1	20	8.1
Al Rayan	3	1.3	2	0.8
Al Riyan	1	0.4		
Al Saadah			1	0.4
Al Safarat (Diplomatic Quarter)	1	0.4	1	0.4
Al Salam	3	1.3	3	1.2
Al Salee	1	0.4	2	0.8
Al Shafa	11	4.7	13	5.3
Al Shimaisi			1	0.4
Al Silay (Sulay or Slay)	1	0.4	1	0.4
Al Silfy	1	0.4	4	1.6
Al Sulaimaniyah	2	0.9	3	1.2
Al Swaidi	14	6		
Al Ta won			3	1.2
Al Takhassussi (KFHS&RC)	2	0.9		
Al Tumair	1	0.4		
Al Tweiq			2	0.8
Al Wadi	1	0.4		
Al Wezarat	2	0.9	8	3.2
Al Yamamah	1	0.4	1	0.4
Amir Abdullah	1	0.4		
Ashbiliyah			3	1.2
Badr			1	0.4
Dakhl Mahdood	6	2.6	20	8.1
Dhahrat Laban			1	0.4
Ghernatah	1	0.4	4	1.6
Janadriyah	1	0.4	2	0.8
Jareer			1	0.4
Jazira	1	0.4	5	2
Khamassin	1	0.4		
Khanshalilah	1	0.4		
Manfuha	4	1.7	5	2
Mleheya			1	0.4
Otaiqah			2	0.8
Prince Mesh al			1	0.4
Sderia/Sdeer/Sdair	1	0.4		
Shagra	4	1.7	4	1.6
Shobra	4	1.7	1	0.4
Sultanah	1	0.4	8	3.2
Thelaim	1	0.4		
Umm Alhamam	3	1.3	4	1.6
Wadi Ad Dawaser	6	2.6		
Unknown, Riyadh City	3	1.3		
Father from Riyadh	12	5.1		
Total	234	100	247	100
Fathers from Riyadh but currently living outside Riyadh				
Ranyah, Asir	1	0.4		
Dammam, EP	4	1.7		
Hafre Al Batin, EP	1	0.4		
Al Hasa, EP	2	0.9		
Al Khobar	1	0.4		
Al Taif	1	0.4		
Al Hasa, EP	1	0.4		
Al Tahliah, Jeddah	1	0.4		

Geographical distribution of congenital heart defects in Saudi Arabia

W. Greer, PhD; A.L. Sandridge, MSc; M. Al-Menieir, BSc; A. Al Rowais, MPH

BACKGROUND: Congenital heart defects (CHD), which are caused by abnormalities early in fetal life, encompass over 50 diagnoses. Since the detailed etiology is unknown, the geographical distribution of defects might suggest likely risk factors.

METHODS: The geographical distribution of 5 865 Saudi Arabian nationals with CHD was studied by cross-matching their residential provinces and towns with a geographical information system provided by the General Directorate for Military Survey. Population data were obtained from the 1413H census.

RESULTS: CHD cases were mostly distributed across the provinces in proportion to their total population but due to their size and inhomogeneity, province-based thematic maps were found to be misleading. City-based maps were preferable and showed similar geographic distributions for cases registered in successive years. Thematic maps of the distribution of the CHD burden highlighted the southwestern provinces, near the border with Yemen, and the northeast section of the Eastern Province.

CONCLUSIONS: Patterns of disease in Saudi Arabia are best studied at the level of individual towns and villages. The CHD registry has already attained good national coverage and can therefore support nationwide epidemiological studies. Southwestern Saudi Arabia and the northern part of the Eastern Province appear to exhibit a higher burden of CHD.

From the Biostatistics, Epidemiology and Scientific Computing Department, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia

Correspondence to:
William Greer, PhD
KFSH&RC
P.O. Box 3354 (MBC 03)
Riyadh 11211
Saudi Arabia
E-mail: greer@kfshrc.edu.sa

Accepted for publication:
September 2004

Ann Saudi Med 2005; 25(1): 63-69

Congenital heart defects (CHD) can encompass over 50 diagnoses. According to Mitchell,[1] a CHD can be defined as "a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance." The majority of CHD cases are probably due to a genetic predisposition coupled with exposure to a teratogen[2] (either endogenous[3] or exogenous[4]). However, the etiology is still largely unknown and the role of environmental factors is difficult to establish, given the rarity of the disease and the fact that most structural defects occur inter-utero in the first trimester of pregnancy. Establishing the geographical distribution of CHD patients would provide a convenient platform for the exploration of putative risk factors, such as exposure to mutagens,[5-12] inbreeding[13] and environment.[7,14]

CHD patients have been referred to the Cardiovascular Department at the King Faisal Specialist Hospital and Research Centre (KFSHRC) since its inception in 1977. An Internet-based CHD registry (CHDR) was established in 1998 for both clinical and research purposes.[15] By linking the CHDR data to a geographical information system (GIS) currently used by the Saudi Arabian Ministry of Defense and Aviation (MoDA), we have been able to explore the geographical distributions of CHDR patients. A GIS is a software package dedicated to the storage and display of geographic information. This paper focuses on the development of the system and the initial results. Since there appear to have been no prior GIS publications related to health care or epidemiology in Saudi Arabia, it may be worth mentioning that this system can be adapted to study the geographical distribution of other diseases.

Methods

Definition of CHD. The CHDR routinely codes patients according to both ICD-9-CM (745.0 to 747.9, including Wolf Parkinson White syndrome, 426.7, and supraventricular tachycardia (SVT), 427.89)[16] and the newly established European Pediatric Cardiac Code.[17] No effort is made to distinguish congenital from acquired SVT. Patients with isolated patent ductus arteriosus (PDA) diagnosed at less than 90 days of age are excluded, and cases of mitral valve prolapse are not registered.[18-19] All cases were confirmed by echocardiogaraphy, cardiac catheterization or cardiac surgery (autopsy within Saudi Arabia is performed only in exceptional circumstances). The CHD cases were analyzed as a group to avoid errors that might result from the small number of cases for some specific diagnoses.

Map data. The GIS themes (i.e., sets of related geographical features) presented here were obtained in their entirety from the Saudi Arabian Ministry of Defense and Aviation, with the exception of the cities of CHDR patients; these were supplemented by information from the "Digital Chart of the World," an Environmental Systems Research Institute, Inc. (ESRI) product that was freely downloaded across the Internet. The MoDA cities theme initially comprised 994 entries, but after eliminating locations that were not habitations (i.e., had no population), and multiple entries for identical x,y coordinates, 970 unique city names remained.

Data analysis. GIS analysis was carried out using the ArcView software package (v3.2a, ESRI Systems Inc.). Other data-analysis made use of the JMP statistics package (v3.2.5). The scatterplots, line-plots and histograms were produced by Origin v5.1 (Microcal).

Independence of measurement. Families with more than one case of CHD in the registry were located using a family membership identifier (assigned to each case upon registration, and based upon information from the parents), in conjunction with a retrospective computer search of the entire registry (using family name, grandfather's name, father's name, telephone number, province and cities of residence and origin). When multiple children with CHD from the same family were detected, only the first-born child was retained.

Demographic data. The city and province of current residence (i.e., the residence of the father at the time of registration) were obtained from a parent of the child during a face-to-face interview. Within the Kingdom, this is expected to closely reflect the mother's residence and will be largely unaffected by the location at which the woman actually delivers. Since most cases were registered very early in life and the pool of migrant indigenous workers has traditionally been small, this should be a good indicator of where the child was gestated. The term "city" applies here to a specific geographical location, as opposed to the more general location indicated by the administrative province; this may refer to an actual city, or a town, or even a small village. Estimates of the Saudi populations of each city were taken from the 1413 Hejra (1992-1993 Gregorian) census.[20]

Results

Description of CHD Cases. The patient population comprised all 6649 patients registered in the KFSHRC Congenital Heart Disease Registry (CHDR) between 1 January 1998 and 1 November 2002. Five hundred and twenty-two non-Saudi cases, 51 subsequent registrations from the same families, 84 cases resident outside the Kingdom of Saudi Arabia (KSA) at the time of their interview, and 127 cases which were never interviewed, were all excluded, leaving 5865 cases for further study. The province-of-residence was known for all 5865 cases, and the city-of-residence was available for 5764, of which only 5209 could be successfully linked to a specific geographical location (Table 1).

Construction of the GIS Map (Provinces). In both the CHDR and the MoDA databases, province names were coded as English transliterations of the original Arabic names. Although there was some variation in spelling, each province was easily identified because there were only 14 different entities. The names of the provinces in the MoDA database were modified to correspond to those used in the CHDR. During this process it was observed that the CHDR data contained one additional province, Qurayyat, which the MoDA database had included as part of the Jawf province. This situation arose because of changes in the administrative boundaries during the last 10 years. The CHDR designation was changed from Qurayyat to Jawf.

Construction of the GIS Map (Cities). This CHDR dataset contained 186 unique names for city-of-residence and 162 for city-of-origin, which together comprised 202 unique city-names. The original intention was to obtain the geographical coordinates of these cities by automatically screening each name against the MoDA database of 970 cities with their associated longitude and latitude. As with the province names, the city names had been coded (in both databases) as English transliterations of the original Arabic. However, since there were so many more city-names than province-names, the different transliterations meant that it was not possible to automatically match each of the CHDR

Table 1. Distribution of cases in the KFSHRC Congenital Heart Disease Registry among the different provinces.

Province		Number of cases		
Name	Saudi population	Total cases	Cities with known geographical location	Cities with unknown geographical location
Asir	1 149 618	349	296‡	53‡
Al Baha	289 890	140	128	12
Eastern Province	1 898 462	1 469	1 464	5
Hail	346 180	41	38	3
Jawf	224 040	138	138	0
Jizan	734 078	202	193	9
Medina	836 764	369	363	6
Makkah	2 780 458	1 054	1 051	3
Najran	242 066	161	157	4
Northern Province	178 389	79	79	0
Qasim	611 462	241	156¶	85¶
Qurayyat†	n/a	82	79	3
Riyadh	2 613 228	1 300	1 286	14
Tabuk	401 256	240	233	7
Total	12 305 891	5 865	5 209	66

* Population statistics taken from the last published census, 1413 Hejra (1992-1993 Gregorian).

† For analysis, Qurayyat province has been included in the statistics for Jawf province.

‡ 44 cities of residence for Asir had invalid codes.

¶ 59 cities of residence for Qasim had invalid codes.

cities to its corresponding MoDA entry. After a simultaneous match-merge operation using province and city names, 82 of the 202 cities (approximately 40%) remained unidentified. Sixty-nine of these were subsequently identified by closely inspecting the transliterations of each CHDR city-name and (where possible) manually identifying the corresponding name in the MoDA database. Five more cities were identified using an alternative city database and the names of the eight remaining cities whose geographical coordinates could not be identified were set to missing (19 CHDR cases, 11 cities-of-residence and 16 cities-of-origin). Two pairs of cities were discovered to have identical longitude and latitude in the MoDA database (Ad Dammam/Dammam and Ballahmar/Ballasmar); Dammam and Ballahmar were therefore deleted from the list of city names, and their six corresponding entries in the CHDR dataset were also changed. Two hundred city names remained in the final CHDR dataset.

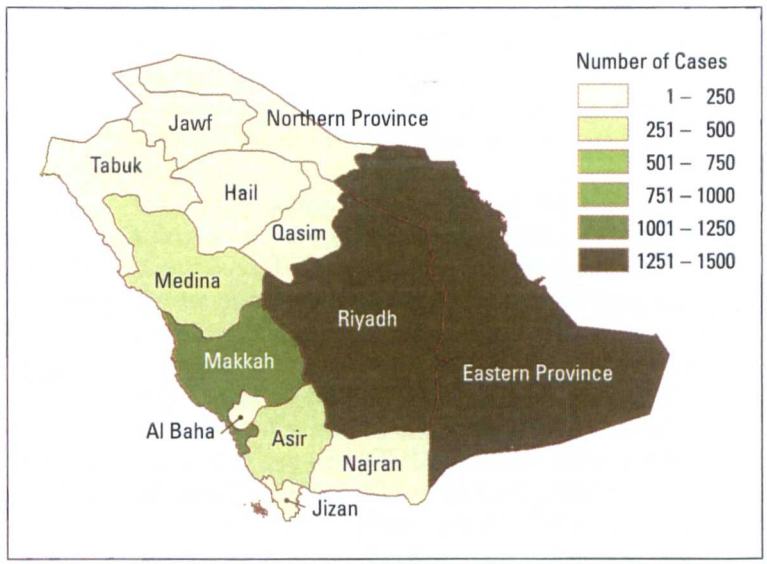


Figure 1. Geographical distribution of KFSH&RC congenital heart defect cases among the provinces of Saudi Arabia (1998-2002).

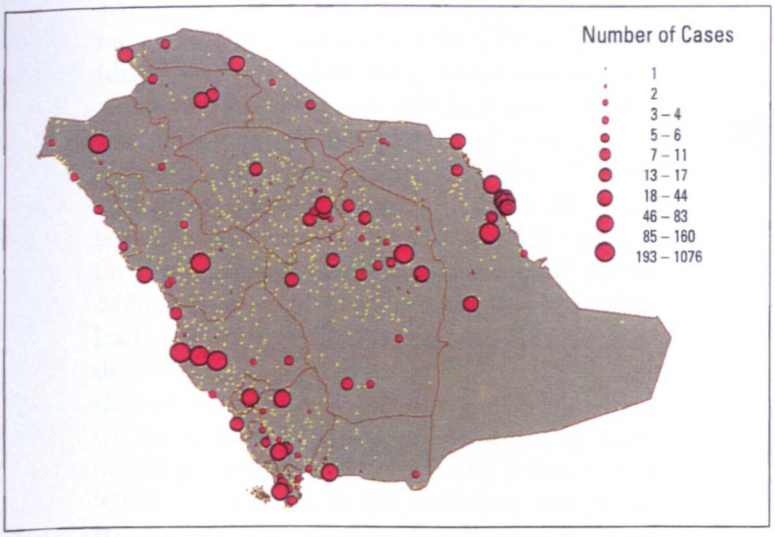


Figure 2. Distribution of KFSH&RC congenital heart defect cases among the cities of Saudi Arabia. (Cities classified into ten quantiles. Cities with no cases shown as small yellow dots.)

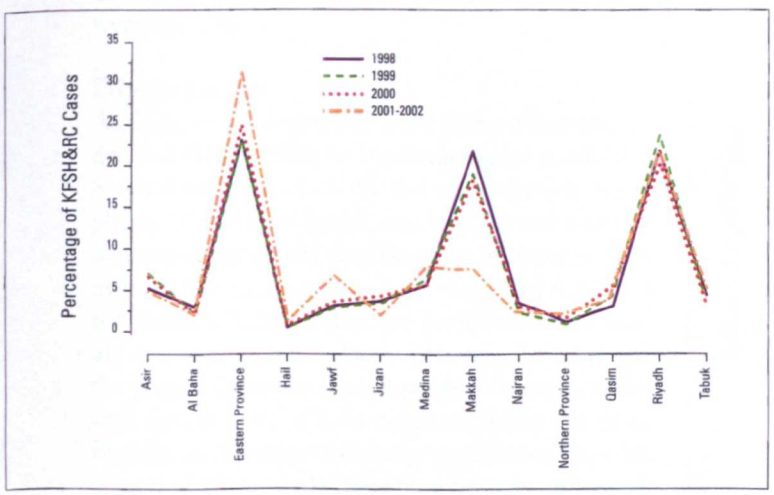


Figure 3. Percentage distribution of KFSH&RC congenital heart defect cases registered each year in the provinces of Saudi Arabia. (Cases for 2001-2002 are incomplete)

Table 2. Distribution of registered congenital heart disease cases by year.

Year	Number of registrations
1998	2053
1999	1707
2000	1125
2001	732*
2002	248*

* Not all cases registered in 2001 and 2002 had been processed when the dataset was abstracted.

Geographical distribution of CHDR cases. The geographical distribution of CHD (Figure 1) reflected the regional population density. The largest number of cases were from the Riyadh, Eastern and Makkah provinces, forming an east-west "axis" across the centre of the country. However, due to the large size and inhomogeneity of the Saudi provinces, the population densities underlying these maps were not uniformly distributed within each province, thereby creating a misleading impression of the true geographical distribution. In a thematic map based on cities-of-residence (Figure 2), the "axis" is less obvious and is more clearly focused only around the 3 largest cities–Dammam (east coast), Riyadh (central) and Jeddah (west coast). What was not so evident from the map of the provinces is that there is also clustering of cases.

Registry stability and coverage. The CHDR has been functional since 1998. Due to the existence of a sizable and well-established outpatient population, more than 2000 new cases were registered during its first year of operation (Table 2). The number of new cases registered each year has subsequently declined to approximately 1000. However a time-series of thematic maps (not shown) suggested that the geographical distribution has remained very similar on an annual basis. The annual change in the percentage of new registrations appeared similar across the provinces (Figure 3), and this was confirmed by the corresponding thematic map for cities (Figure 4), between the years 1998 and 2000. A comparison between the number of CHD cases per province, and the population of each province at the 1413H census (Figure 5) lends support to the notion of representative CHDR coverage, except for the Eastern Province which has a significantly higher number of cases.

The CHD burden. A geographical analysis based solely on numbers of cases can reach only limited conclusions. To obtain a more accurate picture of the disease distribution, the sizes of the underlying city populations need to be considered. A map of prevalence estimates would be ideal, but currently there is only limited available information for birthrates at the level of detail required. An indication of the underlying CHD "burden" (CHDB) can be estimated by dividing the number of cases for each province or city by its population (expressed per 100 000). Although this is not a true prevalence measure, it does provide a convenient way to normalize the results. Because this estimate is based on 1413H census data, those CHD cases born outside a "window" of ±5 years around

1413H were excluded from this analysis, resulting in a 10-year subset of 3151 CHDR patients (distributed across 139 cities) whose birthdays occurred between 1988 and 1997 inclusive. A further 109 cases were eliminated because their city-of-residence was either missing (11 cities, 45 cases) or had an unknown location (3 cities, 64 cases), leaving 3042 cases distributed across 125 cities for further study. The Saudi population could not be definitively established for a further 19 cities (15%) leading to missing CHDB estimates. The resulting distribution of CHDB (Figure 6) was positively skewed and contained only one "outlier" -Al Baha (in the Al Baha province) with a CHDB estimate of 748 per 100 000 (70 cases from a population of 9364). This city lies in the southwest, and an inspection of the geographical distribution of CHDB (Figure 7) showed that the southwest provinces as a whole appeared to be the region that had the largest number of cities with a substantial CHD burden, although several cities in the Eastern Province were also affected.

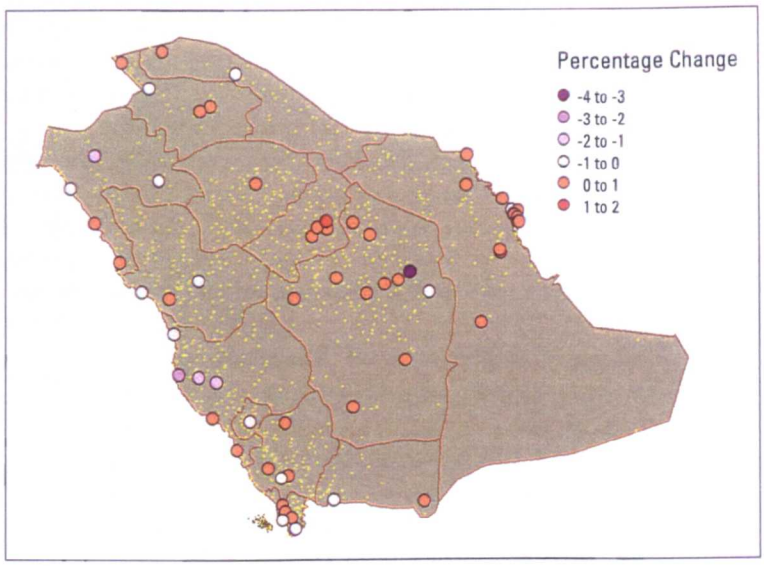


Figure 4. Change in percentage distribution of KFSH&RC congenital heart defect cases among the cities of Saudi Arabia, registered 1998-2000. (Small yellow dots represent cities with no cases.)

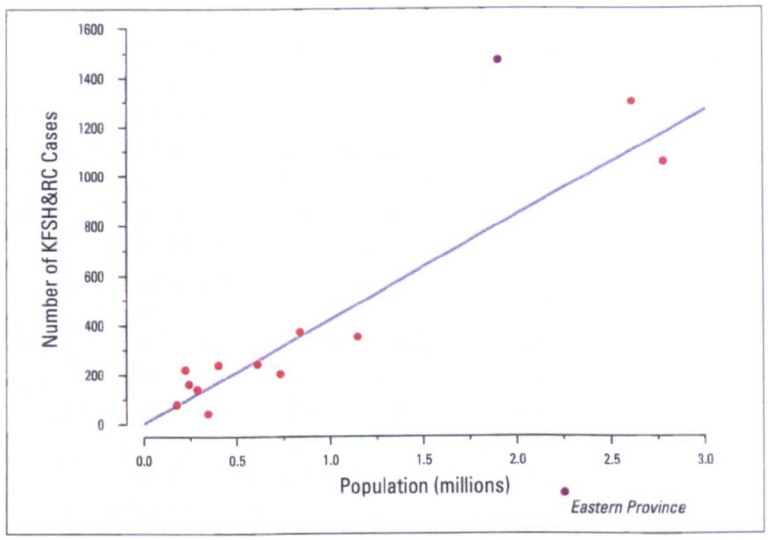


Figure 5. Number of KFSH&RC congenital heart defect cases per province vs. the population of each province in the 1413H census.

Discussion

As far as we are aware, this is the first publication of a detailed GIS suitable for epidemiological research in Saudi Arabia. Paradoxically, the major obstacle in applying GIS to local health care issues is not a lack of accurate geographical data (indeed a number of GIS maps of the Kingdom can be downloaded free from the Internet[21]), but rather the problem of establishing the appropriate linkages between the map and the project databases. This is partly a language problem: data in key fields (in either database) can be in English, so that success in merging such data depends upon how consistently these have been transliterated. Even in Arabic, the names of the smaller towns or villages can be ambiguous because the same city may be known by different names. There is also a problem in obtaining accurate demographic data, because the population structure has changed so quickly since the last published census (10 years ago) that simple interpolation is inappropriate, and there is no guarantee that data from different ministries can be correlated (e.g., different administrative boundaries may be used).

This is also the first attempt to portray the geographical distribution of CHD in KSA, and our preliminary maps have revealed several important features. Although the CHDR population distribution reflects the central axis of population, cities in the southwestern provinces (Jizan, Asir, Najran and Al Baha) exhibit high disease burdens. Indeed, Al Baha city appears to have the largest CHD burden of any city in the Kingdom, although since the city has the same name as the province, the possibility of some data-capture errors cannot be ruled out. The CHD problem in the southwest may reflect the unique physical terrain of that region, which is more mountainous than other parts of the Kingdom. Alternatively it may be associated with cultural

factors that have been imported from its southern neighbor, Yemen. Traditionally, the Kingdom's border has been more permeable here than elsewhere in the Kingdom.

The value of these results depends strongly on the extent to which the CHDR data represents the entire Kingdom. This is admittedly difficult to gauge since it depends largely upon the referral pattern. However, for a rare disease such as CHD we would argue that the existence of a small number of referral hospitals should guarantee a nationwide dimension. Apart from KFSHRC, there are currently only two other hospitals in KSA that treat CHD patients. Our current estimate is that KFSHRC alone captures approximately 50% of the total CHD burden. Since the cardiovascular department at KFSHRC has been treating CHD cases for more than 15 years before the registry began, it is likely that the catchment area would have become stabilized, and our results appear to confirm this.

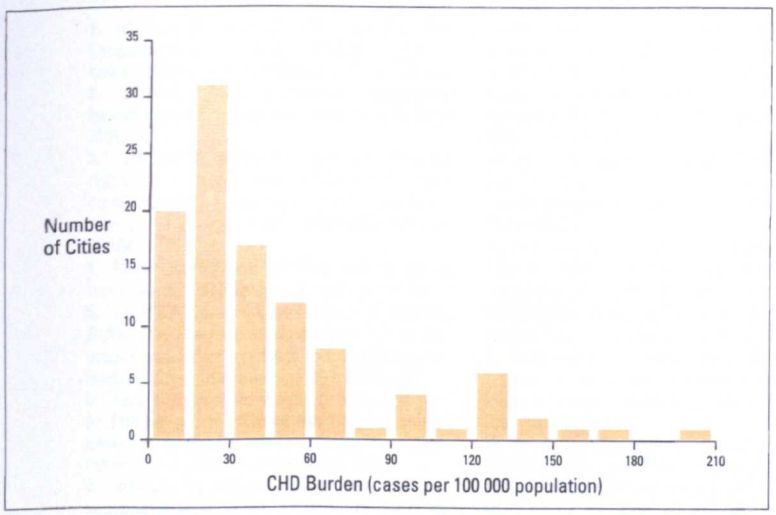


Figure 6. Congenital heart defect burden of KFSH&RC CHD cases among the cities-of-residence for cases with birth-years between 1988 and 1997 (inclusive). (Al-Baha is regarded as an outlier and therefore not included.)

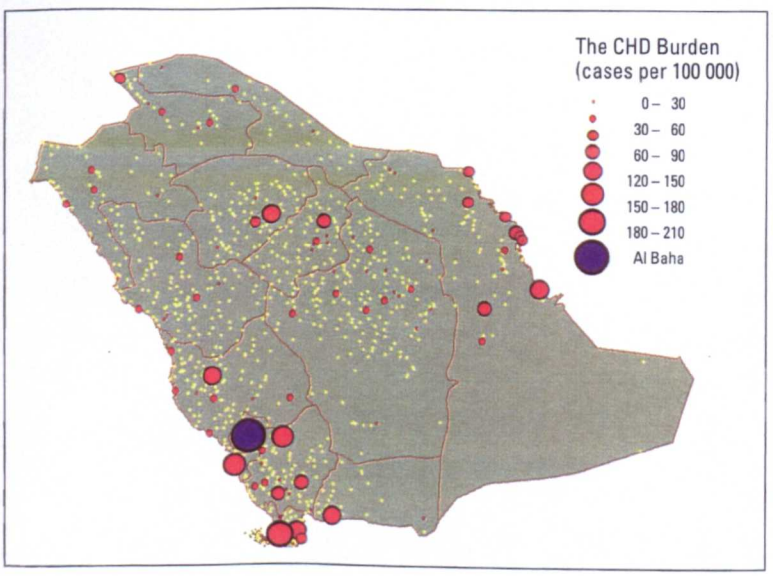


Figure 7. Congenital heart defect burden for KFSH&RC CHD cases with birth-years between 1988 and 1997 (inclusive), distributed among cities-of-residence. (Al-Baha shown in blue because it has a disproportionately high value. Cities with no cases shown as small yellow dots.)

There are several minor factors that may have introduced some bias. It is possible that some cases have not been correctly identified, especially in the provinces. This, and the recent growth of the hospital's "Outreach" program might have led to a degree of inhomogeneity. There were also a small number of cases that were excluded because their geographical location could not be determined. However, the cities for which we could obtain no reliable population statistics represent 15% of the final dataset. This constitutes the most significant source of error in this study.

We have also shown that displaying spatial distributions in KSA using maps based on provinces alone is inadequate in faithfully representing disease distributions in a geographical area as inhomogeneous and sparsely populated as Saudi Arabia. Maps based on cities convey a more accurate impression. Furthermore, by constructing maps of the disease burden only for those cities that actually contain cases, not only do we improve the accuracy of the spatial distribution, but we also minimize any residual bias due to referral patterns by not including populations in the denominator that are not demonstrably included in the catchment area of the registry.

In conclusion, we believe that we have produced a GIS system that is sufficiently accurate to tackle the problem at hand (the spatial distribution of CHD) which can be extended to other disease registries or national studies by including information as it is made available. We hope that through time, this can evolve into a comprehensive epidemiological GIS for the Kingdom of Saudi Arabia.

Acknowledgements

The authors would like to thank the KFSH&RC CHD Registrars–Ms. A. Al Harbi, Ms. S. Black and Ms. R. Chehabedine. We would also like to thank Ms. S. Subhani (database programmer) for making the CHDR data conveniently available, and the KFSH&RC CHD Registry Committee (Dr. Z. Al

Halees, Dr. F. Al Mohanna, Dr. M. Jufan and Dr. E. De Vol) for approving the study. We would like to extend a special thanks to Major Fahad and all the staff at the General Directorate for Military Survey, Ministry of Defence and Aviation for providing us with a limited version of their GIS system which has proved to be invaluable. In particular, we would like to thank the late Dr. Mosaad Allam, who was the Director of the MoDA GIS Unit until his untimely death in July 2002; without his enthusiasm and support this study would never have been completed. Finally we would also like to thank Ms. A. Al Madouj and Mr. Y. Hussain for helping to construct our own database of population statistics.

References

1. Mitchell SC, Korones SB, Berendes HW. Congenital heart disease in 56 109 births. Incidence and a natural history. **Circulation.** 1971; 43: 323-332.

2. O'Rahilly R, Muller F. **Human embryology and teratology**, 3rd Ed. New York: John Wiley & Sons; 2001.

3. Loffredo CA, Wilson PD, Ferencz C. Maternal diabetes: an independent risk factor for major cardiovascular malformations with increased mortality of affected infants. **Teratology.** 2001; 64: 98-106.

4. Kallen K. Maternal smoking and congenital heart defects. **Eur J Epidemiol.** 1999; 15: 731-737.

5. Croen LA, Shaw GM, Sanbonmatsu L, Selvin S, Buffler PA. Maternal residential proximity to hazardous waste sites and risk for selected congenital malformations. **Epidemiology.** 1997; 8: 347-354.

6. Lenz W. Chemicals and malformations in man. In: Fishbein M, ed. **Second international conference on congenital malformations.** New York: International Medical Congress, Ltd; 1964.

7. Cedergren M, Selbing A, Kallen B. Geographic variations in possible risk factors for severe cardiac malformations. **Acta Paediatr.** 2002; 91: 222-228.

8. Goldberg SJ, Lebowitz MD, Graver EJ, Hicks S. An association of human congenital cardiac malformations and drinking water contaminants. **J Am Coll Cardiol.** 1990; 16: 155-164.

9. Ritz B, Yu F, Fruin S, Chapa G, Shaw GM, Harris JA. Ambient air pollution and risk of birth defects in Southern California. **Am J Epidemiol.** 2002; 155(1): 17-25.

10. Zierler S, Theodore M, Cohen A, Rothman KJ. Chemical quality of maternal drinking water and congenital heart disease. **Int J Epidemiol.** 1988; 17(3): 589-594.

11. Tikkanen J, Heinonen OP. Maternal exposure to chemical and physical factors during pregnancy and cardiovascular malformations in the offspring. **Teratology.** 1991; 43: 591-600.

12. Loffredo CA, Silbergeld EK, Ferencz C, Jianyi Z. Association of transposition of the great arteries in infants with maternal exposures to herbicides and rodenticides. **Am J Epidemiol.** 2001; 153(6):529-536.

13. Wong SS, Anokute CC. The effect of consanguinity on pregnancy outcome in Saudi Arabia. **J R Soc Health.** 1990; 4: 146-147.

14. Miao CY, Zuberbuhler JS, Zuberbuhler JR. Prevalence of congenital cardiac anomalies at high altitude. **J Am Coll Cardiol.** 1988; 12(1): 224-228.

15. Mitri W, Sandridge AL, Subhani S, Greer W. The design and development of an Internet registry for congenital heart defects. **Teratology.** 2002; 65: 78-87.

16. US Department of Health and Human Services Public Health Service, Health Care Financing Administration. ICD-9 CM: The international classification of diseases. 9th revision, clinical modification, 2nd Ed. Washington, DC: US GPO. DHHS publication No. 1980.

17. Association for European Paediatric Cardiology. The European Paediatric Cardiac Code, The First Revision. **Cardiol Young.** 2002; 12(Suppl 2): 1-212.

18. Nascimento R, Freitas A, Teixeira F, Pereira D, Cardoso A, Dinis M, Mendonca I. Is mitral valve prolapse a congenital or acquired disease? **Am J Cardiol.** 1997; 79: 226-227.

19. Hoffman JIE. Incidence, mortality and natural history. In: Anderson RH, Baker EJ, McCartney FJ et al. **Paediatric Cardiology.** London: Churchill Livingstone; 2002: 111-140.

20. Census of Saudi Arabia. (-In Arabic-) General Census Department, Riyadh, Saudi Arabia.

21. Geocommunity: Online Resources for GIS and Geospatial Data. *http://www.gisdatadepot.com/catalog/SA/group117.html*; accessed 2003 Jan 9.

The Impact of Altitude on the Burden of Congenital Heart Defects in Saudi Arabia

Sandridge: Impact of Altitude on CHD in KSA

Amy L. Sandridge* MSc, William Greer PhD, Maha Menieir BSc, Abdullah Al Rowais MPH

Biostatistics, Epidemiology and Scientific Computing Department
King Faisal Specialist Hospital and Research Centre
P.O. Box 3354, Riyadh 11211
Saudi Arabia

* **Author to whom correspondence should be sent:**

Amy Sandridge MSc
Medical Education Department
Weill Cornell Medical College in Qatar
P.O. Box 24144
Doha, Qatar.
Tel: +974-492-8318
Email: ams2023@qatar-med.cornell.edu

ABSTRACT

Background: Congenital Heart Disease (CHD) has a complex etiology in which environmental factors play a key role. High altitude is already established as a risk factor for certain types of CHD. Data from the CHD Registry at King Faisal Specialist Hospital and Research Centre in Riyadh were used to explore the impact of lower altitudes on CHD, guided by previous results which indicated that cities in the more mountainous south-western region experienced a higher CHD burden.

Methods: The study group comprised 2,787 Saudi Arabian CHD cases from 104 different cities and villages distributed widely throughout the Kingdom. The altitude for each city was estimated by visual interpolation using a geographical information system. An estimate of the CHD "burden" was derived by normalizing the number of CHD cases per city according to the population.

Results: Cities at higher altitudes (>3000 feet) had an increased average CHD burden, but a comparison of the average CHD burden among cities within each of four quartiles of altitude showed that CHD Burden was also high among cities at the lowest altitude (on the coastal plains); the lowest burdens were at intermediate altitudes. This trend was also visible within both the south-western region and the rest of the country, and was reflected in the behaviour of overall and isolated PDA, ASD and ASDII/PFO subtypes.

Conclusions: Our results suggest that the CHD burden in Saudi Arabia is impacted by at least three different environmental factors: (i) high altitude, (ii) coastal proximity and (iii) a south-western location.

KEYWORDS

Congenital Heart Defects, Geographical Distribution, GIS, Clinical Registry, Spatial Analysis, Altitude, Saudi Arabia, Toxic Exposure

INTRODUCTION

The specific etiology of congenital heart defects (CHD) in Saudi Arabia is largely unknown, reflecting the inherent difficulties in studying a complex condition which encompasses over 50 ICD-9 diagnoses that occur inter-utero in the first 17 to 50 days of gestation **[1]**. In general, most defects are thought to be due to an *a priori* genetic predisposition which potentiates the effect of any exposure to a teratogen **[2]**. Environmental factors therefore play a central etiological role. Some success has already been achieved in identifying some specific environmental causes **[3-5]**. One of these is the altitude at which birth takes place. This has been especially associated with PDA **[6-8]** and is believed to be the result of poor oxygenation.

We recently utilized the CHD Registry at the King Faisal Specialist Hospital and Research Centre in Riyadh to illustrate how Geographical Information Systems (GIS) can be usefully applied to epidemiological studies in Saudi Arabia **[9]**. One interesting outcome of this exercise was the observation that the south-western region of the country apears to have a higher density of cities with large CHD "burdens". We speculated that one explanation might be the higher altitudes associated with these habitations, as was recently found with stroke in Saudi Arabia **[10]**. We have therefore expanded our previous analysis to investigate the detailed impact of altitude on CHD in Saudi Arabia. Specifically we set out to test the hypothesis that the observed higher "burden" in the south-west could be due to higher altitudes prevalent among the mountainous terrain which is one of its principal geographical features.

MATERIALS AND METHODS

A detailed description of methods can be found in our previous publication. Essentially, CHD cases were extracted from the KFSH&RC CHD Registry database; where more than one case came from the same family, the child who was born first was selected for analysis. The city (i.e. a *specific* residential location which could be an actual city or a small village) and province of current residence were obtained from a parent of the child during a face-to-face interview. Within the Kingdom, this is expected to closely reflect the mother's residence. Since most cases were registered very early in life and the pool of migrant indigenous workers has traditionally been small, this should be a good indicator of where the child was gestated.

Because birth statistics in Saudi Arabia were not available at the level of individual cities, true city-based prevalence estimates of CHD were not possible. However the geographical distribution of CHD patients was *normalized* by dividing the number of cases per city by the corresponding total population expressed per 100,000, producing a quantity which can be regarded as the CHD "burden" (CHDB). Estimates of the city populations were taken from the Saudi Arabian 1413 Hejra (H) census (1992-1993 Gregorian). CHD cases born outside a "window" of ± 5 years around 1413H were excluded. The specific CHD sub-diagnostic categories considered more at risk for effects of high altitude were: (a) Any type of ASD with or without PFO (ICD9 = 745.5 (ASD II) or 745.61 (ASD I) or 745.8 (ASD sinus type)), and (b) PDA (ICD9 = 747) when found as isolated defects or in parallel or accompanied by a non-CHD anomaly such as Down or Noonan syndrome.

GIS analysis was carried out using the ArcView software package (v3.2a - ESRI Systems Inc.). GIS themes were obtained from the Saudi Arabian Ministry of Defense and Aviation and supplemented by data from the "Digital Chart of the World" (Environmental Systems Research Institute, Inc.). The altitude of each city was approximated by visual interpolation between known altitudes provided by the GIS system. However the vertical resolution provided by the MoDA database was poor (1000-meter contours) and therefore additional (free) ESRI sources were used (1000-feet contours and spot-heights) leading to some variation in the accuracy of each estimated height.

Statistical analysis was carried out using the JMP statistics package (v3.2.5) and all figures were produced using Origin v5.1 (Microcal). Two-tailed statistical significance of the difference between medians was determined using the Wilcoxon (Rank Sums) test. The Fisher's 95% confidence intervals for overall prevalence estimates were calculated using the WINPEPI software package **[11]**.

RESULTS

Altitudes and CHD Burdens were estimated for all 104 Saudi Arabian cities with residential CHD cases (Table 1) whose geographical locations could be firmly established, as described in our previous publication **[9]**. The cases comprised all apparently-unrelated CHDR patients of Saudi Arabian nationality from the KFSH&RC CHD Registry who were resident in the Kingdom at the time of their registry interview and whose birthdays occurred between 1988 and 1997 inclusive. Based on altitude, the cities comprised three groups (Figure 1): (i) a substantial number situated close to sea-level (less than 500 feet), (ii) a larger group at mid-altitudes (1000-5000 feet), and (iii) a small number above 5000 feet.

Fifty-three percent of the cases were diagnosed at less than 1 year of age and the overall male:female ratio was almost exactly one (Table 2). Fifty-four percent were first-born, 8% had a mother 40 years or older at birth and 14% had a father older than 45 at birth. Thirty-nine percent had an isolated type of CHD, 49% had several different types of defect in parallel, 5% had an isolated type with an associated non-CHD anomaly and 7% had several types of defect, at least one of which was associated with a non-CHD anomaly. The details of the 1199 isolated types are shown in Tables 3 and 4 (16 cases were unique isolated types and in 34 cases the specific type of CHD had not yet been abstracted at the time of data download). There were 887 cases of PDA either in isolation or in parallel, and there were 653 cases of ASDII or PFO either in isolation or in parallel and 697 cases of any type of ASD or PFO in isolation or in parallel.

A statistically significant difference (p=0.023) was observed between the mean CHD burden of cities above and below 3000 feet (an arbitrary threshold). However, categorizing altitude by four approximately equal groups (Figure 2) based on quartiles each containing (in increasing altitude) 24, 23, 29 and 28 cities, revealed a non-linear relationship between altitude and CHD burden (Figure 3A) such that both very low and very high altitudes appeared to be associated with an increased burden. This trend persisted in the absence of Al Baha (the city with the largest CHD burden). By grouping together the populations of those cities with at least 1 CHD within each of the four quartiles of altitude, overall prevalence estimates (and 95% CIs) were obtained (Table 5). The same trend was also visible when the cities from the three mountainous south-west provinces (Jizan, Asir and Al Baha - see inset in Figure 3) were separated from the others (Figure 4B).

Similar results were also evident (Figure 4) when the CHD cases (irrespective of any other concurrent CHD diagnosis) were sub-classified by the presence of ASD with or without PFO (ICD9 = 745.5 (ASD II) or 745.61 (ASD I) or 745.8 (ASD sinus type)) and/or PDA (ICD9 = 747). Also shown in the same figure are the equivalent results for cases with an isolated (i.e. single) diagnosis, although these results are more difficult to interpret because more than half the cities have zero cases for each category.

DISCUSSION

We have explored the detailed relationship between altitude and CHD burden within the Kingdom of Saudi Arabia. It is evident that those cities which lie at higher altitudes tend to be associated with a larger CHD burden. At around 2,500 meters above sea level, Al Baha apparently has the largest reported burden in the Kingdom but since the province has the same name, the possibility of data-capture errors cannot be discounted. However we have demonstrated that a strong altitude effect persists, even when Al Baha is removed from the dataset. Overall, there would appear to be ample evidence to support the notion that altitude is a major contributor to CHD burden in the Kingdom, which could at least partly explain the higher CHD burden among the cities in the mountainous south-west of the country.

The mechanisms underlying the effects of altitude on CHD have already been discussed in the literature in reports emanating from other mountainous regions **[12]** suggesting that it exerts its influence primarily via several specific CHD subtypes. Miao and colleagues **[7-8]** found an increasing prevalence of PDA and ASD with altitude at three sites in China ranging from 2,260 to 4,500 meters. However they did not distinguish between ASD I, ASD II and ASD sinus venous, reflecting one of the ongoing controversies of pediatric cardiology **[13]**. In the mountains of Peru, Alzamora et al **[6]** had previously observed that PDA and ASD II were more common at high altitudes, although their sample-size was small. We have now shown that these observations also hold true among the (relatively smaller) mountainous regions of Saudi Arabia. Furthermore, we have demonstrated that this effect continues to persist when only the isolated diagnoses are considered.

However our analysis also suggests that cities which lie at much lower altitudes (close to sea-level) are also associated with high CHD burdens. In fact, among the 20 highest burdens, 6 cities are in the highest quartile for altitude but 7 are in the lowest quartile. Such an apparent "low-altitude" effect has never been previously reported, suggesting that this may arise here because of confounding. We considered the possibility that this could be due to our definition of CHD burden which normalizes the numbers of CHD cases per city according to total - not birth - population. However the mean city size is not statistically different across the quartiles of altitude, so that we would also have to postulate a significant and systematic decline in birthrate with altitude. Furthermore, should such a general effect exist, it would be likely to eliminate the observed increase in CHD burden at higher altitudes - an effect which is compatible with previous observations.

One alternative explanation, which seems more plausible, is that - since all cities located at low altitudes also lie along the coast - we are observing a "coastal effect" which might be due to toxic exposure from a sea-borne (or airborne) agent. Further statistical analysis revealed no significant difference between the average CHD burdens between the cities on the East and West coasts, suggesting that - whatever the cause - it is not specific to either the Arabian Gulf or the Red Sea. Abushaban et al **[14]** found an increase (from 4 to 10 per 1000 live births) in the incidence of congenital heart defects in Kuwait after the first Gulf War in 1991, when 770 oil wells were set alight. However a systematic review of 559 similar studies **[15]** found that only 21 stated the exposure for the chemicals studied.

Other investigations into the association between petrochemicals and congenital malformations (including congenital heart defects) have not uncovered a significant relationship. On the other hand, polycyclic aromatic hydrocarbons are associated with exposure to weathered crude oil, and are known to disrupt cardiovascular function and morphogenesis in fish **[16]**. Furthermore, Kuehl and Loffredo **[17]** showed a crude association between a cluster of L-TGA and exposure to solvents, chlorinated hydrocarbons and other toxic chemicals. Interestingly, Xu et al **[18]** also discovered an association between petrochemical exposure and spontaneous abortion (thought to be related to severe congenital malformations.

It is therefore probable that the increased CHD burden which is apparent at high altitudes is caused by one factor (decreased oxygen tension) but by another at low altitudes, which might be an exposure to toxic compounds. Unfortunately, Saudi Arabia does not currently maintain an inventory of airborne release of toxic chemicals, which may be the only reliable method of ultimately identifying the risk to pregnancy from the petrochemical industry.

One further outcome from our analyses, is that when the cities were stratified by location (mountainous south-west vs elsewhere), the relationship between CHD burden and altitude was similar for both geographical areas, but the burden in the south-west appeared to be uniformly higher. This suggests the presence of yet another influence, which could be cultural or genetic; the south-west is different from other parts of the Kingdom, and Jizan and its neighboring provinces have inherited some unique cultural factors from their southern neighbor, Yemen.

In conclusion, our results suggest that the CHD burden in Saudi Arabia is probably impacted by three different environmental factors: (i) high altitude, (ii) coastal proximity, and (iii) a south-western location. The influence of high altitude and the unique south-western culture were certainly anticipated. However the finding that there might be some deleterious effect associated with a coastal location was unexpected and requires further exploration to investigate the possibility of toxic effects and to pursue other possible explanations. The CHD Registry at King Faisal Specialist Hospital and Research Centre has expanded significantly since the data for this study was collected, and the results of the recent census are now publicly available. The next step in this investigation should therefore be a more detailed analysis of the current registry data.

REFERENCES

1. O'Rahilly R, Muller F. Human embryology and teratology, 3rd edition. New York. John Wiley and Sons, 2001.

2. Croen LA, Shaw GM, Sanbonmatsu L, Selvin S, Buffler PA. Maternal residential proximity to hazardous waste sites and risk for selected congenital malformations. Epi 1997; 8:347-354.

3. Moss AJ. Clues in diagnosing congenital heart disease. Western J Med 1992; 156(4):392-398.

4. Stoll C, Alembik Y, Roth MP, Dott B, Geeter B. Risk factors in congenital heart disease. Eur J Epidemiol 1989; 5(3):382-391.

5. De la Cruz MV, Munoz-Castellanos L, Nadal-Ginard B. Extrinsic factors in the genesis of congenital heart disease. British Heart Journal 1971; 33:203-213.

6. Alzamora V, Rotta A, Battilana G, Abugattas R, Rubio C, Bouroncle J, Zapata C, Santa-Maria E, Binder T, Subiria R, Paredes D, Pando B, Graham GG. On the possible influence of great altitudes on the determination of certain cardiovascular anomalies. Pediatrics 1953; 12:259-262.

7. Miao CY, Li WX, Geng D, Tao L, Zuberbuhler JS, Zuberbuhler JR. Effect of high altitude on prevalence of congenital heart disease. Chinese Medical Journal 1988; 101(6):415-418.

8. Miao CY, Zuberbuhler JS, Zuberbuhler JR. Prevalence of congenital cardiac anomalies at high altitude. JACC 1988; 12(1):224-228.

9. Greer W, Sandridge AL, Al-Menieir M, Al-Rowais A. Geographical distribution of congenital heart defects in Saudi Arabia. Ann Saudi Med 2005; 25(1):63-69.

10. Al-Tahan A, Buchur J, El Khwsky F, Ogunniyi A, Al-Rajeh S, Larbi E, Daif A, Bamgboye E. Risk factors of stroke at high and low altitude areas in Saudi Arabia. Archives of Medical Research 1998; 29(2):173-177.

11. Abramson JH. WINPEPI (PEPI-for-Windows) computer programs for epidemiologists. Epidemiologic Perspectives & Innovations 2004; 1:6.

12. Cedergren M, Selbing A, Kallen B. Geographic variations in possible risk factors for severe cardiac malformations. Acta Paediatr 2002; 91(2):222-228.

13. Beerman, LB, Zuberbuhler JR. Atrial septal defect. In: Anderson RH, Baker EJ, McCartney FJ, Rigby ML, Shinebourne EA, Tynan M, Editors. Paediatric Cardiology. London: Churchill Livingstone, 2002:901-930.

14. Abushaban L, Al-Hay A, Uthaman B, Salama A, Selvan J. Impact of the Gulf war on congenital heart disease in Kuwait. International Journal of Cardiology 2004; 93:157-162.

15. McMartin KI, Koren G. Proactive approach for the evaluation of fetal safety in chemical industries. Teratology 1999; 60:130-136.

16. Incardona JP, Carls MG, Teraoka H, Sloan CA, Collier TK, Scholz NL. Aryl hydrocarbon receptor-independent toxicity of weathered crude oil during fish development. Environ Health Perspect 2005; 113:1755-1762.

17. Kuehl KS, Loffredo CA. Population-based study of L-transpositoin of the great arteries: possible associations with environmental factors. Birth Defects Research (Part A) 2003; 67:162-167.

18. Xu X, Cho S-I, Sammael M, You L, Cui S, Huang Y, Ma G, Padungtod C, Pothier L, Niu T, Christiani D, Smith T, Ryan L, Wang L. Association of petrochemical exposure with spontaneous abortion. 1998; 55:31-36.

Approximate Altitude (ft)	N Population	N Cases	CHD Burden	Approximate Altitude (ft)	N Population	N Cases	CHD Burden
0	40,872	27	66	2,000	91,084	30	33
0	4,940	1	20	2,000	1,042	1	96
0	80,206	54	67	2,000	61,375	42	68
0	86,151	82	95	2,000	34,896	5	14
0	46,362	9	19	2,000	1,800,032	587	33
0	303,535	208	69	2,000	15,180	2	13
0	34,942	2	6	2,000	8,491	2	24
0	55,838	44	79	2,200	198,631	41	21
0	81,802	4	5	2,360	70,245	8	11
0	3,334	5	150	2,400	13,247	4	30
0	4,867	1	21	2,400	8,195	1	12
0	37,703	78	207	2,429	46,247	10	22
0	87,358	29	33	2,450	22,952	10	44
0	999,124	304	30	2,500	3,601	1	28
0	11,089	19	171	2,500	5,776	3	52
25	11,239	4	36	2,600	32,596	1	3
25	18,030	5	28	2,620	10,093	3	30
50	11,592	8	69	2,620	6,554	1	15
50	52,523	28	53	2,625	8,612	3	35
83	4,923	1	20	2,625	432,681	130	30
83	8,371	4	48	2,625	28,415	3	11
85	23,312	11	47	2,625	15,497	2	13
115	33,331	6	18	2,625	7,206	4	56
164	21,674	4	18	2,625	241,111	98	41
165	13,436	1	7	3,000	6,328	1	16
165	25,100	12	48	3,000	10,203	4	39
165	26,377	6	23	3,000	13,474	2	15
165	12,094	3	25	3,000	15,129	3	20
165	21,953	1	5	3,281	140,497	13	9
300	21,674	7	32	3,281	29,861	12	40
333	3,366	1	30	3,500	5,030	1	20
333	10,548	1	9	3,500	815	1	123
500	185,597	30	16	3,600	3,850	1	26
656	102,539	42	41	3,630	833	1	120
665	17,046	1	6	3,650	22,151	8	36
830	1,404	1	71	3,750	1,480	1	68
1,000	102,539	1	1	3,950	30,193	49	162
1,000	871	1	115	4,000	12,123	3	25
1,000	1,471	2	136	4,000	62,466	78	125
1,000	550,196	148	27	4,600	3,049	1	33
1,235	13,593	1	7	5,000	762	1	131
1,312	3,967	1	25	6,000	1,101	1	91
1,500	25,122	4	16	6,000	4,976	2	40
1,500	121,470	34	28	6,000	320,464	153	48
1,850	9,155	2	22	6,600	172,847	17	10
1,969	11,228	6	53	6,600	6,892	5	73
1,998	2,079	1	48	7,000	8,608	2	23
2,000	20,241	5	25	7,000	19,972	1	5
2,000	51,082	27	53	7,200	9,364	70	748
2,000	17,010	2	12	7,218	8,933	2	22
2,000	2,092	1	48	8,000	84,043	78	93
2,000	11,999	2	17	8,000	4,156	2	48

Table 1. City Altitudes & CHD Burdens. Shading indicates the division of the cases into four quartiles based on altitude.

CHARACTERISTIC	STRATUM	CASES N	(%)
Infant's Sex	Male	1,389	50
	Female	1,398	50
	Total	2,787	100
Infant's Age at Diagnosis	Prenatal	20	<1
	Birth	160	7
	1 day to 1 month	340	15
	1 month to 3 months	216	9
	3 to 6 months	229	10
	6 months to 1 year	278	12
	1 to 2 years	236	10
	More than 2 years	795	36
	Total	2,274	100
Mother's Age at Infant's Birth	16 or less	16	1
	17-19	111	7
	20-24	384	24
	25-29	441	28
	30-34	337	21
	35-39	168	11
	40-44	92	6
	45 or older	32	2
	Total	1,571	100
Father' Age at Infant's Birth	17-19	7	<1
	20-24	140	8
	25-29	393	22
	30-34	431	25
	35-39	317	18
	40-44	229	13
	45-49	134	7
	50-54	59	3
	55-59	37	2
	60-64	20	1
	65 or older	22	1
	Total	1,789	100
CHD	Isolated	1,073	39
	Parallel	1,356	49
	Isolated + Associated Non-CHD	126	5
	Parallel + Associated Non-CHD	199	7
	Total	2,754	100

Table 2. Descriptive Statistics of the CHD cases (the date of diagnosis was missing for 513 children).

DIAGNOSIS	NUMBER OF CASES
Isolated PDA	222
PDA in Parallel	665
Isolated ASD II or Isolated PFO	157
ASD II or PFO in Parallel	496
Isolated ASDI I, ASD II or ASD Sinus or PFO	163
ASD I, ASD II or ASD sinus or PFO, in Parallel	534

Table 3. CHD Diagnoses Known to be More Common at High Altitude.

CHD Type	N	%
ASDII	156	5.7
AVSD	33	1.2
Aneurysm of aorta	6	0.2
Anomalies of pulmonary artery	4	0.1
Aortic valve stenosis	81	2.9
Bicuspid aortic valve	7	0.3
COA	36	1.3
Cardiomyopathy	23	0.8
Common truncus	8	0.3
Complete transposition of great vessels (classical)	2	0.1
Congenital mitral stenosis	3	0.1
Congenital anomaly of heart (valvular: aortic, mitral, tricuspid)	18	0.7
Coronary artery anomaly	5	0.2
Electrical signal problems	42	1.5
Ostium primum defect	5	0.2
PAPVR/TAPVR	3	0.1
Patent ductus arteriosus	222	8.1
Pulmonary valve stenosis	173	6.3
Tetralogy of Fallot	89	3.2
VSD	267	9.7
Other	16	0.6
Multiple congenital anomalies	1,555	56.5
Total	2,754	100

Table 4. CHD Diagnoses.

	Quartile of Altitude			
	1	2	3	4
Total Population	2,063,118	1,282,825	3,266,183	999,600
Total CHD Cases	938	307	1,029	513
CHD Burden	45.46	23.93	31.5	51.32
Lower 95% CI	42.6	21.33	29.61	46.98
Upper 95% CI	48.47	26.76	33.49	55.96

Table 5. Cumulative results over each individual quartile of altitude.

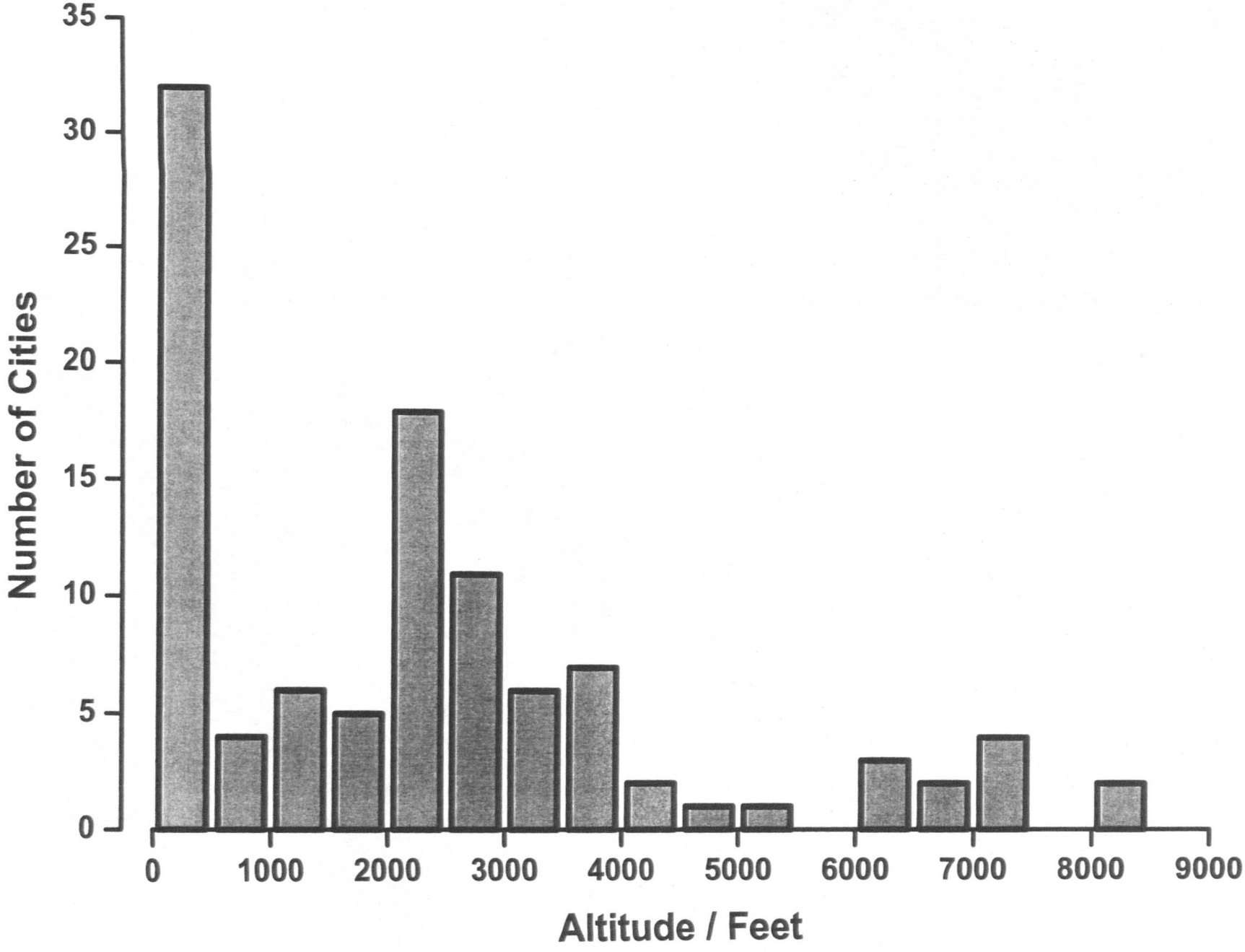
LEGENDS FOR FIGURES

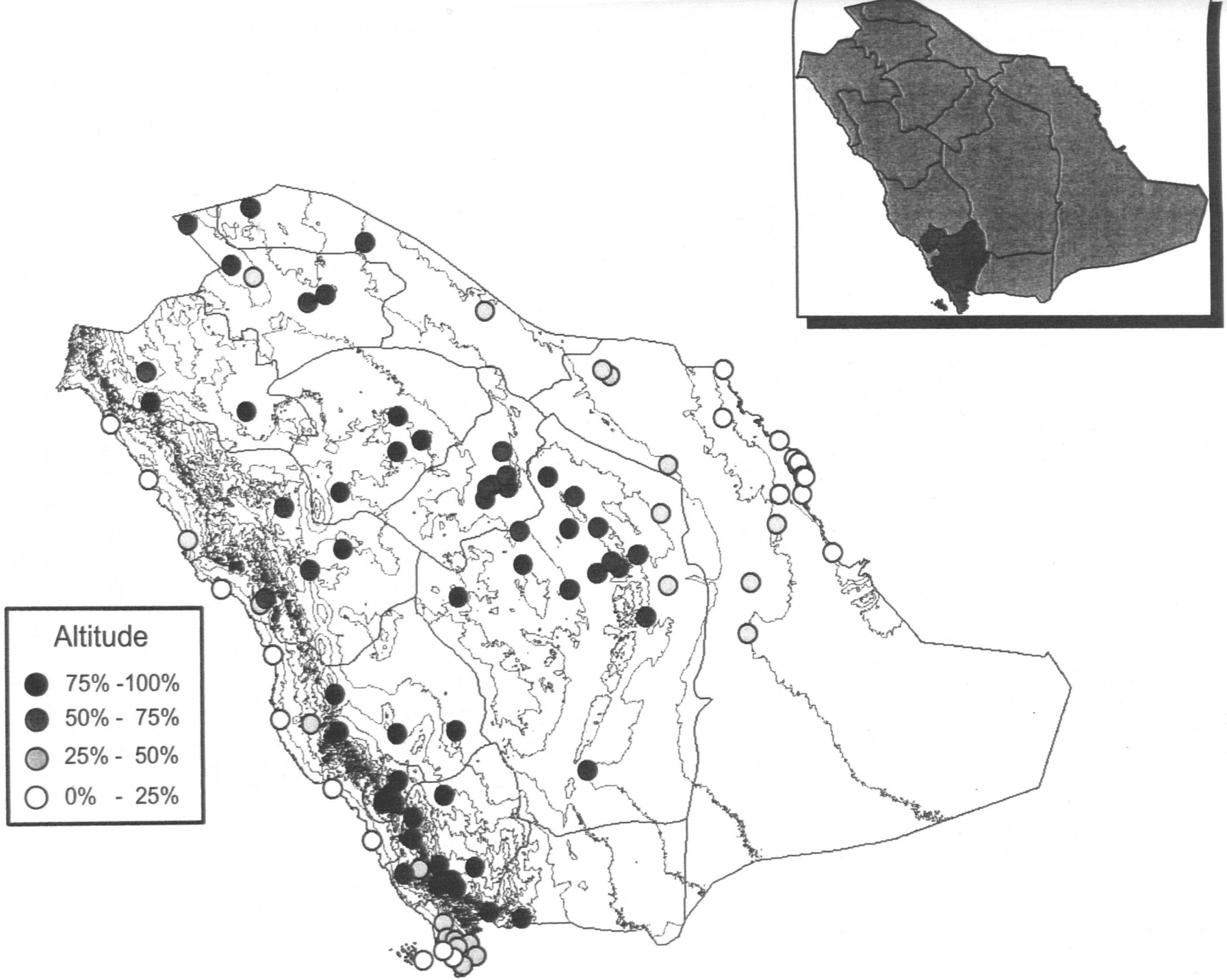
Figure 1. Bar-chart of the altitude of each of the 104 cities (Al Baha is not shown because it has such a high value).

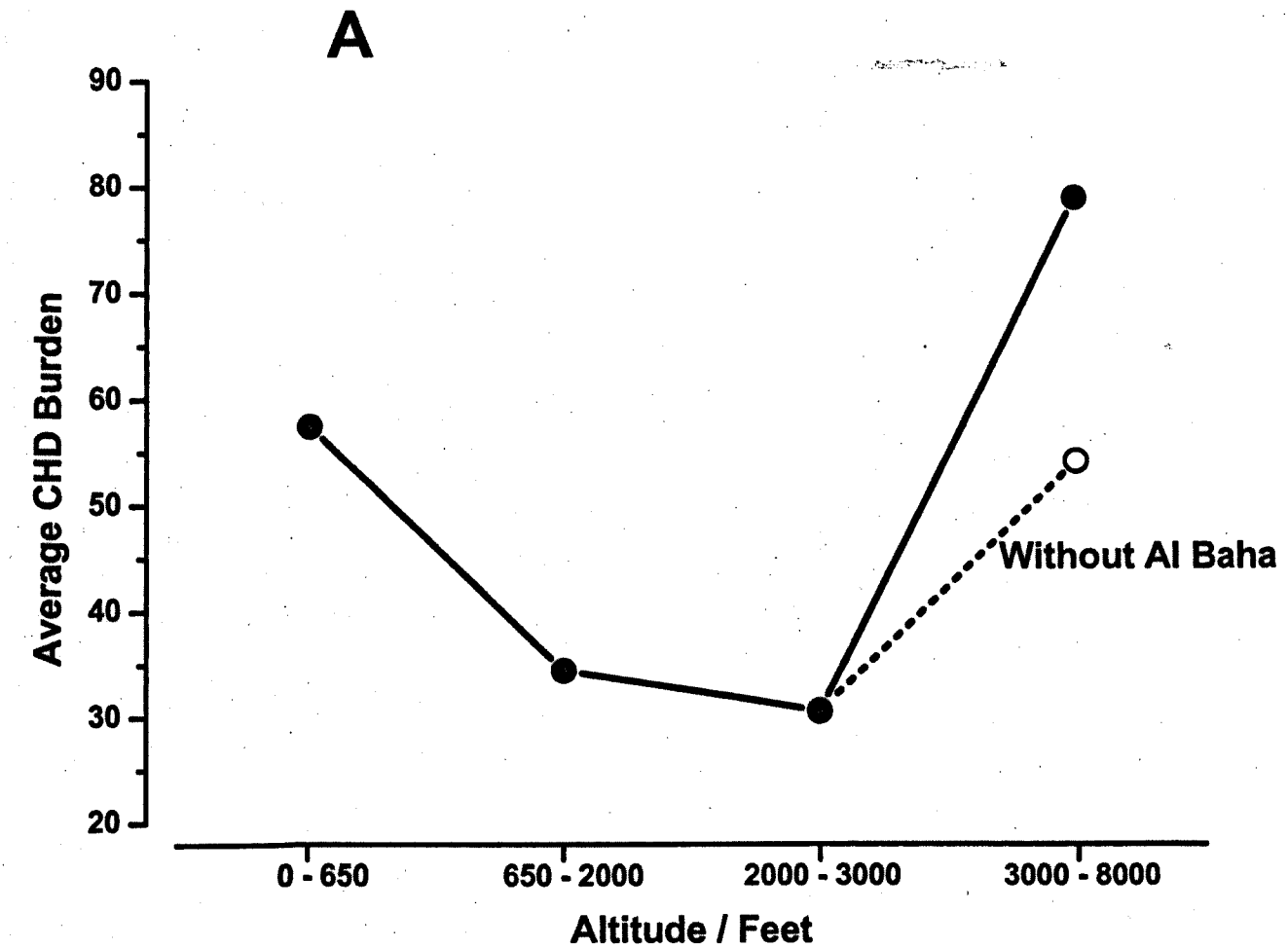
Figure 2. Thematic map showing the locations of all 104 cities which contain CHD cases, superimposed on map contours indicating altitude. The inset highlights the three south-western provinces (Jisan, Asir and Al Baha) in a darker gray.

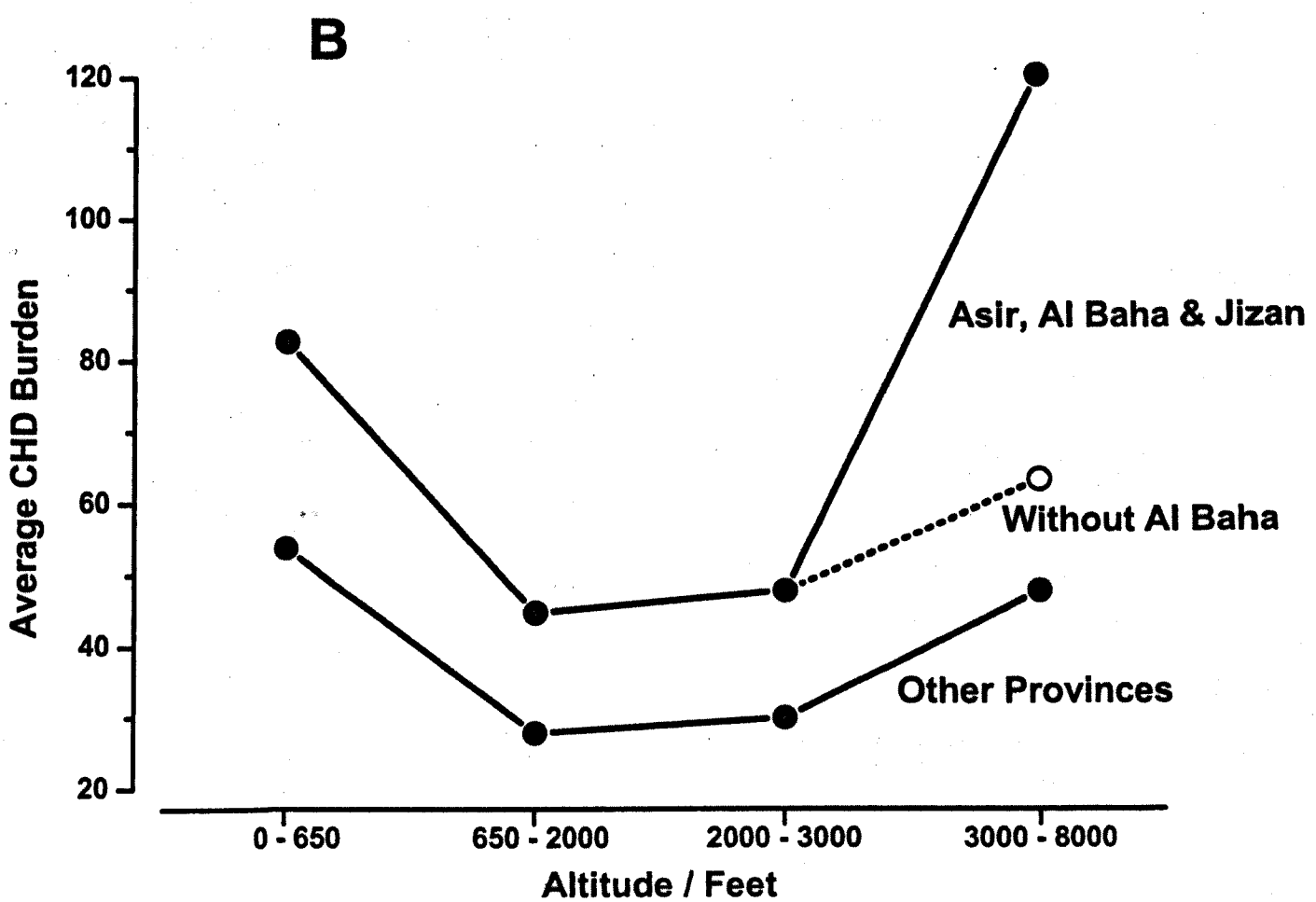
Figure 3 (A) Line-and-symbol plot showing the relationship between mean CHD burden (number of CHD cases per 100,000 population) per quartile of altitude. (B) Line-and-symbol plots of the same data, stratified by geographical location (3 south-western provinces vs all other provinces).

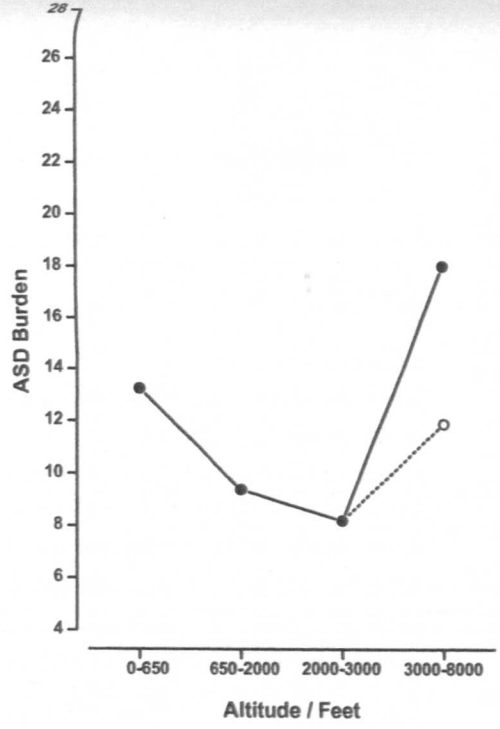
Figure 4. Line-and-symbol plots showing the relationship between mean CHD burden (number of CHD cases per 100,000 population) per quartile of altitude, for three diagnoses: all ASD, all PDA and ASDII & PFO combined. The three lower plots depict the results from *isolated* sub-diagnoses.

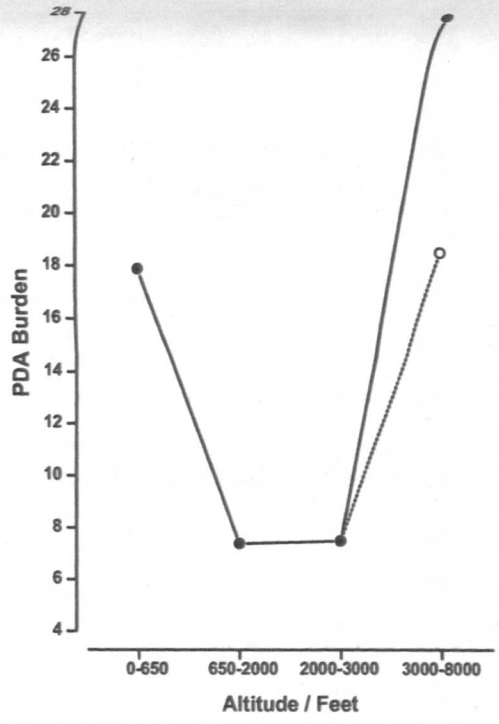

Number of Cities
35
30
25
20
15
10
5
0
0
1000
2000
3000
4000
5000
6000
7000
8000
9000
Altitude / Feet

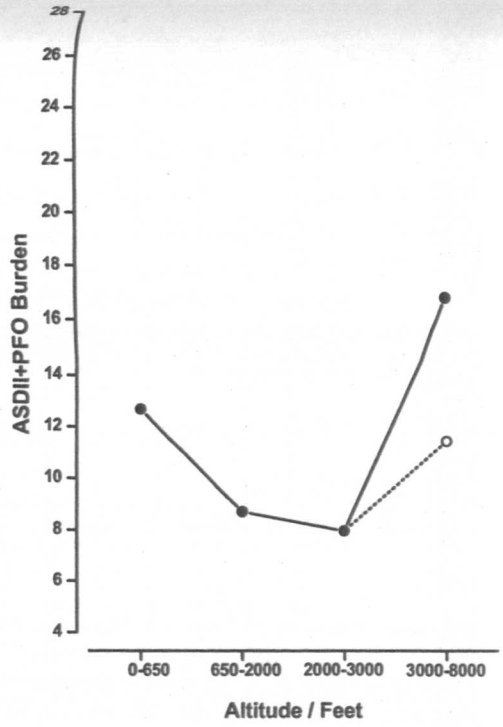

Altitude
75% -100%
50% - 75%
25% - 50%
0% - 25%


A
90
80
70
60
50
40
30
20
Average CHD Burden
Without Al Baha
0 - 650
650 - 2000
2000 - 3000
3000 - 8000
Altitude / Feet

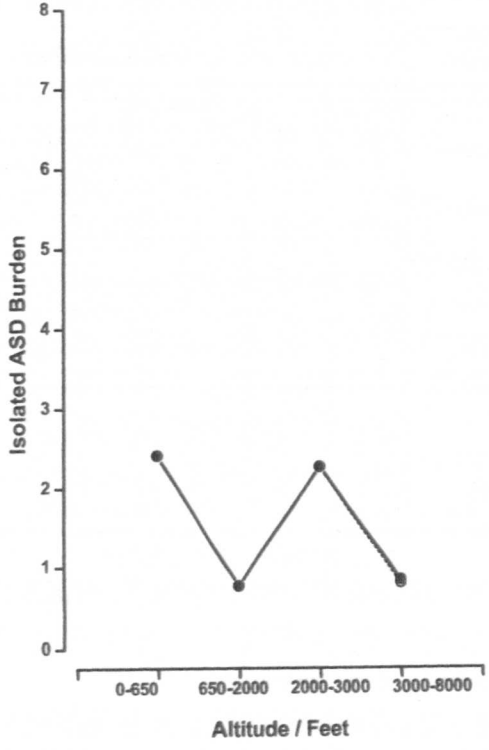

B
120
100
80
60
40
20
Average CHD Burden
Asir, Al Baha & Jizan
Without Al Baha
Other Provinces
0 - 650
650 - 2000
2000 - 3000
3000 - 8000
Altitude / Feet

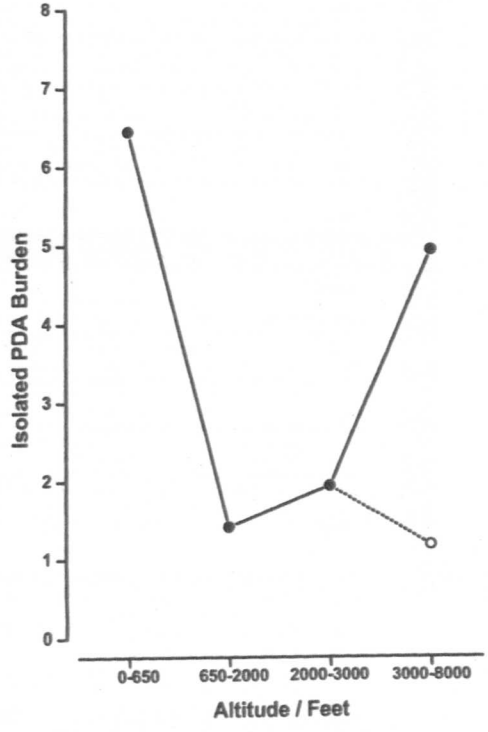

ASD Burden
28
26
24
22
20
18
16
14
12
10
8
6
4
0-650
650-2000
2000-3000
3000-8000
Altitude / Feet

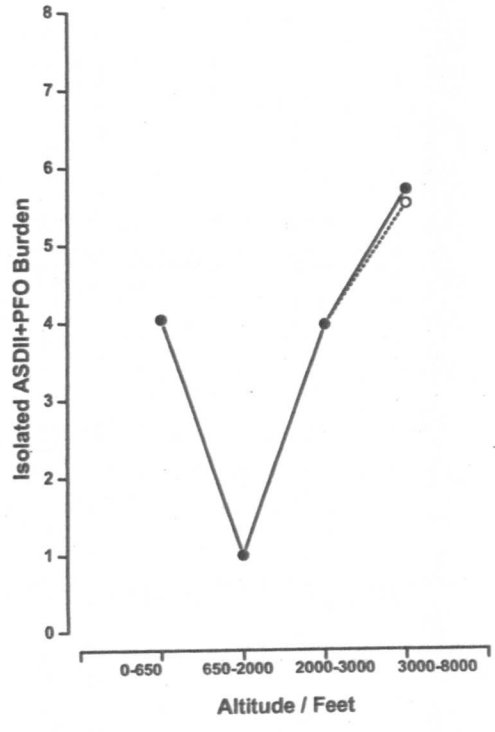

PDA Burden
28
26
24
22
20
18
16
14
12
10
8
6
4
0-650
650-2000
2000-3000
3000-8000
Altitude / Feet


ASDII+PFO Burden
28
26
24
22
20
18
16
14
12
10
8
6
4
0-650
650-2000
2000-3000
3000-8000
Altitude / Feet

332


Isolated ASD Burden
8
7
6
5
4
3
2
1
0
0-650
650-2000
2000-3000
3000-8000
Altitude / Feet


Isolated PDA Burden
8
7
6
5
4
3
2
1
0
0-650
650-2000
2000-3000
3000-8000
Altitude / Feet


Isolated ASDII+PFO Burden
8
7
6
5
4
3
2
1
0
0-650
650-2000
2000-3000
3000-8000
Altitude / Feet

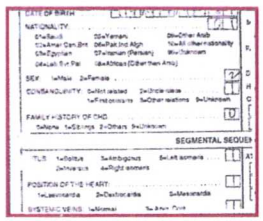
A CASE-CONTROL STUDY OF CONGENITAL HEART DEFECTS IN SAUDI ARABIAN INFANTS

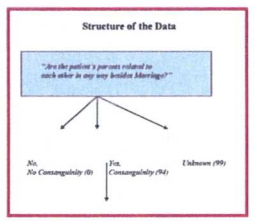
SANDRIDGE AL,[1,7] DOYLE P,[2] AL-JUFAN M,[3] AL KHALIFA I,[4] KURDI W,[5] KATTAN H,[6] AL-ROWAIS A[1]

Department of Biostatistics and Epidemiology, Research Centre, KFSH&RC[1]; Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine[2]; Department of Cardiovascular Diseases, KFSH&RC[3]; Department of Family and Community Medicine, Riyadh Armed Forces (Military) Hospital[4]; Department of Obstetrics and Gynecology, KFSH&RC[5]; Department of Pediatrics, KFSH&RC[6]

Society of Epidemiology Research
Summer 21-24, 2006
Seattle, Washington, USA

CLASSIFYING CONSANGUINITY





Traditional -v- Phylogram Classification

Examples of Phylograms

IMPACT OF DIABETES

Stratum	ALL DIABETES DIAGNOSES Cases (%)	Controls (%)	OR (95% CI)	Adj. OR (95% CI)	p	ISOLATED CARDIAC DIAGNOSES ONLY Cases (%)	Controls (%)	OR (95% CI)	Adj. OR (95% CI)	p
No Diabetes Or Gestational Diabetes	212 (95.9)	233 (99.6)	1.0	1.0	0.12	136 (97.1)	228 (99.6)	1.0	1.0	0.13
Overt	9 (4.1)	1 (0.4)	9.9 (1.2-80.1)	5.1 (0.05-50.8)		4 (2.9)	1 (0.4)	6.7 (0.7-61.6)	4.9 (0.5-49.4)	
Total	221 (100.0)	234 (100.0)				140 (100.0)	229 (100.0)			

Stratum	EMBRYOLOGICALLY EARLIEST Cases (%)	Controls (%)	OR (95% CI)	Adj. OR (95% CI)	p	EMBRYOLOGICALLY LATEST Cases (%)	Controls (%)	OR (95% CI)	Adj. OR (95% CI)	p
No Diabetes Or Gestational Diabetes	42 (97.7)	228 (99.6)	1.0	1.0	0.59	79 (97.5)	229 (99.6)	1.0	1.0	0.40
Overt	1 (2.3)	1 (0.4)	5.4 (0.3-88.2)	2.7 (0.16-44.3)		2 (2.5)	1 (0.4)	5.8 (0.5-64.8)	2.9 (0.2-36.2)	
Total	43 (100.0)	229 (100.0)				81 (100.0)	230 (100.0)			

Stratum	CRUDE EMBRYOLOGICALLY EARLIEST Controls	Crude OR (95% CI)	p	CRUDE EMBRYOLOGICALLY LATEST Crude OR (95% CI)	p
No Diabetes Or Gestational Diabetes	239 (99.6)	43 (97.7) 1.0	0.25	79 (95.2) 1.0	0.01
Overt	1 (0.4)	1 (2.3) 5.6 (0.3-90.6)		4 (4.8) 12.1 (1.3-109.9)	
Total*	240 (100)	44 (100)		83 (100)	

ISOLATED AND PARALLEL CASES

Characteristic	Stratum	Cases N (%)	Controls N (%)	Crude OR (95% CI)	Adjusted Odds Ratio (95% CI)	p
Multiple gestations	Singleton	133	95.0	207	99.1	1.0	1.0	0.03
	Twins or higher	7	5.0	2	.9	5.5 (1.2-25.2)	5.5 (1.0-30.5)	
	Total	140	100.0	209	100.0			
Mother's Ethnicity	Bedouin Ethnicity	59	39.3	54	27.3	2.2 (1.4-3.5)	2.1 (1.3-3.5)	0.00
	Urban Ethnicity	85	60.7	179	77.7	1.0	1.0	
	Total	140	100.0	209	100.0			
Mother's Age at Infant's Birth (years)	14-20	12	5.6	34	14.6		0.9 (0.4-1.7)	0.05
	21-28	54	38.6	114	49.8			
	29+	74	52.9	81	35.4		3.0 (1.7-5.3)	
	Total	140	100.0	209	100.0			
Father's Age (N=343)	19-24	13	9.6	14	6.7		1.5 (1.1-3.1)	0.02
	25-34	50	37.0	129	62.7		1.0	
	35+	72	53.3	74	35.6		1.5 (0.8-2.9)	
	Total	135	100.0	209	100.0			
Father's Ethnicity	Bedouin Ethnicity	97	40.7	54	21.6	2.2 (1.3-3.5)	1.4 (0.8-2.5)	0.59
	Urban Ethnicity	83	59.3	175	78.4	1.0	1.0	
	Total	140	100.0	209	100.0			
Chemical hair dye use in time-window	Yes	32	22.9	21	12.5	1.9 (1.1-3.3)	2.0 (1.1-3.8)	0.02
	No	108	77.1	188	86.5	1.0		
	Total	140	100.0	209	100.0			
House sprayed with pesticide in time-window	Yes	30	20.4	20	14.2	1.4 (0.7-2.6)	1.7 (0.8-3.6)	0.16
	No	117	79.6	120	85.8	1.0	1.0	
	Total	147	100.0	209	100.0			

INTRODUCTION

Congenital heart defects (CHD) are one of the most common groups of birth defects in the Western population with between 4/1000 and 12/1000 live births affected (Hoffman, 2002). The European Register of Congenital Anomalies found CHD to be the most common defect (EUROCAT, 2001) and the UK Congenital Malformations Registration Scheme (ONS, 2001) found it to be third. In the Middle East, Al-Abdulgader (2001) reported an incidence of 10.7 per 1000 in the referral centre for the whole of the Al Hassa region of Saudi Arabia. A population based registry for the United Arab Emirates (UAE), which has a population which is genetically similar to Saudi Arabia, is part of the International Clearinghouse for Birth Defects Monitoring Systems and reported in 2000 that the rate of TGA was 0; the rate of TOF was 2.67/10,000, the rate of HLHS was 2.67/10,000 and the rate of COA was 1.33/10,000 (Lowry, 2000). In a separate study they also report 0.6/1000 incidence of CHD (Al-Gazali et al. 1995). In Oman, CHD was detected in 992 live births from a population of 139,707 registered from 1994-96 (incidence 7.1) (Subramanyan et al, 2000).

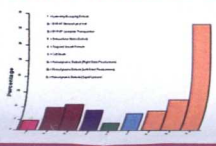
METHODS

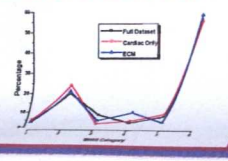
This is an unmatched, well-powered case-control study of risk factors for all structural congenital heart defects in children resident in Riyadh, Saudi Arabia. The primary exposure of interest was consanguinity (up to and including second cousin once removed, second half cousin, or first cousin twice removed). Cases were recruited from the King Faisal Specialist Hospital and Research Centre (KFSH&RC), a large tertiary care 600 bed facility. Inclusion criteria were : (1) Newly registered case from the KFSH&RC CHD registry, (2) Structural CHD confirmed by echocardiogram, cardiac catheterization or surgery, (3) Interview completed for this study prior to the child's 4th (Gregorian) birthday, and (4) Father's current residence in Riyadh (or originally from Riyadh region). The exclusion criteria were: (1) Non Saudi Arabian citizens, (2) Mother not available for interview, (3) Second sibling from a previously interviewed family, (4) Non-structural CHD. Controls were taken from the "Well-Baby Clinic" at the Riyadh Al Kharj Armed Forces Hospital's Department of Family and Community Medicine, which operates as a drop-in clinic. Using a detailed and reverse translated questionnaire, a face to face interview was conducted with both case and control mothers by research assistants fluent in the local dialects. Mothers were asked to consider their exposure to risk factors as being within a six month window (3 months prior to conception and 3 months post conception). The questionnaire predominantly followed the style of the Baltimore Washington Infant Survey with specific questions that addressed factors unique to Saudi Arabia. Consanguinity was collected using a phylogram approach. Results were adjusted for maternal Bedouin status, multiple gestation, mother's age, maternal use of hair dye, maternal exposure to pesticides and having a non-CHD defect. P-values were obtained using the likelihood ratio test to compare the fit of the reduced model (as described above) plus the variable under test, with the fit of the reduced model alone. Note that where the adjusting variable itself was under test, then that variable was not included in the model.

CONCLUSIONS

1. To ensure accuracy in future studies, consanguinity data should be collected using the phylogram method.
2. Consanguinity was not found to be a risk factor for CHD in Saudi Arabia.
3. The most significant risk factors are: pesticide use, hair coloring, maternal ethnicity, twinning and mother's age.
4. Although diabetes was not found to be a significant risk factor, the statistical power for this was extremely low; A positive result was found in the crude analysis of the embryologically-latest diagnoses.
5. Further research into risk factors for CHD in Saudi Arabia should be conducted under the auspices of a national study.

BWIS-BASED CLASSIFICATION





PRINCIPAL RESULTS

Characteristic	Stratum	Cases N (%)	Controls N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	p
Consanguinity (Binary)	Yes	112	50.7	117	99.0	1.0 (0.24-4.0)	1.0 (0.24-4.0)	0.97
	No	109	49.3	117	99.6	1.0 (-)	-	
	Total	221	100.0	234	100.0			
Consanguinity (Detailed)	1st cousin or closer	52	23.5	59	25.2	0.9 (0.6-1.3)	1.1 (0.6-2.0)	0.40
	All lesser 1st cousins	36	16.3	30	12.8	1.3 (0.7-2.3)	0.6 (0.3-1.3)	
	All 2nd and 3rd cousins	22	10.0	29	12.0	0.8 (0.5-1.7)	0.9 (0.5-1.8)	
	Non-consanguineous	109	49.3	117	99.6	1.0 (-)	-	
	Total	221	100.0	234	100.0			

Consanguinity

Characteristic	Stratum	Cases N (%)	Controls N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	p
Multiple gestations	Singleton	210	95.0	232	99.1	1.0	1.0	0.00
	Twins or higher	11	5.0	2	.9	5.1 (1.1-23.7)	5.8 (1.1-30.5)	
	Total	221	100.0	234	100.0			
Mother's Ethnicity	Bedouin Ethnicity	92	37.1	54	21.8	2.1 (1.4-3.2)	2.2 (1.4-3.6)	0.00
	Urban Ethnicity	139	62.9	183	78.2	1.0	1.0	
	Total	221	100.0	234	100.0			
Mother's Age at Infant's Birth (years)	14-20	17	7.7	35	15.0	0.5 (0.4-1.4)	0.9 (0.4-1.7)	0.00
	21-28	75	33.9	116	49.6	1.0	1.0	
	29-36	97	43.9	71	30.3	2.1 (1.4-3.2)	1.8 (1.1-3.0)	
	36+	32	14.5	12	5.1	4.1 (2.0-8.5)	3.5 (1.5-8.1)	
	Total	221	100.0	234	100.0			
Father's Age at Infant's Birth (years)	19-24	15	7.1	14	6.6	1.7 (0.8-3.7)	1.7 (0.8-3.7)	0.00
	25-34	78	37.1	122	57.5	1.0	1.0	
	35-44	87	41.4	58	27.4	2.3 (1.5-3.5)	1.5 (0.9-2.5)	
	45+	30	14.3	18	8.5	2.0 (1.0-3.9)	0.7 (0.2-2.0)	
	Total	210	100.0	212	100.0			
Father's Ethnicity	Bedouin Ethnicity	80	38.9	54	23.1	2.1 (1.4-3.2)	1.2 (0.8-2.0)	0.72
	Urban Ethnicity	126	61.1	180	76.9	1.0	1.0	
	Total	221	100.0	234	100.0			

Maternal & Paternal Characteristics

Characteristic	Stratum	Cases N (%)	Controls N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	p
Household income per capita per month (excluding servants)	Poor	30	15.0	33	10.0	1.6 (0.9-2.8)	0.9 (0.4-2.0)	0.10
	Middle	138	69.0	169	80.1	1.0	1.0	
	Well-Off	34	17.0	19	9.0	2.2 (1.2-4.1)	2.2 (1.1-4.5)	
	Total	200	100.0	211	100.0			
Mother's Education	None	182	96.9	221	94.4	3.6 (1.3-9.1)	3.0 (1.0-8.7)	0.05
	Some (Includes adult)	29	13.1	13	5.6	1.0	1.0	
	Total	221	100.0	234	100.0			
Mother's Father's Occupation	Military	44	23.7	108	51.2	0.3 (0.2-0.5)	0.4 (0.2-0.7)	0.00
	White Collar	93	50.0	68	31.9	1.0	1.0	
	Trade and Manual	49	26.3	35	16.9	1.9 (0.9-1.7)	0.7 (0.4-1.4)	
	Total	186	100.0	207	100.0			

Socioeconomic Status

Characteristic	Stratum	Cases N (%)	Controls N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	p
Skin lightening creams	Yes	39	13.4	40	17.3	0.7 (0.4-1.2)	0.6 (0.3-1.1)	0.01
	No	198	86.6	191	82.7	1.0	1.0	
	Total	217	100.0	231	100.0			
Chemical hair dye (within time-window)	Yes	49	22.2	32	13.7	1.8 (1.1-2.9)	1.9 (1.1-3.3)	0.01
	No	172	77.8	202	86.3	1.0	1.0	
	Total	221	100.0	234	100.0			
House sprayed with pesticide (within time-window)	Yes	77	34.9	33	14.1	3.2 (2.1-5.0)	3.0 (1.9-4.7)	0.00
	No	144	65.2	201	85.9	1.0	1.0	
	Total	221	100.0	234	100.0			
Nausea	Yes	162	73.3	178	76.1	0.9 (0.6-1.3)	1.4 (0.9-2.4)	0.18
	No	59	26.7	56	23.9	1.0	1.0	
	Total	221	100.0	233	99.6			
Heartburn	Yes	149	68.0	136	57.3	1.6 (1.1-2.3)	1.7 (1.1-2.8)	0.02
	No	70	32.0	101	42.7	1.0	1.0	
	Total	219	100.0	234	100.0			
Caffeinated beverages (within time-window)	Yes	207	95.7	212	90.6	1.5 (0.8-3.1)	1.9 (0.9-4.0)	0.10
	No	14	6.3	22	9.4	1.0	1.0	
	Total	221	100.0	234	100.0			
Number of days of fasting (within time-window)	Less than 1 week	75	33.9	82	35.0	1.0	1.0	0.47
	1 to 3 weeks	17	7.7	21	9.0	0.9 (0.4-1.8)	0.8 (0.3-1.8)	
	3 to 5 weeks	49	22.2	82	35.0	0.6 (0.4-1.0)	0.8 (0.5-1.4)	
	More than 5 weeks	80	27.1	49	20.9	1.3 (0.9-2.0)	1.3 (0.7-2.3)	
	Total	221	100.0	234	100.0			

Environmental & Nutritional Factors

Characteristic	Stratum	Cases N (%)	Controls N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	p
Did this pregnancy use IVF?	Yes	8	3.6	3	1.3	2.9 (0.8-11.0)	1.0 (0.1-7.4)	0.99
	No	213	96.4	231	98.7	1.0	1.0	
	Total	221	100.0	234	100.0			
Was this pregnancy planned?	Yes	100	45.2	79	33.8	1.0	1.0	0.19
	No	121	54.8	155	66.2	0.6 (0.4-0.9)	0.7 (0.5-1.2)	
	Total	221	100.0	234	100.0			
Pregnancy losses	1 or fewer losses	185	83.7	219	93.6	1.0	1.0	0.07
	2 or more losses	36	16.3	15	6.4	2.6 (1.5-5.4)	2.0 (0.9-4.2)	
	Total	221	100.0	234	100.0			
Bleeding for more than 1 day	Yes	24	10.9	9	3.8	3.0 (1.4-6.7)	2.5 (1.0-6.3)	0.06
	No	197	89.1	225	96.2	1.0	1.0	
	Total	221	100.0	234	100.0			
All non-CHD reported anomalies	None	140	63.3	229	97.9	1.0	1.0	0.00
	Other problem	81	36.7	5	2.1	25.5 (10.5-67.0)	28.1 (10.8-73.4)	
	Total	221	100.0	234	100.0			

Index Pregnancy Characteristics

ver

Risk Factors for Congenital Heart Defects in Saudi Infants

Departments of Biostatistics, Epidemiology & Scientific Computing, Cardiovascular Diseases, Pediatrics and Obstetrics and Gynaecology

Study Number or MRN: .....

Identification	
Participants's name:	Referred by :
Physician's name:	Patient type:
	Interview location:
Riyadh Patient: Residence Origin	Consent to Family Interview documented in chart
Centre: KFSH&RC RPHCC	Consent to Medical Records

Questions	Coding Categories
1 *Interviewer*: Records the interview date and time المقابل : يسجل تاريخ ووقت المقابلة	Date: 6-4-2003 Hour: 14 : Minutes: 30

Recruitment Section

Questions	Coding Categories		SKIP TO
2 Case Status: وضع الحالة :	Case حالة	(1)	
	Control حالات مقارنة	2	
3 In what month and year was this child born? متى ولد الطفل ؟	Month *Code as 99 if unknown* 2 digit Gregorian رمز الشهر ٩٩ إذا كان مجهولاً		
	Year *Code as 9999 if unknown* 4 digit Gregorian		
4 How old is this child now? كم عمر الطفل الآن (إذا كان عمر الطفل أكثر من ٤ سنين توقف عن المقابلة) *Interviewer:* If child is greater than 4 years old END INTERVIEW	Age in completed years العمر بالسنوات		
	and months و الأشهر		
5 Nationality of child: جنسيه الطفل؟	Saudi سعودي	(1)	
	Other Arab عربي (غير سعودي)	2	END
	Non-Arab غير عرب	3	END
6 In what month and year was this child diagnosed with CHD? متى تم تشخيص الطفل بتشوه القلب؟ *Leave blank if not applicable*	Month الشهر *Code as 99 if unknown* 2 digit Gregorian	01-1423	
	Year السنة *Code as 9999 if unknown* 4 digit Gregorian رمز السنة ٩٩٩٩ إذا كان مجهولاً	2002	

24-10-2000

يتوقف

3

during plastic surgery

Risk Factors for Congenital Heart Defects in Saudi Infants

Departments of Biostatistics, Epidemiology & Scientific Computing, Cardiovascular Diseases, Pediatrics and Obstetrics and Gynaecology

Demographic Section

Questions	Coding Categories		SKIP TO
7 In what area do you live in? *Haya'a.* في أي حي تسكنون حاليا؟	Record from coding manual Al Rawadh	___	
8 Where is this child's father from (i.e., where was he born - what is his hometown)? (للمقابل: هل ولد الطفل في نفس المنطقة التي ينتمي اليها) أين ولد والد الطفل؟ أي مدينة ينتمى اليها؟	Record patrilocality from coding manual Hail	406	
9 For most of the time until you were 12 years old, did you (the mother) live in a city/town or in a village/desert? أين كانت الأم تسكن في الإثنتي عشرة عاما الأولى من حياتها؟ هل كانت تسكن في مدينه/بلده أو قرية/ صحراء؟	City/Town (Urban) مدينة / بلدة	1	
	Village/Desert (Rural) قرية / صحراء	(2)	
10 How would you describe the location of the house where you and your family live most the time now? كيف تصفين موقع المسكن؟	On a busy street (Urban) على طريق عام مزدحم	1	
	Near an industry (Urban) قرب مصنع	2	
	In a residential area (Urban) في حي سكني	(3)	
	Rural (in a village, in the desert, on a farm) منطقه نائية	4	
	Other أخر	5	
10a If other please describe إذا كان الجواب بأخر .. صفي ..	_____ _____ _____	___	
11 Ethnicity of mother: أصل الأم ؟	Saudi سعودية	(1)	
	Other Arab عربية (غير سعودية)	2	15
	Non-Arab غير عربية	3	15
12 If the mother is Saudi, is she from إذا كانت سعودية هل هي من:	Central (Njed) المنطقة الوسطى	(1)	
	Eastern المنطقة الشرقية	2	
	Western (Hijazi) المنطقة الغربية	3	
	Northern المنطقة الشمالية	4	
	Southern المنطقة الجنوبية	5	
13 Is the mother a Bedouin? هل الأم بدويه ؟	Yes نعم	(1)	
	No لا	2	15
	Uncertain غير مؤكد	9	15

Riyadh

Questions	Coding Categories		SKIP TO
14 How was this determined? كيف اكتشف المقابل أن الأم بدويه؟	Mother declared صرحت الأم	1	
	Interviewer assessed by accent عرف المقابل عبر اللهجة	2	
	Interviewer assessed by manner عرف المقابل عبر التصرف	3	
15 Ethnicity of father: ما هو اصل الأب؟	Saudi سعودي	1	
	Other Arab عربي (غير سعودي)	2	19
	Non-Arab غير عربي	3	19
16 If the father is Saudi, is he from إذا كان الأب سعودي هل هو من:	Central (Njed) المنطقة الوسطى	1	
	Eastern المنطقة الشرقية	2	
	Western (Hijazi) المنطقة الغربية	3	
	Northern المنطقة الشمالية	4	
	Southern المنطقة الجنوبية	5	
17 Is the father a Bedouin? هل الأب بدوي ؟	Yes نعم	1	
	No لا	2	19
	Uncertain غير مؤكد	9	19
18 How was this determined? كيف اكتشف المقابل أن الأب بدوي؟	Mother declared صرحت الأم	1	
	Interviewer assessed by accent	2	
	Interviewer assessed by manner عرف المقابل عبر التصرف	3	
	Father declared صرح الأب	4	
	Other: Specify _____	5	
19 In which hospital was this child born? في أي مستشفى ولد الطفل؟تؤخذ المعلومات من اللائحة الخاصة If KFSH&RC or KFSH Jeddah obtain MRN of the mother: |_|_|_|_|_|_| (إذا كان من مواليد مستشفى الملك فيصل التخصصي في الرياض أو في جدة (يسجل رقم ملف الأم) *Interviewer:* Does this agree with current area of residence or patrilocality question?	Code from coding manual. 999 = unknown Alyamamah غير معروف = ٩٩٩ 888 = hospital outside the Middle East مستشفى خارج الشرق الأوسط = ٨٨٨ 777 = homebirth attended by midwife في المنزل.. بواسطة قابلة = ٧٧٧ 776 = unattended homebirth في المنزل.. من غير وجود القابلة = ٧٧٦		
20 As far as you know, where were you living when you became pregnant with this child? أين كانت تقيم الأم عندما أصبحت حامل؟	Record town/village from coding manual Riyadh	1317	
21 Current weight of the mother وزن الأم الآن؟ (المقابل :خذ وزن الأم .	Measured kg الوزن يقاس بالكيلوجرام)	~~FSH~~ 50	

Risk Factors for Congenital Heart Defects in Saudi Infants

Departments of Biostatistics, Epidemiology & Scientific Computing, Cardiovascular Diseases, Pediatrics and Obstetrics and Gynaecology

Questions	Coding Categories		SKIP TO
22 Height of the mother (without shoes) طول الأم بدون لبس الحذاء	Measured cm يقاس الطول بالمتر	154	
22a Have you gained weight, lost weight or have you stayed the same since that pregnancy? هل ازداد وزنك؟ هل نقص وزنك؟ أو ما يزال وزنك هو نفس الوزن الذي كنت عليه في فترة حملك بهذا الطفل؟	Gained ازداد وزنك	1	
	Lost نقص وزنك	2	
	Stayed the same ما يزال وزن الحمل	3	
	Unknown (may include currently pregnant) يمكن أن يتضمن حمل حالي	9	
22b If you've gained or lost weight approximately how many kilos have you gained or lost? إذا كان وزنك قد ازداد أو نقص، تقريباً كم كيلوجرام ازداد/نقص؟	Kilos GAINED or LOST كيلوجرام ازداد/ نقص		

CHD or Malformation in Mother

تشوهات خلقيه في القلب أو إعاقة لدى الأم :

Questions	Coding Categories		SKIP TO
23 Do you, or did you, have congenital heart disease, that is, a heart condition which was present from birth, such as those that are listed on this card? Let me read them with you. هل سبق أن شخص لك أي نوع مشكلة خلقيه في القلب ؟ (للمقابل: الأمثلة موجودة على البطاقة) *Interviewer: Show CHD heart disease card.*	Yes نعم	1	Complete Card 1
	No لا	2	24
	Unknown غير معروف	9	23a
23a If unknown, state explanation: إذا كانت الإجابة بغير معروف أرجو الشرح			
24 Do you, or did you, have any other type of heart condition, such as those listed on this card? Let me read them with you. هل لديك أي نوع من أمراض القلب غير خلقي؟ إذا كانت الإجابة بنعم يلزم تكملة نموذج خاص بالقلب مرفق بالاستمارة. *Interviewer: Show Acquired heart disease card.*	Yes نعم	1	Complete Card 2
	No لا	2	
	Unknown غير معروف	9	
25 Do you, or did you, have a problem with easy bruising, a bleeding tendency, or a blood disorder such as those listed on this card? Let me read them with you. هل لديك أي نوع من أنواع اضطرا بات الدم ؟ (للمقابل:يوضح أنواع اضطرابات الدم الموضحة بالبطاقة) *Interviewer: Show Blood disorders card.*	Yes نعم	1	Complete Card 3
	No لا	2	
	Unknown غير معروف	9	
26 Do you, or did you, have any other birth defects, malformations, or conditions which were present from birth, such as those listed on this card. Let me read them with you. هل لديك او كان لديك أي نوع من انواع مشكلة الخلقية ؟ *Interviewer: Show Birth defects card.*	Yes نعم	1	Complete Card 4
	No لا	2	
	Unknown غير معروف	9	

(للمقابل: يوضح أنواع التشوهات الخلقية الموضحة بالبطاقة)

البطاقة ١ البطاقة ٢ البطاقة ٣ البطاقة ٤

CHD or Malformation in Father of the Baby

تشوهات خلقيه فى القلب أو إعاقة لدى الأب:

Questions	Coding Categories		SKIP TO
27 Does the baby's father have congenital heart disease, that is, a heart condition which was present from birth, such as those that are listed on this card? Let me read them with you. هل سبق أن شخص لك أي نوع مشكلة خلقيه في القلب ؟ *(للمقابل: الأمثلة موجودة على البطاقة)* *Interviewer: Show CHD heart disease card. Code unknown if father abandonned family or father died.*	Yes نعم	1	Complete Card 1
	No لا	2	28
	Unknown غير معروف	9	28
27a If unknown, state explanation: إذا كانت الإجابة بغير معروف أرجو الشرح	_____	☐☐	
28 Does the baby's father have any other type of heart condition, such as those listed on this card? Let me read them with you. هل لديك أي نوع من أمراض القلب غير خلقي؟ *(للمقابل: يقوم المقابل بتوضيح أنواع أمراض القلب المقصودة الموضحة في البطاقة)* *Interviewer: Show Acquired heart disease card.*	Yes نعم	1	Complete Card 2
	No لا	2	
	Unknown غير معروف	9	
29 Does the baby's father have a problem with easy bruising, a bleeding tendency, or a blood disorder such as those listed on this card? Let me read them with you. هل لديك أي نوع من أنواع اضطرابات الدم ؟ *(للمقابل:يوضح أنواع اضطرابات الدم الموضحة بالبطاقة)* *Interviewer: Show Blood disorders card.*	Yes نعم إذا كانت الإجابة بنعم يلزم تكملة نموذج خاص بالقلب مرفق بالاستمارة.	1	Complete Card 3
	No لا	2	
	Unknown غير معروف	9	
30 Does the baby's father have any other birth defects, malformations, or conditions which were present from birth, such as those listed on this card. Let me read them with you. هل لديك او كان لديك أي نوع من أنواع مشكلة الخلقية ؟ *"المقابل: يوضح أنواع التشوهات الخلقية الموضحة بالبطاقة)* *Interviewer: Show Birth defects card.*	Yes نعم	1	Complete Card 4
	No لا	2	
	Unknown غير معروف	9	

البطاقة ١ البطاقة ٢ البطاقة ٣ البطاقة ٤

CHD or Malformation in Parents of the Mother of the Baby

تشوهات خلقيه فى القلب أو إعاقة لدى والدى الأم:

Questions	Coding Categories		SKIP TO
31 Now, I'd like to ask you some questions about your family. Did your mother have any of the conditions listed below on this card? هل تعاني والدتك من أي مشكلة خلقية في القلب ؟ *Interviewer: Show CHD heart disease card.* *(للمقابل:الأمثلة موجودة على البطاقة)*	Yes نعم	1	Complete Card 1
	No لا	2	32
	Unknown غير معروف	9	32

البطاقة ١

Questions	Coding Categories			SKIP TO
31a	If unknown, state explanation: إذا كانت الإجابة غير معروفة أرجو الشرح		⌊⌊	
32	Does your mother have any other type of heart condition, such as those listed on this card? Let me read them with you. هل تعاني والدتك أي نوع من أنواع أمراض القلب الغير خلقية؟ الأمثلة موجودة في البطاقة *Interviewer: Show Acquired heart disease card.*	Yes	نعم	1	Complete Card 2
		No	لا	2	
		Unknown	غير معروف	9	
33	Does your mother have a problem with easy bruising, a bleeding tendency, or a blood disorder such as those listed on this card? Let me read them with you. هل عانت والدتك أو مازالت تعاني من أمراض أو اضطرابات في الدم ؟ الأمثلة موضحة في البطاقة *Interviewer: Show Blood disorders card.*	Yes	نعم	1	Complete Card 3
		No	لا	2	
		Unknown	غير معروف	9	
34	Does your mother have any other birth defects, malformations, or conditions which were present from birth, such as those listed on this card. Let me read them with you. هل تعاني والدتك أو كانت تعاني من مشكلات خلقية أخرى؟ (للمقابل : الأمثلة موجودة على البطاقة) *Interviewer: Show Birth defects card.*	Yes	نعم	1	Complete Card 4
		No	لا	2	
		Unknown	غير معروف	9	
35	Did your father have any of the conditions listed below on this card? هل يعاني والدك من أي نوع من مشكلات خلقية في القلب ؟ (للمقابل : الأمثلة موجودة على البطاقة) *Interviewer: Show CHD heart disease card.*	Yes	نعم	1	Complete Card 1
		No	لا	2	36
		Unknown	غير معروف	9	36
35a	If unknown, state explanation: إذا كانت الإجابة بغير معروف أرجو الشرح :		⌊⌊		
36	Does your father have any other type of heart condition, such as those listed on this card? Let me read them with you. هل يعاني والدك من أي نوع من أنواع أمراض القلب الغير خلقية ؟ (للمقابل : الأمثلة موجودة على البطاقة) *Interviewer: Show Acquired heart disease card.*	Yes	نعم	1	Complete Card 2
		No	لا	2	
		Unknown	غير معروف	9	
37	Does your father have a problem with easy bruising, a bleeding tendency, or a blood disorder such as those listed on this card? Let me read them with you. هل يعاني والدك أو كان يعاني من أمراض أو اضطرابات في الدم ؟ *Interviewer: Show Blood disorders card.*	Yes	نعم	1	Complete Card 3
		No	لا	2	
		Unknown	غير معروف	9	

البطاقة ٢ البطاقة ٣ البطاقة ٤ البطاقة ١ البطاقة ٢ البطاقة ٣

Questions	Coding Categories		SKIP TO
38 Does your father have any other birth defects, malformations, or conditions which were present from birth, such as those listed on this card. Let me read them with you. هل يعاني والدك أوكان يعاني من مشكلات خلقية أخرى؟ *Interviewer: Show Birth defects card.*	Yes نعم	1	Complete Card 4
	No لا	(2)	
	Unknown غير معروف	9	

البطاقة ٤

CHD or Malformation in Parents of the Father of the Baby

تشوهات خلقية في القلب أو إعاقة لدى والدي الأب :

Questions	Coding Categories		SKIP TO
39 Now, I'd like to ask you some questions about your husband's family. Did the baby's father's mother have any of the conditions listed below on this card? هل جدة الطفل من أبيه تعاني من أي مشاكل في القلب ؟ *Interviewer: Show CHD heart disease card.*	Yes نعم	1	Complete Card 1
	No لا	(2)	40
	Unknown غير معروف	9	40
39a If unknown, state explanation: إذا كانت الإجابة بغير معروف أرجو الشرح :		⌊⌋	
40 Does the baby's father's mother have any other type of heart condition, such as those listed on this card? Let me read them with you. هل تعاني جدة الطفل من أبيه أي نوع من أنواع أمراض القلب الغيرخلقية ؟ (الأشلة موجودة في البطاقة) *Interviewer: Show Acquired heart disease card.*	Yes نعم	1	Complete Card 2
	No لا	(2)	
	Unknown غير معروف	9	
41 Does the baby's father's mother have a problem with easy bruising, a bleeding tendency, or a blood disorder such as those listed on this card? Let me read them with you. هل تعاني جدة الطفل من أبيه أمراض أو اضطرابات في الدم ؟ *Interviewer: Show Blood disorders card.*	Yes نعم	1	Complete Card 3
	No لا	(2)	
	Unknown غير معروف	9	
42 Does the baby's father's mother have any other birth defects, malformations, or conditions which were present from birth, such as those listed on this card. Let me read them with you. هل تعاني أوكانت تعاني جدة الطفل من أبيه من مشكلات خلقية ؟ *Interviewer: Show Birth defects card.*	Yes نعم	1	Complete Card 4
	No لا	(2)	
	Unknown غير معروف	9	

البطاقة ١

البطاقة ٢

البطاقة ٣

البطاقة ٤

Questions	Coding Categories		SKIP TO
43 Did the baby's father's father have any of the conditions listed below on this card? هل يعاني جد الطفل من أبيه من أمراض أومشكلات خلقية في القلب؟ *Interviewer: Show CHD heart disease card.*	Yes نعم	1	Complete Card 1
	No لا	2	44
	Unknown غير معروف	9	44
43a If unknown, state explanation: إذا كانت الإجابة بغير معروف أرجو الشرح	_____	⌊⌊⌋⌋	
44 Does the baby's father's father have any other type of heart condition, such as those listed on this card? Let me read them with you. هل يعاني جد الطفل من أبيه من أي نوع من أنواع أمراض القلب الغير خلقية ؟ *Interviewer: Show Acquired heart disease card.*	Yes نعم	1	Complete Card 2
	No لا	2	
	Unknown غير معروف	9	
45 Does the baby's father's father have a problem with easy bruising, a bleeding tendency, or a blood disorder such as those listed on this card? Let me read them with you. هل يعاني جد الطفل من أبيه من أي نوع من أمراض أو اضطرابات في الدم ؟ *Interviewer: Show Blood disorders card.*	Yes نعم	1	Complete Card 3
	No لا	2	
	Unknown غير معروف	9	
46 Does the baby's father's father have any other birth defects, malformations, or conditions which were present from birth, such as those listed on this card. Let me read them with you. هل يعاني أوكان يعاني جد الطفل من أبيه من مشكلات خلقية أخرى؟ *Interviewer: Show Birth defects card.*	Yes نعم	1	Complete Card 4
	No لا	2	
	Unknown غير معروف	9	

CHD or Malformation in Siblings of the Mother of the Baby تشوهات خلقية في القلب أو إعاقة لدى إخوان وأخوات أم الطفل

Questions	Coding Categories		SKIP TO
47 How many liveborn full sisters (same mother and same father) do you (or did you) have? كم عدد أخوات الأم الشقيقات (من نفس الأم والأب) اللاتي ولدن أحياء (ليس بالضرورة الآن أحياء) ؟	Number of full sisters عدد الشقيقات	04	
48 How many liveborn half sisters (same mother with different father OR same father with different mother) do you (or did you) have? كم عدد أخوات الأم الغير شقيقات (نفس الوالد مع أم مختلفة أو نفس الوالدة مع أب مختلف) اللاتي ولدن أحياء (ليس بالضرورة الآن أحياء) ؟	Number of half sisters عدد الغير شقيقات	03	

Questions	Coding Categories		SKIP TO
49 How many liveborn full brothers (same mother and same father) do you (or did you) have? كم عدد إخوان الأم الأشقاء (من نفس الأم والأب) اللذين ولدوا أحياء (ليس بالضرورة الآن أحياء)	Number of full brothers عدد الأشقاء	02	
50 How many liveborn half brothers (same mother with different father OR same father with different mother) do you (or did you) have? كم عدد إخوان الأم الغير أشقاء (نفس الوالد مع أم مختلفة أو نفس الوالدة مع أب مختلف) اللذين ولدوا أحياء (ليس بالضرورة الآن أحياء)؟	Number of half brothers عدد الغير أشقاء	08	
51 Do/did any of your brothers or sisters have any of the conditions listed on these cards? هل كان يعاني أو مازال يعاني أي من إخوانك أو أخواتك أي من الأمراض الموجودة في البطاقات؟ *Interviewer: Show CHD heart disease, Acquired heart disease card and birth defects card.* للمقابل: اعرض البطاقات	Yes نعم	1	Cards 1,2,3,4 as required
	No لا	(2)	
	Unknown غير معروف	9	

CHD or Malformation in children of mother's brothers and sisters

Questions	Coding Categories		SKIP TO
52 Do/did any of your full sisters or full brothers have children? Exclude half brothers and sisters and adopted children and stepchildren. هل لدى/ كان لدى أي من أشقائك أو شقيقاتك أولاد؟ ماعدا الإخوان أو الأخوات الغير أشقاء ومن لديهم أطفال بالتبني أو أطفال من الزوج أو غيره؟ *Interviewer: Not applicable: mother does not have full brothers or sisters*	Yes نعم	(1)	
	No لا	2	53
	Not applicable غير مطابق (ليس لدى الأم أشقاء/شقيقات من نفس الأم أو الأب)	3	
	Don't know لا أدري	4	

First name of mother's full-sibling اسم الأخ / الأخت (للأم)	Her / His children: Total Number العدد كامل — Girls بنات	Boys أولاد	Number with العدد مع — CHD	Blood Disorders	Birth Defects
1	—	1	1	0	0
2					
3					
4					
5					
6					
7					
8					
9					
10					

(1)

dead heart defect

Risk Factors for Congenital Heart Defects in Saudi Infants

Departments of Biostatistics, Epidemiology & Scientific Computing, Cardiovascular Diseases, Pediatrics and Obstetrics and Gynaecology

تشوهات خلقية في القلب أو إعاقة لدى إخوان أو أخوات الأب :

CHD or Malformation in Siblings of the Father of the Baby

Questions	Coding Categories		SKIP TO
53 How many liveborn full sisters (same mother and same father) does the baby's father (or did) have? كم عدد أخوات الأب الشقيقات (من نفس الأم والأب) اللاتي ولدن أحياء (ليس بالضرورة الآن أحياء) ؟	Number of full sisters عدد الشقيقات	06	
54 How many liveborn half sisters (same mother with different father OR same father with different mother) does the baby's father (or did) have? كم عدد أخوات الأب الغير شقيقات (نفس الوالد مع أم مختلفة أو نفس الوالدة مع أب مختلف) اللاتي ولدن أحياء (ليس بالضرورة الآن أحياء) ؟	Number of half sisters عدد الغير شقيقات	03	
55 How many liveborn full brothers (same mother and same father) does the baby's father (or did) have? كم عدد إخوان الأب الأشقاء (من نفس الأم والأب) اللذين ولدوا أحياء (ليس بالضرورة أحياء الآن) ؟	Number of full brothers عدد الأشقاء	06	
56 How many liveborn half brothers (same mother with different father OR same father with different mother) does the baby's (or did) have? كم عدد إخوان الأب الغير أشقاء (نفس الوالد مع أم مختلفة أو نفس الوالدة مع أب مختلف) اللذين ولدوا أحياء (ليس بالضرورة أحياء الآن) ؟	Number of half brothers عدد الغير أشقاء	06	
57 Do/did any of his brothers or sisters have any of the conditions listed on these cards? هل كان يعاني أو مازال يعاني أي من إخوان أو أخوات الأب أي من الأمراض الموجودة في البطاقة ؟ *Interviewer: Show CHD heart disease, Acquired heart disease card and birth defects card.*	Yes نعم	1	Cards 1,2,3,4 as required
	No لا	2	
	Unknown غير معروف	9	

CHD or Malformation in Children of baby's father's brothers and sisters

Questions	Coding Categories		SKIP TO
58 Do/did any the baby's father's full sisters or full brothers have children? Exclude half brothers and sisters and adopted children and stepchildren. هل لدى أي من أشقاء أو شقيقات الأب أولاد ؟ ماعدا الإخوان أو الأخوات الغير أشقاء ومن لديهم أطفال بالتبني أو أطفال الزوج أو غيره *Interviewer: Not applicable: father does not have full brothers or sisters*	Yes نعم	1	
	No لا	2	59
	Not applicable غير مطابق (ليس لدى الأب أشقاء / شقيقات من نفس الأم أو الأب)	3	
	Don't know لا أدري	4	

	First name of father's full-sibling اسم الأخ / الأخت (للأب)	Her / His children — Total Number العدد كامل: Girls بنات	Boys أولاد	Number with العدد مع: CHD	Blood Disorders	Birth Defects
1	[redacted]	1	2	0	0	0
2	[redacted]	3	2	0	0	0
3	[redacted]	—	—	0	0	0
4	[redacted]	—	—	0	0	0
5	[redacted]	—	—	0	0	0
6	[redacted]	1	3	0	0	0
7						
8						
9						
10						

12

مراحل الحمل لدى الأم

Mother's Pregnancy Section

	Questions	Coding Categories		SKIP TO
59	How many times have you been pregnant, including the pregnancy for this child? كم من المرات حملتي بالإضافة إلى حملك الحالي ؟	Record gravidity	03	Complete Reproductive History Supplemental Pages
60	Have you ever used the birth control pill (oral contraception) or Depo Provera or any other type of synthetic contraceptive estrogen? هل استخدمت الأم (في أي وقت من الأوقات) حبوباً لمنع الحمل أو إبراً لمنع الحمل ، أو أي طريقة لمنع الحمل ؟	Yes نعم	1	
		No لا	2	62
		Unknown غير معروف	9	
61	Were you using this product when you became pregnant with this child? هل استخدمت هذا العلاج عندما أصبحت حاملاً بهذا الطفل ؟	Yes نعم	1	
		No لا	2	
		Unknown غير معروف	9	

أول يوم أستخدم فيه مانع للحمل

Pill Use:

First date of contraceptive estrogen use
(truncate to *3 months prior* date)

Greg ميلادي: D D / M M / Y Y Y Y

Hejira هجري: D D / M M / Y Y Y Y

ي ي ش ش س س س س

آخر يوم أستخدم فيه مانع الحمل

Last date of contraceptive estrogen use

D D / M M / Y Y Y Y

D D / M M / Y Y Y Y

ي ي ش ش س س س س

Risk Factors for Congenital Heart Defects in Saudi Infants

Departments of Biostatistics, Epidemiology & Scientific Computing, Cardiovascular Diseases, Pediatrics and Obstetrics and Gynaecology

Questions	Coding Categories		SKIP TO
62 Mother's Rubella status prior to this pregnancy? وضع الحصبة (حصبة ألماني) عند الأم قبل الحمل الحالي؟	Positive إيجابي	1	
	Negative سلبي	(2)	
	Unknown غير معروف	9	
63 Mother exposed to Rubella during this pregnancy? هل تعرضت الأم للحصبة الألمانية خلال هذا الحمل؟	Yes نعم	1	
	No لا	(2)	
	Unknown غير معروف	9	
64 Congenital Rubella diagnosed in this infant? هل تم تشخيص الطفل المولود بأن لديه حصبة ألمانية خلقية؟	Yes نعم	1	
	No لا	(2)	
	Unknown غير معروف	9	

يوم ولادة الطفل - فترة الحمل بالطفل = يوم حدوث الحمل (ح)

Interviewer calculates *Exposure Window:* *Date of Birth - Gestation (9 months) = Conception*

(ح) ٣- شهر قبل حدوث الحمل — Three months prior to conception — Approx Conception date تاريخ حدوث الحمل تقريباً — Three months post conception — (ح) ٣+ شهر بعد حدوث الحمل

	ي ي	ش ش	س س س س	ي ي	ش ش	س س س س
Greg ميلادي				27-10-1420		
	D D	M M	Y Y Y Y	D D	M M	Y Y Y Y
Hejira هجري		0 7	1 4 2 0		0 1	1 4 2 1
	D D	M M	Y Y Y Y	D D	M M	Y Y Y Y
	ي ي	ش ش	س س س س	ي ي	ش ش	س س س س

Exposures — تعرض الأم لعوامل مختلفة منعاً

Questions	Coding Categories		SKIP TO
65 Thinking back to the 3 months before you got pregnant and the three months after you got pregnant, did the holy month of Ramadan fall during this period? هل كان شهر رمضان من ضمن الثلاث أشهر التي سبقت الحمل أو الثلاثة أشهر الأولى من الحمل؟	Yes نعم	(1)	
	No لا	2	68
	Unknown غير معروف	9	
66 Did you fast on any day during that Ramadan? هل صمتِ خلال رمضان؟	Yes نعم	(1)	
	No لا	2	
	Unknown غير معروف	9	
67 How many days did you fast during that Ramadan? كم يوماً صمتِ من رمضان؟ الرمز ٩٩ إذا كانت الإجابة غير معروف *Code as 99 if unknown*		23	

إذا كانت الإجابة لا اذهب إلى سؤال ٦٨

Questions	Coding Categories		SKIP TO
68 Did you observe any other fasting days during that time period? هل صمتي أياماً غير شهر رمضان خلال حملك 1- 6 Days of Shawwal الأيام الست من شوال 2- Ashurah (Muharram) Red Sea عاشوراء (محرم) 3- Arafah (9 Dhu al Hijjah) عرفة (التاسع من ذي الحجة) 4- Monday / Thursday (Al Ithnane & Al Hamees) الإثنين / الخميس 5- 13/14/15 of the month الأيام البيض (١٣-١٤-١٥) من كل شهر. 6- Make up menstrual days from previous Ramadan قضاء أيام رمضان.	Yes نعم	1	
	No لا	2	70
	Unknown غير معروف	9	
69 How many days did you fast in total (excluding previously (Q67) counted Ramadan days)? كم عدد الأيام التي صمتها خلال حملك عدا أيام رمضان؟		00	
70 Have you ever been told that you have diabetes? هل سبق أن شخصت بمرض السكر من قبل؟	Yes نعم	1	Complete diabetes form
	No لا	2	
	Unknown غير معروف	9	
71 Are you related to this child's father in any other way than by marriage? (Including if your parents or the parents of this child's father are related in any way other than by marriage.) هل توجد أي صلة قرابة بينك وبين والد الطفل عدا أنه زوجك؟ (يتضمن ذلك إذا كان والديك، ووالديه بينهم أي صلة قرابة)؟	Yes نعم	1	Complete pedigree chart
	No لا	2	
	Unknown غير معروف	9	

إذا كان الجواب: لا انتقل إلى سؤال رقم ٧٠

Skin-Lightening Cream

كريم مبيض للبشرة

Questions	Coding Categories		SKIP TO
72 Did you use skin-lightening cream from three months prior to conception to three months post conception? هل استخدمت كريم مبيض للبشرة خلال الثلاثة أشهر قبل الحمل، أو الثلاث أشهر بعد الحمل؟	Yes نعم	1	73
	No لا	2	79
	Unknown غير معروف	9	79
73 If yes, please specify the brand name إذا كانت الإجابة بنعم، أعطي اسم الكريم المبيض. إذا لم تتذكر ٩٩ *Doesn't remember=99* إذا كان الكريم غير تجاري بضاعة محلية ٩٨ *Not a commercial product = 98*	_____		

Questions	Coding Categories		SKIP TO
74 Where did you buy this cream? من أين اشتريت الكريم المبيض ؟	Pharmacy, Store صيدلية	1	76
	Abroad من الخارج (مستورد)	2	
	Herbalist (from herbs) عطار	3	
	Beauty shop محل تجميل	4	
	Can't remember لا أتذكر	9	
75 Tell me about the cream that you use أعطني فكرة مختصرة عن مصدر صناعة كريم المبيض وطريقة تركيبته .	_____ _____ _____	⌊⌊⌋	
76 How often did you apply the product the three months prior to and the three months after getting pregnant, on average? كم عدد المرات التي استعملت فيها الكريم المبيض خلال الثلاث أشهر قبل الحمل ، والثلاثة أشهر الأولى للحمل؟	Daily يومياً	1	
	Weekly أسبوعياً	2	
	Monthly شهرياً	3	
	Irregular (from time to time) غير منتظم (من وقت لآخر)	4	
	Unknown غير معروف	9	
77 Where did you apply it? في أي منطقة استعملت كريم المبيض؟ *Circle Y for Yes and N for No* ضعي دائرة عند الإجابة (ن) إذا ذكرتها الأم و (لا) إذا لم تذكرها الأم	Face الوجه	Y N	
	Hands اليدين	Y N	
	Back الظهر	Y N	
	Legs الرجلين	Y N	
	Arms الذراعين	Y N	
	Neck الرقبة	Y N	
	Chest الصدر	Y N	
78 How long had you been using it prior to the time you got pregnant? منذ متى وأنت تستخدمين الكريم المبيض قبل حملك هذا؟	Number of months of use? عدد الأشهر *Code as 999 if unknown* ٩٩٩ إذا كانت الإجابة غير معروفة	⌊⌊⌋	

Hair Treatment

علاج للشعر

Questions	Coding Categories		SKIP TO
79 Did you colour your hair from three months prior to conception to three months post conception? (Not lemon juice and not tea) هل صبغتي شعرك خلال الثلاث أشهر قبل الحمل أو الثلاثة أشهر الأولى للحمل ؟	Chemical dyes صبغة للشعر	Y (N)	If no to all three skip to Q82
	Peroxide أوكسجين	Y (N)	
	Henna حناء	Y (N)	
79a If yes, please specify the brand name إذا كانت الإجابة بنعم أرجو إعطاء اسم المنتج	_____	⌊⌊⌋	

إذا كانت الإجابة لا اذهب إلى ٨٢

Risk Factors for Congenital Heart Defects in Saudi Infants

Departments of Biostatistics, Epidemiology & Scientific Computing, Cardiovascular Diseases, Pediatrics and Obstetrics and Gynaecology

Questions	Coding Categories		SKIP TO
80 How often did you apply the colour, on average كم مرة استخدمت الصبغة أو الحناء؟	Less than every two weeks أقل من	1	
	Every two weeks كل أسبوعين	2	
	Monthly شهرياً	3	
	Every 6 weeks or more كل ٦ أسابيع أو أكثر	4	
	Irregularly غير منتظم (من وقت لآخر)	5	
	Unknown غير معروف	9	
81 How long had you been using hair colour prior to the time you got pregnant? منذ متى وأنتِ تستخدمين صبغة الشعر؟ أو الحناء خلال فترة	Number of months of use? عدد الأشهر *Code as 999 if unknown* ٩٩٩ إذا كانت الإجابة غير محددة	☐☐☐	

Traditional Cosmetics

مساحيق التجميل التقليدية :

Questions	Coding Categories		SKIP TO
82 Did you use kohl from three months prior to conception to three months post conception? هل استخدمت الكحل خلال الأشهر الثلاثة قبل الحمل أو الأشهر الأولى من الحمل؟ *Interviewer: Do not include Eyeliners from Revlon, Clinique, etc.* (ما عدا الماركات المعروفة مثل ريفلون كلينيك وغيره)	Yes نعم	1	
	No لا	2	86
	Unknown غير معروف	9	86
83 Where did you buy it? من أين اشتريته؟ *Interviewer: If Pharmacy, Store or Abroad, make sure not a commercially purchased product.* إذا كانت الإجابة صيدلية / متجر أو مستورد تأكد من أن المنتج ليس تجارياً (ماركة معروفة)	Pharmacy, Store صيدلية / متجر	1	
	Abroad من الخارج (مستورد)	2	
	Herbalist (from herbs) عطار	3	
	Beauty shop محل تجميل	4	
	Can't remember لا أتذكر	9	
84 How often did you apply it? كم مرة استخدمت الكحل؟	More often than once a day أكثر من مرة في اليوم	1	
	Daily يومياً	2	
	Weekly أسبوعياً	3	
	Monthly or more شهرياً أو أكثر	4	
	Irregularly من وقت لآخر	5	
	Unknown غير محدد	9	
85 How long had you been using kohl prior to the time you got pregnant with this child? منذ متى وأنتِ تستخدمين الكحل؟	Number of months عدد الشهور *Code as 999 if unknown* ٩٩٩ إذا غير محدد	☐☐☐	

العلاج الشعبي :

Traditional Medicines

Questions	Coding Categories		SKIP TO
86 Did you use noqd from three months prior to conception to three months post conception? هل استخدمت النقوض خلال الأشهر الثلاث الأولى قبل الحمل أو الثلاثة الأولى من الحمل ؟ Unknown: She doesn't know what it is *I don't know: She doesn't know if it was used*	Yes نعم	1	
	No لا	2	89
	Unknown/I don't know غير معروف / لا أعلم	9	89
87 How often did you apply it? كم كان عدد الأيام التي استخدمت فيها النقوض خلال فترة الثلاثة أشهر قبل الحمل أو الأشهر الأولى من الحمل؟	Several times a day مرات عديدة في اليوم	1	
	At least once a day على الأقل مرة في اليوم	2	
	Weekly أسبوعياً	3	
	Monthly شهرياً	4	
	Irregularly غير منتظم	5	
	Unknown غير معروف	9	
88 How many days in total did you use noqd 3 months before and after you got pregnant? كم كان عدد الأيام التي استخدمت فيها النقوض خلال فترة الثلاث أشهر قبل الحمل أو الأشهر الأولى من الحمل أو الأشهر الثلاثة الأولى من الحمل؟	Number of days عدد الأيام *Code as 999 if unknown* ٩٩٩ – غير معروف	⌊⌊⌊⌋	
89 Did you use saoot from three months prior to conception to three months post conception? هل استخدمت السعوط خلال الأشهر الثلاثة الأولى قبل الحمل أو الثلاثة الأولى من الحمل؟ *Unknown: She doesn't know what it is* *I don't know: She doesn't know if it was used*	Yes نعم	1	
	No لا	2	91
	Unknown/I don't know غير معروف / لا أعلم	9	91
90 How many days in total did you use saoot 3 months before and after you got pregnant? كم كان عدد الأيام التي استخدمت فيها السعوط خلال فترة الثلاثة أشهر قبل الحمل أو الأشهر الأولى من الحمل ، أو أو الأشهر الثلاثة الأولى من الحمل ؟	Number of days عدد الأيام *Code as 999 if unknown* ٩٩٩ – غير معروف	⌊⌊⌊⌋	
91 Do you use any other traditional medicines? هل استخدمت أي طب شعبي آخر من محلات العطارة ؟	Yes نعم	1	
	No لا	2	93
	Unknown غير معروف	3	93
92 If yes, please describe it (them) إذا كانت الإجابة بنعم ، صفي لنا ذلك .	_____ _____ _____	⌊⌊⌋	

Vitamins

Questions	Coding Categories		SKIP TO
93 Did you take vitamins during the period 3 months prior to and 3 months post conception? هل أخذت فيتامينات خلال فترة الأشهر الثلاثة قبل الحمل أو الأشهر الأولى من الحمل ، أو الثلاثة أشهر الأولى من الحمل ؟ *Interviewer to show sample*	Yes نعم	1	
	No لا	2	95
	Unknown غير معروف	9	95
94 When did you start taking vitamins? منذ متى وأنتِ تستخدمين الفيتامينات ؟	3 months or more before I got pregnant ثلاثة أشهر أو أكثر قبل الحمل	1	
	Between 2 and 3 months before I got pregnant من شهرين إلى ثلاثة قبل الحمل	2	
	Between 1 and 2 months before I got pregnant من شهر إلى شهرين قبل الحمل	3	
	Around the time I got pregnant (60day period) تقريباً منذ بداية الحمل (فترة ٦٠ يوم)	4	
	1 month after I got pregnant بعد شهر من حدوث الحمل	5	
	Between 1 and 2 months after I got pregnant بين شهر أو شهرين بعد الحمل	6	
	Between 2 and 3 months after I got pregnant من شهرين إلى ثلاثة أشهر بعد الحمل	7	
	More than 3 months after I got pregnant أكثر من ثلاثة أشهر بعد الحمل	8	
	Unknown غير معروف	9	
95 Did you take folic acid during the period 3 months prior to and 3 months post conception? هل استخدمت حامض الفوليك خلال الأشهر الثلاثة الأولى قبل الحمل ، أو الثلاثة أشهر بعد الحمل ؟ *Interviewer to show sample*	Yes نعم	i	
	No لا	2	96
	Unknown غير معروف	9	96
96 When did you start taking folic acid? منذ متى بدأتِ تأخذين حامض الفوليك ؟	3 months or more before I got pregnant ثلاثة أشهر أو أكثر قبل الحمل	1	
	Between 2 and 3 months before I got pregnant من شهرين إلى ثلاثة قبل الحمل	2	
	Between 1 and 2 months before I got pregnant من شهر إلى شهرين قبل الحمل	3	
	Around the time I got pregnant تقريباً منذ بداية الحمل	4	
	1 month after I got pregnant (60 day period) بعد شهر من حدوث الحمل (فترة ٦٠ يوم)	5	
	Between 1 and 2 months after I got pregnant بين شهر أو شهرين بعد الحمل	6	
	Between 2 and 3 months after I got pregnant من شهرين إلى ثلاثة أشهر بعد الحمل	7	
	More than 3 months after I got pregnant أكثر من ثلاثة أشهر بعد الحمل	8	
	Unknown غير معروف	9	

Nausea during Pregnancy

الغثيان أثناء الحمل :

Questions	Coding Categories		SKIP TO
97 During this pregnancy did you experience any nausea? هل كان لديك غثيان (وحم) خلال الأشهر الثلاثة الأولى من هذا الحمل ؟	Yes نعم	1	
	No لا	2	105
	Unknown غير معروف	9	

Questions	Coding Categories		SKIP TO
98 In which month of pregnancy did the nausea start? في أي شهر من الحمل بدأت تشعرين بالغثيان ؟	Month (Don't know = 99) الشهر ٩٩ - غير معروف / لا أعلم	02	
99 How often did the nausea occur? ما هي عدد مرات حدوث الغثيان ؟	Several times a day أكثر من مرة في اليوم	(1)	
	At least once a day على الأقل مرة في اليوم	2	
	Several times a week أكثر من مرة في الأسبوع	3	
	At least once a week على الأقل مرة في الأسبوع	4	
	Several times a month أكثر من مرة في الشهر	5	
	At least once a month على الأقل مرة في الشهر	6	
	Irregularly غير منتظم	7	
	Unknown غير معروف	9	
100 How many months did the nausea last? كم استغرقت فترة الغثيان ؟ *Code 1 through 9*	Month (Don't know = 99) الشهر ٩٩ - غير معروف / لا أعلم	05	
101 Did you take any medicine for your nausea? هل استخدمت أي علاج لإيقاف الغثيان ؟	Yes نعم	(1)	
	No لا	2	105
	Unknown غير معروف	9	
102 If yes, please specify إذا كانت الإجابة نعم ، صفي لنا ذلك . *Interviewer to show samples*	small white tablet	5	
103 In what week of pregnancy did you start taking this medicine? في أي أسبوع من الحمل بدأت تأخذين أدوية الغثيان ؟	Week (Don't know = 99) الأسبوع ٩٩ - لا أعلم	03 months (12) weeks	
104 How many weeks did you take it? كم أسبوعاً استخدمت علاج الغثيان ؟	Week (Don't know = 99) الأسبوع ٩٩ - لا أعلم	10 days	

Heartburn during Pregnancy

حرقان المعدة في فترة الحمل :

Questions	Coding Categories		SKIP TO
105 During this pregnancy did you experience any heartburn? هل كان عندك حرقان في المعدة خلال هذا الحمل ؟	Yes نعم	1	
	No لا	(2)	113
	Unknown غير معروف	9	

Questions	Coding Categories		SKIP TO
106 In which month of pregnancy did the heartburn start? في أي شهر من الحمل بدأتِ تشعرين بحرقان المعدة ؟	الشهر ٩٩ - لا أعلم Month (Don't know = 99)	⌊⌊⌋	
107 How often did the heartburn occur? ما هي عدد مرات حدوث حرقان المعدة ؟	Several times a day أكثر من مرة في اليوم	1	
	At least once a day على الأقل مرة في اليوم	2	
	Several times a week أكثر من مرة في الأسبوع	3	
	At least once a week على الأقل مرة في الأسبوع	4	
	Several times a month أكثر من مرة في الشهر	5	
	At least once a month على الأقل مرة في الشهر	6	
	Irregularly غير منتظم	7	
	Unknown غير معروف	9	
108 How many months did the heartburn last? كم استغرقت فترة حرقان المعدة ؟ *Code 1 through 9*	Month (Don't know = 99) الشهر (٩٩ - لا أعلم	⌊⌊⌋	
109 Did you take any medication for your heartburn? هل استخدمت أي علاج لإيقاف حرقان المعدة ؟	Yes نعم	1	
	No لا	2	113
	Unknown غير معروف	9	
110 If yes, please specify إذا كانت الإجابة بنعم ، حددي نوع الدواء المستعمل *Interviewer to show samples*	_____	⌊⌊⌋	
111 In what week of pregnancy did you start taking this medicine? في أي أسبوع من الحمل بدأت تأخذين أدوية لحرقان المعدة ؟	Week (Don't know = 99) الأسبوع ٩٩ - لا أعلم	⌊⌊⌋	
112 How many weeks did you take it? كم أسبوعاً استخدمت علاج حرقان المعدة ؟	Week (Don't know = 99) الأسبوع ٩٩ - لا أعلم	⌊⌊⌋	

Illness

الأمراض :

Questions	Coding Categories		SKIP TO
113 At any time during this pregnancy were you ill with a fever or a cold? في وقت من الأوقات خلال فترة الحمل ، هل تعرضتِ لارتفاع في الحرارة ، أو أصبتِ ببرد ؟	Yes نعم	1	
	No لا	2	119 انتقل إلى سؤال ١١٩
	Unknown غير معروف	9	
114 Try to remember the week of pregnancy that you got sick for the first time حاولي تذكر الأسبوع الذي مرضتِ فيه من الحمل ؟	Week (Don't know = 99) الأسبوع ٩٩ - لا أعلم	06 week ⌊⌊⌋	117

Questions	Coding Categories		SKIP TO
115 Try to remember the month of pregnancy حاولي تذكر الشهر الذي مرضتِ فيه من الحمل يسأل هذا السؤال فقط إذا كانت الإجابة لسؤال ١١٤ "لا أعرف" *Ask only if Q114 unknown otherwise* *Interviewer to complete*	Month (Don't know = 98) الشهر (٩٨ = لا أعلم)	☐☐	117
116 Try to remember the trimester of pregnancy حاولي تذكر فترة الثلاثة أشهر من الحمل التي مرضتِ فيها يسأل هذا السؤال فقط إذا كانت الإجابة للسؤال ١١٤ و ١١٥ = "لا أعرف" *Ask only if Q114 and Q115 unknown otherwise* *Interviewer to complete*	Trimester (Don't know = 98) فترة الثلاثة أشهر من الحمل (٩٨ = لا أعلم)	☐☐	
117 Number of days that you were sick that first time, in total. عدد الأيام التي كنتِ فيها مريضة لأول مرة (مجموع الأيام)		02 ☐☐	
118 Was there any fever? هل كان عندكِ ارتفاع في الحرارة ؟	Yes نعم	(1)	
	No لا	2	
	Unknown غير معروف	9	

Medications

الأدوية

Questions	Coding Categories		SKIP TO
119 At any time during this pregnancy did you take any medications not already discussed? هل أخذت أدوية خلال فترة الحمل لم تكن مصروفة لكِ من قبل الطبيب ، وخاصة بالحمل ؟	Yes نعم	1	
	No لا	(2)	125
	Unknown غير معروف	9	
120 Try to remember the week of pregnancy حاولي أن تتذكري أسبوع الحمل الذي أخذتِ فيه العلاجات ؟	Week (Don't know = 98) الأسبوع (٩٨ = لا أعلم)	☐☐	123
121 Try to remember the month of pregnancy حاولي أن تتذكري شهر الحمل الذي أخذتِ فيه العلاجات ؟ (يسأل هذا السؤال إذا كانت الإجابة على السؤال ١٢٠ لا أعرف . *Ask only if Q120 unknown otherwise* *Interviewer to complete*	Month (Don't know = 98) الشهر (٩٩٩ = لا أعلم)	☐☐	123
122 Try to remember the trimester of pregnancy حاولي أن تتذكري في أي فترة من فترات الحمل أخذتِ تلك العلاجات (الفترة الأولى / الفترة الثانية / الفترة الثالثة) *Ask only if Q120 and Q121 unknown otherwise* *Interviewer to complete* اسأل فقط في حالة أن إجابة السؤال ١٢١ و ١٢٠ غير معروف	Trimester (Don't know = 98) فترة الثلاثة أشهر من الحمل (٩٨ = لا أعلم)	☐☐	
123 Number of days that you took this medication. ما هو عدد الأيام التي أخذتِ فيها هذا الدواء ؟		☐☐	
124 Describe the medication صف هذا العلاج .	_____ _____ _____	☐☐	

Other Exposures

مؤثرات أخرى

Questions	Coding Categories		SKIP TO
125 Were you exposed to cigarette smoke at any time from 3 months prior to conception to 3 months post conception? هل تعرضتِ لدخان السجائر في مدة الثلاثة شهور السابقة للحمل أو الثلاثة أشهر الأولى من الحمل ؟ *Interviewer:* Remind mother of exposure window	Yes نعم	1	
	No لا	2	131
	Unknown غير معروف	9	
126 How frequently were you exposed to cigarette smoke? كم مرة تكرر تعرضكِ لدخان السجائر ؟	Several times a day, in the house أكثر من مرة في اليوم داخل المنزل	1	
	Once a day, in the house مرة واحدة في اليوم داخل المنزل	2	
	Less often than once a day, in the house أقل تكراراً من مرة في اليوم داخل المنزل	3	
	Only out of doors خارج المنزل فقط	4	
	Unknown غير معروف	9	
127 Did you smoke any cigarettes 3 months prior to the time you got pregnant and 3 months after you got pregnant? هل كنتِ تدخنين خلال الثلاثة أشهر التي سبقت الحمل أو الثلاثة أشهر الأولى من الحمل ؟ *Interviewer:* Remind mother of exposure window	Yes نعم	1	
	No لا	2	
	Unknown غير معروف	9	
128 Did the father of this child smoke any cigarettes within 3 months prior to the time you got pregnant and 3 months after you got pregnant? هل كان والد الطفل يدخن خلال الثلاثة أشهر لما قبل الحمل ، أو الثلاثة أشهر الأولى من الحمل ؟ *Interviewer:* Remind mother of exposure window	Yes نعم	1	
	No لا	2	
	Unknown غير معروف	9	
129 Did you or the father chew or smoke anything else within 3 months prior to or following conception? (Muassal or Sheesha) هل دخنتِ أنتِ أو والد الطفل أي شيء آخر غير السجائر (شيشة أو معسل) خلال الثلاثة أشهر الأولى من الحمل ، أو الثلاث أشهر السابقة للحمل؟ *Interviewer:* Remind mother of exposure window	Yes نعم	1	
	No لا	2	131
	Unknown غير معروف	9	
130 If yes, please describe exposure. إذا كانت الإجابة بنعم ، صفي هذة المادة	_____ _____ _____	⌊⌊⌋	

انتقل إلى ١٣١

Caffeine

Questions	Coding Categories		SKIP TO
131 Did you drink coffee during the three months prior to and the three months after you got pregnant? هل كنتِ تشربين القهوة خلال فترة الثلاثة أشهر السابقة للحمل ، أو الثلاثة أشهر الأولى من الحمل ؟ يتضمن جميع الأنواع بالحليب أو من دونه *Include all types of coffee here. With and without milk.*	Yes نعم	1	
	No لا	2	133 اذهب إلى ١٣٣
132 If yes, how many cups of coffee did you drink per day during that six month time, on average? إذا كانت الإجابة بنعم ، كم كوباً من القهوة تشربينها في اليوم ؟	Number of cups عدد الأكواب	___	
133 Did you drink tea during the three months prior to and the three months after you got pregnant? هل كنتِ تشربين الشاي خلال فترة الثلاث شهور السابقة للحمل ، أو الثلاث شهور الأولى من الحمل ؟ *Include all types of tea here (except herbal). With and without milk.* يتضمن جميع الأنواع بالحليب أو من دونه (ماعدا أكياس الأعشاب)	Yes نعم	1	
	No لا	2	135 اذهب إلى ١٣٥
134 If yes, how many cups of tea do you drink per day? إذا كانت الإجابة بنعم ، كم كوباً من الشاي تشربين في اليوم ؟	Number of cups عدد الأكواب	٥١	
135 Did you drink Coke and pepsi during the three months before and after you got pregnant? هل كنتِ تشربين البيبسي والكوكا خلال فترة الثلاث شهور السابقة للحمل ، والثلاثة أشهر الأولى من الحمل ؟ *e.g., Coke and Pepsi.* عدا البيرنا - سفن آب *Not 7-up, Sprite, Miranda, Fanta* سبرايت	Yes نعم	1	
	No لا	2	137 اذهب إلى ١٣٧
136 If yes, how many cans of colas did you drink per week? إذا كان نعم ، كم علبة تشربين في الأسبوع ؟ العلبة المقصودة هي ٣٣٠ ملل ، وليست الصغيرة *A "can" is the 330 ml can - not the small one.*	Number of 330 ml cans عدد العلب ٣٣٠ ملل	___	

Licorice

Questions	Coding Categories		SKIP TO
137 Did you eat licorice or anisette seeds during your pregnancy? هل أكلتِ عرق السوس أثناء حملكِ ؟	Never ١- أبداً	1	
	Rarely (once a month at the most) ٢- نادراً (مرة في الشهر)	2	
	Seldom (once a week at the most) ٣- أحياناً (مرات قليلة في الأسبوع)	3	
	Often (almost every day) ٤- أحياناً (تقريباً كل يوم)	4	
	Frequently (several times a day) ٥- كثيراً (مرات عديدة في اليوم)	5	
	Unknown ٦- غير معروف	9	

Chemical/Pesticides Exposure

المؤثرات الكيميائية والمبيدات

Questions	Coding Categories		SKIP TO
138 When you were pregnant with this child were pesticides sprayed inside your house? خلال حملك بهذا الطفل هل تعرضت لأي مبيد حشري داخل منزلك؟	Yes نعم	1	
	No لا	2	142
	Unknown غير معروف	9	142
139 How often was this done? كم مرة حدث ذلك	Weekly or more often أسبوعياً أو أكثر	1	
	Less often then weekly شهرياً	2	
	Seasonally في كل فصل من فصول العام	3	
	Unknown غير معروف	9	
140 Did you yourself do this spraying of pesticides in the house? هل كنت ترشين المبيدات الحشرية بنفسك في المنزل؟	Yes, all of it (90% or more) نعم كلها تقريباً ٩٠٪ أو أكثر	1	
	Yes, most of it (50-89%) نعم أغلبها (٥٠٪ - ٨٩٪)	2	
	Yes, some of it (11 to 49%) نعم بعضها (١١٪ - ٤٩٪)	3	
	None of it (0 to 10%) لا (٠٪ - ١٠٪)	4	
	Don't remember/Unknown لا أتذكر	9	
141 Did you take precautions when pesticides were being applied in your house? هل تأخذين الاحتياطات اللازمة عند رش المبيدات الحشرية بمنزلك؟ مثل (تغطية الطعام، تنظيف أدوات الطعام، تجنبك وأفراد عائلتك التعرض المباشر *E.g., Coverage of food. Coverage of eating utensils. Removing self and family members from immediate contact.*	Yes نعم	1	
	No لا	2	
	Unknown غير معروف	9	

اذهب إلى ١٤٢

Rodenticides Exposure

التعرض لسم الفئران

Questions	Coding Categories		SKIP TO
142 When you were pregnant with this child were rodenticides sprayed inside your house? خلال حملك بهذا الطفل هل رششتي مادة سم الفئران داخل المنزل؟	Yes نعم	1	
	No لا	2	145
	Unknown غير معروف	9	145
143 How often was this done? كم مرة حدث ذلك؟	Weekly or more often أسبوعياً أو أكثر	1	
	Less often then weekly شهرياً	2	
	Seasonally في كل فصل من فصول العام	3	
	Unknown غير معروف	9	
144 Did you yourself do the application of rodenticides in the house? هل كنت ترشين سم الفئران بنفسك في المنزل؟	Yes, all of it (90% or more) نعم كلها تقريباً ٩٠٪ أو أكثر	1	
	Yes, most of it (50-89%) نعم أغلبها (٥٠٪ - ٨٩٪)	2	
	Yes, some of it (11 to 49%) نعم بعضها (١١٪ - ٤٩٪)	3	
	None of it (0 to 10%) لا (٠٪ - ١٠٪)	4	
	Don't remember/Unknown لا أتذكر	9	

اذهب إلى ١٤٥

Air Cooling

Questions	Coding Categories		SKIP TO
145 What type of air cooling did your home have when you got pregnant? ماهو نوع التكييف الذي استخدم بالمنزل عندما كنتِ حاملاً؟	Air conditioning تكييف مركزي	1	
	Air cooling تكييف صحراوي		
	Fan مروحة		
	Nothing بدون	2	
	Unknown غير معروف	9	
146 Do you remember getting especially warm at any time during the time you were pregnant? هل تتذكرين أنك تعرضتِ لحرارة غير معتادة في أي وقت من الأوقات أثناء فترة حملك ؟	Yes نعم	1	
	No لا	2	
	Don't remember لا أتذكر	9	

مؤثرات اجتماعية واقتصادية

Socio-Economic Status Section: Education and work

Questions	Coding Categories		SKIP TO
147 Have you ever attended school? هل سبق أن ذهبتِ إلى المدرسة ؟	Yes: Currently نعم ؛ الآن	1	
	Yes: Not currently نعم ؛ في السابق	2	
	No لا	3	
148 What (is/ was) the highest level of education you attended? ماهو أعلى مستوى تعليمي حصلتِ عليه ؟	Illiterate أمية	1	
	No schooling, but literate تقرأ وتكتب ولم تلتحق بالمدرسة	2	
	Literacy class محو الأمية	3	
	Primary ابتدائي	4	
	Preparatory متوسط	5	
	Secondary ثانوي	6	
	Diploma دبلوم	7	
	University جامعي	8	
149 Have you ever done any work regularly for which were paid in cash? هل عملتِ عملاً منتظماً كنتِ تأخذين عليه أجراً ؟	Yes نعم	1	
	No لا	2	151
150 What kind of work do you mainly do? Interviewer: Write response exactly as given ماهو نوع العمل الذي تقومين به ؟	_____ _____ _____		
151 What is your civil status? ماهو الوضع الاجتماعي الحالي لديكِ ؟	Married to the baby's father متزوجة من والد الطفل	1	
	Divorced from baby's father مطلقة من والد الطفل	2	
	Separated from baby's father منفصلة عن والد الطفل	3	
	Widowed from baby's father أرملة من والد الطفل	4	

Questions	Coding Categories		SKIP TO
152 Has this baby's father ever attended school? هل ذهب والد الطفل إلى المدرسة ؟	Yes: Currently نعم : الآن	1	
	Yes: Not currently نعم : في السابق	(2)	
	No لا	3	
	Don't know لا أعلم	4	
153 What (is/ was) the highest level of education the father of this baby attended? ما هو أعلى مستوى تعليمي حصل عليه والد الطفل ؟	Illiterate أمي	1	
	No schooling, but literate يقرأ ويكتب ولم يلتحق بالمدرسة	2	
	Literacy class محو الأمية	3	
	Primary ابتدائي	4	
	Preparatory متوسط	(5)	
	Secondary ثانوي	6	
	Diploma دبلوم	7	
	University جامعي	8	
	Don't know لا أعلم	9	
154 Has the father of this child ever done (ever did) any work regularly for which he was paid in cash? هل عمل والد الطفل عملاً منتظماً كان يأخذ عليه أجراً ؟	Yes نعم	(1)	
	No لا	2	
	Don't know لا أعلم	9	
155 What kind of work does he mainly do? ما هي طبيعة عمل والد الطفل ؟ إذا كان والد الطفل متوفياً ، سجل طبيعة العمل الذي يقوم به العائل الحالي للأم والطفل Interviewer: *Write response exactly as given* *If father is dead record the the work of the next of kin who supports this mother and child*	كاتب في قصر الملك Clerk at King palce	96	
156 Who was responsible financially for you (the mother) when you were growing up? من كان مسئولاً عنكِ مالياً في صغركِ وفترة تضوجك قبل زواجكِ ؟	Father الأب	(1)	158
	Someone besides the mother's (your) father أحد آخر غير أو بجانب والد أم الطفل	2	
157 If your father was not financially responsible for you when you were a child who was? لو لم يمن والدك ، فمن كان مسئولاً عنكِ ؟	_____	⌊⌊	
158 Did the mother's father (your father) (or who-ever was responsible for the your financial maintenance) ever attend school? هل ذهب والدكِ أو من كان مسئولاً عنكِ إلى المدرسة ؟	Yes نعم	1	
	No لا	(2)	
	Don't know لا أعلم	9	

Questions	Coding Categories		SKIP TO
159 What (is/was) the highest level of education this person attended? ما هي أعلى درجات التعليم التي حصل عليها ؟	Illiterate أمي	1	
	No schooling, but literate يقرأ ويكتب ولم يلتحق بالمدرسة	2	
	Literacy class محو الأمية	3	
	Primary ابتدائي	4	
	Preparatory متوسط	5	
	Secondary ثانوي	6	
	Diploma دبلوم	7	
	University جامعي	8	
	Unknown غير معروف	9	
160 Did/does this person ever do any work regularly for which he was paid in cash? هل سبق لهذا الشخص أن عمل أي عمل منتظم مقابل أجر نقدي ؟	Yes نعم	1	
	No لا	2	
	Unknown غير معروف	9	
161 What kind of work did/does he mainly do? ماهي طبيعة العمل الذي يقوم/ قام به ؟ *Interviewer: Write response exactly as given If mother's father was not supporter of mother record the work of the next of kin who did support this mother as a child*			

Socio-Economic Status Section: Assets and Responsibilities

Questions	Coding Categories		SKIP TO
162 Reported household income in SR per month اذكر الدخل الكلي للعائلة في الشهر .	Refused = 88888 رفض ٨٨٨٨٨ Unknown=99999 لا أعرف ٩٩٩٩٩	4700	
163 Number of household members supported by this income اذكر عدد أفراد الأسرة الذين يعتمدون على هذا الدخل.	Number in household عدد الأفراد	05	
164 Of these household members how many are servants? كم عدد خدم أفراد الأسرة ؟	Number of servants عدد الخدم	00	

Risk Factors for Congenital Heart Defects in Saudi Infants

Departments of Biostatistics, Epidemiology & Scientific Computing, Cardiovascular Diseases, Pediatrics and Obstetrics and Gynaecology

Questions	Coding Categories		SKIP TO
165 How many cars are owned by members of the household? كم عدد سيارات أفراد الأسرة ؟	Number of cars owned (Don't know = 99)	01	
166 How many acres of land are owned by the members of this household? كم عدد الممتلكات العقارية لأفراد هذه الأسرة ؟	Number of acres of land owned (Don't know = 999)	00	
167 Does your family own any livestock (sheep, camels, hens, goats, horses)? هل تملك هذه الأسرة مواشي (أغنام، جمال، ماعز، خيول، دجاج	Yes نعم	1	
	No لا	(2)	
168 How many weeks pregnant were you when you *knew* that you were pregnant? في أي أسبوع كان حملك، عندما علمت أنك حامل ؟	Number of weeks pregnant at self-awareness عدد الأسابيع (Don't know = 99) لا أعلم = ٩٩	04	
169 Last question: What do you think causes congenital heart defects? ماذا تتوقعين سبب حدوث التشوهات القلبية الخلقية بعد مشيئة الله	God's will مشيئة الله	(Y) N	
Circle Y for Yes and N for No	Exposure to video display terminals التعرض لشاشة الألعاب الإليكترونية	Y (N)	
	Consanguinity زواج الأقارب	Y (N)	
	Feeling angry during 6 month window الشعور بالغضب خلال ٦ أشهر الأولى من الحمل وبعده	Y (N)	
	Exposure to environmental toxins التلوث البيئي	Y (N)	
	Other غير ذلك.	Y (N)	
170 Other: أخرى			

Interviewer's Observations

رأي المقابل وتقييمه :

Questions	Coding Categories		SKIP TO
A Degree of cooperation? درجة التعاون	Poor ضعيف	1	
	Fair مقبول	2	
	Good جيد	(3)	
	Very good جيد جداً	4	
B Degree of privacy? درجة الخصوصية	No others present لم يكن أحد موجوداً غير الأم	1	
	Others present during part of the interview حضر آخرون لوقت محدود	2	
	Others present during all of the interview حضر آخرون طوال المقابلة	(3)	
C If 'Others' present : Mark whether any of the following were present during the interview? إذا كان هناك أشخاص آخرين حضروا المقابل ، فهل كانوا :	The infant participant الطفل المعني بالدراسة	✓	
	Children under 10 أطفال تحت العشر سنوات		
	Husband الزوج	✓	
	Other Females أفراد آخرين من العائلة		
	Other Males رجال آخرون		
Interviewer: Records the end time المقابل يسجل وقت الانتهاء Interviewer: _____	Hour: الساعة 15		
	Minutes: الدقائق 05		

CHD Registry/Chart Abstraction Form

Questions	Coding Categories		SKIP TO
171 Severity of condition at diagnosis	Codes to be developed with Cardiologists	⌊⌊	
172 Embryological categorization		⌊⌊	
173 Situs:	Solitus	1	
	Right isomeris	2	
	Left isomeris	3	
	Inversus	4	
	Ambiguous	5	
	Unknown (not stated)	9	
174 Position of the Heart:	Laevocardia	1	
	Dextrocardia	2	
	Mesocardia	3	

ICD-9 Diagnosis	
175 CHD ICD-9 Diagnosis	⌊⌊⌊.⌊
176 CHD ICD-9 Diagnosis	⌊⌊⌊.⌊
177 CHD ICD-9 Diagnosis	⌊⌊⌊.⌊

EEPC Code
EEPC Code: □□ - □□ - □□
EEPC Code: □□ - □□ - □□
EEPC Code: □□ - □□ - □□

178 Associated ICD-9 Diagnosis	⌊⌊⌊.⌊

EEPC Code: □□ - □□ - □□

KACST LGP 5-14

BESC 012/2000

6 Pregnancy Form

Amy L. Sandridge, PI

Abdullah Al Rowais

Mansour Al Jufan

Hoda Kattan

Wesam Kurdi

ERU, CVD, RCF, RDMCF

8 September 2002 (rev 11 Feb 2003)

THIS SECTION ASKS ABOUT the WOMAN's PREGNANCIES 11 February 2003

Thinking about each of your pregnancies in turn, please answer the following questions:	First pregnancy	Second pregnancy
Is this the Study pregnancy? هل هذا الحمل هو الطفل المعني بالدراسة ؟	1 ☐ Yes نعم 2 ☐ No لا	1 ☐ Yes نعم 2 ☐ No لا
a. What was the date of birth, or date the pregnancy ended? *(if exact date not known please give an approximation)* متى كان ميلاد الطفل ؟	☐☐ day ☐☐ month ☐☐☐☐ year (Due date, if pregnant now)	☐☐ day ☐☐ month ☐☐☐☐ year (Due date, if pregnant now)
b. What was the outcome of the pregnancy? ما هي نتيجة الحمل ؟	1 ☐ Liveborn baby طفل حي 2 ☐ Stillbirth طفل ميت 3 ☐ Miscarriage فقد الجنين 4 ☐ Ectopic حمل خارج الرحم 5 ☐ Termination/abortion (for medical reasons) إجهاض 6 ☐ Molar pregnancy تشوه 7 ☐ Other أخرى (please describe below) 55 ☐ Current pregnancy	1 ☐ Liveborn baby طفل حي 2 ☐ Stillbirth طفل ميت 3 ☐ Miscarriage فقد الجنين 4 ☐ Ectopic حمل خارج الرحم 5 ☐ Termination/abortion (for medical reasons) إجهاض 6 ☐ Molar pregnancy تشوه 7 ☐ Other أخرى (please describe below) 55 ☐ Current pregnancy
c. Was this a multiple pregnancy? هل كان هذا الحمل لتوأم ؟ → If YES, please fill in one pregnancy column per baby	1 ☐ No, Singleton لا ١ 2 ☐ Yes, Twin ٢ توأم 3 ☐ Yes, Triplet ٣ توأم 4 ☐ Yes, higher number أكثر 9 ☐ Don't know لا أعلم	1 ☐ No, Singleton لا ١ 2 ☐ Yes, Twin ٢ توأم 3 ☐ Yes, Triplet ٣ توأم 4 ☐ Yes, higher number أكثر 9 ☐ Don't know لا أعلم
d. What was the sex of the baby (if known)? ما هو جنس الطفل ؟	1 ☐ Boy ذكر 2 ☐ Girl أنثى 9 ☐ Not known غير معلوم	1 ☐ Boy ذكر 2 ☐ Girl أنثى 9 ☐ Not known غير معلوم
e. How many weeks were you when the pregnancy ended (i.e. weeks of gestation)? *(Please put what the woman was told by the medical staff. If she was not told or does not remember tick Don't remember.)* كم كان عدد أسابيع الحمل ؟	☐☐ weeks (+ ☐☐ days, if known) (Current gestation, if pregnant now) 99 ☐ Don't remember لا أتذكر	☐☐ weeks (+ ☐☐ days, if known) (Current gestation, if pregnant now) 99 ☐ Don't remember لا أتذكر
f. What was the weight of the baby (if applicable)? ما هو وزن الطفل عند الولادة ؟	☐☐ lbs ☐☐ ozs OR ☐☐☐☐ grams غير معلوم ☐ Not known / Not applicable	☐☐ lbs ☐☐ ozs OR ☐☐☐☐ grams غير معلوم ☐ Not known / Not applicable
g. How old were you when the pregnancy ended? كم كان عمرك عند الولادة ؟	☐☐ Years	☐☐ Years
h. What was the date of birth of the father of this pregnancy? *(If actual date not known, please give the approximate year he was born. Please tick "same father" if father is the same as for previous pregnancy)* كم كان عمر الأب عند ولادة الطفل ؟	☐ Same father نفس الأب ☐☐ day ☐☐ month ☐☐☐☐ year 9 ☐ Don't know لا أعلم **Please turn page for more questions about this pregnancy**	☐ Same father نفس الأب ☐☐ day ☐☐ month ☐☐☐☐ year 9 ☐ Don't know لا أعلم **Please turn page for more questions about this pregnancy**

THIS SECTION ASKS ABOUT the WOMAN's PREGNANCIES 11 February 2003

Third pregnancy	Fourth pregnancy	Fifth pregnancy	Sixth pregnancy
هل هذا الحمل هو الطفل المعني بالدراسة ؟			
1 ☐ Yes نعم 2 ☐ No لا	1 ☐ Yes نعم 2 ☐ No لا	1 ☐ Yes نعم 2 ☐ No لا	1 ☐ Yes نعم 2 ☐ No لا
متى كان ميلاد الطفل ؟			
☐☐ day ☐☐ month ☐☐☐☐ year (Due date, if pregnant now)	☐☐ day ☐☐ month ☐☐☐☐ year (Due date, if pregnant now)	☐☐ day ☐☐ month ☐☐☐☐ year (Due date, if pregnant now)	☐☐ day ☐☐ month ☐☐☐☐ year (Due date, if pregnant now)
ما هي نتيجة الحمل ؟			
1 ☐ Liveborn baby طفل حي	1 ☐ Liveborn baby طفل حي	1 ☐ Liveborn baby طفل حي	1 ☐ Liveborn baby طفل حي
2 ☐ Stillbirth طفل ميت	2 ☐ Stillbirth طفل ميت	2 ☐ Stillbirth طفل ميت	2 ☐ Stillbirth طفل ميت
3 ☐ Miscarriage فقد الجنين	3 ☐ Miscarriage فقد الجنين	3 ☐ Miscarriage فقد الجنين	3 ☐ Miscarriage فقد الجنين
4 ☐ Ectopic حمل خارج الرحم	4 ☐ Ectopic حمل خارج الرحم	4 ☐ Ectopic حمل خارج الرحم	4 ☐ Ectopic حمل خارج الرحم
5 ☐ Termination/abortion (for medical reasons) اجهاض	5 ☐ Termination/abortion (for medical reasons) اجهاض	5 ☐ Termination/abortion (for medical reasons) اجهاض	5 ☐ Termination/abortion (for medical reasons) اجهاض
6 ☐ Molar pregnancy تشوه	6 ☐ Molar pregnancy تشوه	6 ☐ Molar pregnancy تشوه	6 ☐ Molar pregnancy تشوه
7 ☐ Other أخرى (please describe below)	7 ☐ Other أخرى (please describe below)	7 ☐ Other أخرى (please describe below)	7 ☐ Other أخرى (please describe below)
55 ☐ Current pregnancy	55 ☐ Current pregnancy	55 ☐ Current pregnancy	55 ☐ Current pregnancy
هل كان هذا الحمل لتوأم ؟			
1 ☐ No, singleton لا 2 ☐ Yes, Twin توأم ٢ 3 ☐ Yes, Triplet توأم ٣	1 ☐ No, singleton لا 2 ☐ Yes, Twin توأم ٢ 3 ☐ Yes, Triplet توأم ٣	1 ☐ No, singleton لا 2 ☐ Yes, Twin توأم ٢ 3 ☐ Yes, Triplet توأم ٣	1 ☐ No, singleton لا 2 ☐ Yes, Twin توأم ٢ 3 ☐ Yes, Triplet توأم ٣
4 ☐ Yes, higher number أكثر 9 ☐ Don't know لا أعلم	4 ☐ Yes, higher number أكثر 9 ☐ Don't know لا أعلم	4 ☐ Yes, higher number 9 ☐ Don't know لا أعلم	4 ☐ Yes, higher number 9 ☐ Don't know لا أعلم
ما هو جنس الطفل ؟			
1 ☐ Boy ذكر 2 ☐ Girl أنثى 9 ☐ Not known غير معلوم	1 ☐ Boy ذكر 2 ☐ Girl أنثى 9 ☐ Not known غير معلوم	1 ☐ Boy ذكر 2 ☐ Girl أنثى 9 ☐ Not known غير معلوم	1 ☐ Boy ذكر 2 ☐ Girl أنثى 9 ☐ Not known غير معلوم
كم كان عدد أسابيع الحمل ؟			
☐☐ weeks (+ ☐☐ days,) If known (Current gestation, if pregnant now)	☐☐ weeks (+ ☐☐ days,) If known (Current gestation, if pregnant now)	☐☐ weeks (+ ☐☐ days,) If known (Current gestation, if pregnant now)	☐☐ weeks (+ ☐☐ days,) If known (Current gestation, if pregnant now)
99 ☐ Don't remember لا أتذكر	99 ☐ Don't remember لا أتذكر	99 ☐ Don't remember لا أتذكر	99 ☐ Don't remember لا أتذكر
ما هو وزن الطفل عند الولادة ؟			
☐☐ ☐☐ OR ☐☐☐☐ lbs ozs grams ☐ Not known / Not applicable غير معلوم	☐☐ ☐☐ OR ☐☐☐☐ lbs ozs grams ☐ Not known / Not applicable غير معلوم	☐☐ ☐☐ OR ☐☐☐☐ lbs ozs grams ☐ Not known / Not applicable غير معلوم	☐☐ ☐☐ OR ☐☐☐☐ lbs ozs grams ☐ Not known / Not applicable غير معلوم
☐☐ Years	☐☐ Years	☐☐ Years	☐☐ Years
كم كان عمرك عند الولادة ؟			
☐ Same father نفس الأب ☐☐ day ☐☐ month ☐☐☐☐ year 9 ☐ Don't know لا أعلم	☐ Same father نفس الأب ☐☐ day ☐☐ month ☐☐☐☐ year 9 ☐ Don't know لا أعلم	☐ Same father نفس الأب ☐☐ day ☐☐ month ☐☐☐☐ year 9 ☐ Don't know لا أعلم	☐ Same father نفس الأب ☐☐ day ☐☐ month ☐☐☐☐ year 9 ☐ Don't know لا أعلم
كم كان عمر الأب عند ولادة الطفل ؟			
Please turn page for more questions about this pregnancy	**Please turn page for more questions about this pregnancy**	**Please turn page for more questions about this pregnancy**	**Please turn page for more questions about this pregnancy**

THIS SECTION ASKS ABOUT the WOMAN's PREGNANCIES 11 February 2003

	First pregnancy	Second pregnancy
i. Type of delivery: ما هو نوع الولادة ؟	1 ☐ طبيعي Vaginal 2 ☐ قيصرية C-birth	1 ☐ طبيعي Vaginal 2 ☐ قيصرية C-birth
j. Was the pregnancy planned? هل كان الحمل مخطط له ؟	1 ☐ نعم Yes 2 ☐ لا No 9 ☐ لا تتذكر Don't remember	1 ☐ نعم Yes 2 ☐ لا No 9 ☐ لا تتذكر Don't remember
→ If YES, how long did you try before you got pregnant? إذا كانت الإجابة نعم، كم كانت عدد المرات التي حاولت فيها ؟	1 ☐ Less than 3 months أقل من ٣ أشهر 2 ☐ 3 to 6 months من ٣ - ٦ أشهر 3 ☐ 7 to 12 months ٧ – ١٢ شهر 4 ☐ More than 12 months أكثر من ١٢ شهر 9 ☐ Don't remember لا تتذكر	1 ☐ Less than 3 months أقل من ٣ أشهر 2 ☐ 3 to 6 months من ٣ - ٦ أشهر 3 ☐ 7 to 12 months ٧ – ١٢ شهر 4 ☐ More than 12 months أكثر من ١٢ شهر 9 ☐ Don't remember لا تتذكر
k. Did this pregnancy result from fertility treatment? هل كان الحمل عن طريق الأنابيب ؟	1 ☐ نعم Yes 2 ☐ لا No 9 ☐ لا تتذكر Don't remember	1 ☐ نعم Yes 2 ☐ لا No 9 ☐ لا تتذكر Don't remember
→ If YES, please tick the type of fertility treatment you had إذا كانت الإجابة نعم، وضح الطريقة ؟ Include endometrial biopsy, D&C, dye in tubes, special test after intercourse, blood tests or laparoscopy in 'Other' Include male fertility treatment and/or advice in other	1 ☐ Drugs only (i.e. Clomid) أدوية فقط 2 ☐ IVF, GIFT or ICSI 3 ☐ AID, AIH, IUI with drugs to induce ovulation 4 ☐ AID, AIH, IUI without drugs to induce ovulation 5 ☐ Other (please specify)	1 ☐ Drugs only (i.e. Clomid) أدوية فقط 2 ☐ IVF, GIFT or ICSI 3 ☐ AID, AIH, IUI with drugs to induce ovulation 4 ☐ AID, AIH, IUI without drugs to induce ovulation 5 ☐ Other (please specify)
l. Were any abnormalities detected in the baby, either during the pregnancy or after birth? هل كان هناك أي مشكلة في الطفل سواء أثناء الحمل أو بعد الولادة ؟	1 ☐ Yes نعم 2 ☐ No لا 9 ☐ Not known غير معروف	1 ☐ Yes نعم 2 ☐ No لا 9 ☐ Not known غير معروف
→ If YES, please could you describe the problem/s إذا كانت الإجابة نعم، صفي المشكلة ؟		
m. Is this child still alive? هل ما زال الطفل على قيد الحياة ؟	1 ☐ نعم Yes 2 ☐ لا No 9 ☐ Not known غير معروف	1 ☐ نعم Yes 2 ☐ لا No 9 ☐ Not known غير معروف
→ If NO, please record date of death - code 15 if day unknown. Work with mother to determine best estimate of month and year إذا كانت الإجابة لا، ما هو يوم الوفاة ؟	☐☐ day ☐☐ month ☐☐☐☐ year	☐☐ day ☐☐ month ☐☐☐☐ year
n. During the pregnancy, did you have any bleeding or spotting with blood that lasted more than one day? في فترة الحمل، هل تعرضت للنزيف لمدة أكثر من يوم ؟	1 ☐ نعم Yes 2 ☐ لا No 9 ☐ غير معروف Not known	1 ☐ نعم Yes 2 ☐ لا No 9 ☐ غير معروف Not known
→ If YES, please could you describe the problem/s or treatment/s: إذا كانت الإجابة نعم، صفي المشكلة والعلاج ؟		
→ Did the doctor prescribe complete bed rest? هل نصح الطبيب بالراحة في السرير ؟	1 ☐ Yes نعم 2 ☐ No لا 9 ☐ Not known غير معروف	1 ☐ Yes نعم 2 ☐ No لا 9 ☐ Not known غير معروف
→ Did you take any medication for this bleeding? هل أخذت علاج للنزيف ؟	1 ☐ Yes 2 ☐ No 9 ☐ Not known	1 ☐ Yes 2 ☐ No 9 ☐ Not known
o. Were you diagnosed with any other health problems or given any medical treatment during this pregnancy? هل شخصت لك أي مشكلة صحية أو أعطي لك علاج خلال هذا الحمل ؟	1 ☐ نعم Yes 2 ☐ لا No 9 ☐ غير معروف Not known	1 ☐ نعم Yes 2 ☐ لا No 9 ☐ غير معروف Not known
→ If YES, please could you describe the problem/s or treatment/s: إذا كانت الإجابة نعم، صفي لنا المشكلة والعلاج ؟ EXCLUDE: Minor colds/flu covered elsewhere ما عدا البرد والأنفلونزا		
	Please continue onto next pregnancy, or to Question 67 if no more pregnancies	Please continue onto next pregnancy, or to Question 67 if no more pregnancies

THIS SECTION ASKS ABOUT the WOMAN's PREGNANCIES 11 February 2003

Third pregnancy	Fourth pregnancy	Fifth pregnancy	Sixth pregnancy
ما هو نوع الولادة ؟	ما هو نوع الولادة ؟	ما هو نوع الولادة ؟	ما هو نوع الولادة ؟
1 ☐ طبيعي 2 ☐ قيصرية Vaginal C-birth	1 ☐ طبيعي 2 ☐ قيصرية Vaginal C-birth	1 ☐ طبيعي 2 ☐ قيصرية Vaginal C-birth	1 ☐ طبيعي 2 ☐ قيصرية Vaginal C-birth
هل كان الحمل مخطط له ؟	هل كان الحمل مخطط له ؟	هل كان الحمل مخطط له ؟	هل كان الحمل مخطط له ؟
1 ☐ Yes 2 ☐ No 9 ☐ Don't remember	1 ☐ Yes 2 ☐ No 9 ☐ Don't remember	1 ☐ Yes 2 ☐ No 9 ☐ Don't remember	1 ☐ Yes 2 ☐ No 9 ☐ Don't remember
عدد المرات التي حاولت فيها ؟	إذا كانت الإجابة بنعم، كم كانت		
1 ☐ Less than 3 months أقل من ٣ أشهر	1 ☐ Less than 3 months أقل من ٣ أشهر	1 ☐ Less than 3 months أقل من ٣ أشهر	1 ☐ Less than 3 months أقل من ٣ أشهر
2 ☐ 3 to 6 months من ٣ - ٦ أشهر	2 ☐ 3 to 6 months من ٣ - ٦ أشهر	2 ☐ 3 to 6 months من ٣ - ٦ أشهر	2 ☐ 3 to 6 months من ٣ - ٦ أشهر
3 ☐ 7 to 12 months ٧ – ١٢ شهر	3 ☐ 7 to 12 months ٧ – ١٢ شهر	3 ☐ 7 to 12 months ٧ – ١٢ شهر	3 ☐ 7 to 12 months ٧ – ١٢ شهر
4 ☐ More than 12 months أكثر من ١٢ شهر	4 ☐ More than 12 months أكثر من ١٢ شهر	4 ☐ More than 12 months أكثر من ١٢ شهر	4 ☐ More than 12 months أكثر من ١٢ شهر
9 ☐ Don't remember لا أتذكر	9 ☐ Don't remember لا أتذكر	9 ☐ Don't remember لا أتذكر	9 ☐ Don't remember لا أتذكر
هل كان الحمل عن طريق الأنابيب ؟	هل كان الحمل عن طريق الأنابيب ؟	هل كان الحمل عن طريق الأنابيب ؟	هل كان الحمل عن طريق الأنابيب ؟
1 ☐ Yes 2 ☐ No 9 ☐ Don't remember	1 ☐ Yes 2 ☐ No 9 ☐ Don't remember	1 ☐ Yes 2 ☐ No 9 ☐ Don't remember	1 ☐ Yes 2 ☐ No 9 ☐ Don't remember
إذا كانت الإجابة بنعم، وضحي الطريقة ؟	إذا كانت الإجابة بنعم،		
1 ☐ Drugs only (i.e. Clomid) أدوية فقط	1 ☐ Drugs only (i.e. Clomid) أدوية فقط	1 ☐ Drugs only (i.e. Clomid) أدوية فقط	1 ☐ Drugs only (i.e. Clomid) أدوية فقط
2 ☐ IVF, GIFT or ICSI	2 ☐ IVF, GIFT or ICSI	2 ☐ IVF, GIFT or ICSI	2 ☐ IVF, GIFT or ICSI
3 ☐ AID, AIH, IUI with drugs to induce ovulation	3 ☐ AID, AIH, IUI with drugs to induce ovulation	3 ☐ AID, AIH, IUI with drugs to induce ovulation	3 ☐ AID, AIH, IUI with drugs to induce ovulation
4 ☐ AID, AIH, IUI without drugs to induce ovulation	4 ☐ AID, AIH, IUI without drugs to induce ovulation	4 ☐ AID, AIH, IUI without drugs to induce ovulation	4 ☐ AID, AIH, IUI without drugs to induce ovulation
5 ☐ Other (please specify)	5 ☐ Other (please specify)	5 ☐ Other (please specify)	5 ☐ Other (please specify)
هل كان هناك اي مشكلة في الطفل سواء أثناء الحمل أو بعد الولادة ؟	هل كان هناك اي مشكلة في الطفل	سواء أثناء الحمل أو بعد الولادة ؟	هل كان هناك اي مشكلة في الطفل
1 ☐ Yes 2 ☐ No 9 ☐ Not known	1 ☐ Yes 2 ☐ No 9 ☐ Not known	1 ☐ Yes 2 ☐ No 9 ☐ Not known	1 ☐ Yes 2 ☐ No 9 ☐ Not known
إذا كانت الإجابة نعم، صفي المشكلة ؟	إذا كانت الإجابة نعم، صفي المشكلة ؟		
هل ما زال الطفل على قيد الحياة ؟	هل ما زال الطفل على قيد الحياة ؟	هل ما زال الطفل على قيد الحياة ؟	هل ما زال الطفل على قيد الحياة ؟
1 ☐ Yes 2 ☐ No 9 ☐ Not known	1 ☐ Yes 2 ☐ No 9 ☐ Not known	1 ☐ Yes 2 ☐ No 9 ☐ Not known	1 ☐ Yes 2 ☐ No 9 ☐ Not known
إذا كانت الإجابة لا، ما هو يوم الوفاة ؟	إذا كانت الإجابة لا،	ما هو يوم الوفاة ؟	إذا كانت الإجابة
day ☐☐ month ☐☐ year ☐☐☐☐	day ☐☐ month ☐☐ year ☐☐☐☐	day ☐☐ month ☐☐ year ☐☐☐☐	day ☐☐ month ☐☐ year ☐☐☐☐
في فترة الحمل، هل تعرضت للتزيف استمر أكثر من يوم ؟	في فترة الحمل، هل تعرضت للتزيف استمر أكثر من يوم ؟		
1 ☐ Yes 2 ☐ No 9 ☐ Not known	1 ☐ Yes 2 ☐ No 9 ☐ Not known	1 ☐ Yes 2 ☐ No 9 ☐ Not known	1 ☐ Yes 2 ☐ No 9 ☐ Not known
إذا كانت الإجابة نعم، صفي المشكلة و العلاج ؟	إذا كانت الإجابة نعم، صفي المشكلة و العلاج ؟		
هل نصح الطبيب بالراحة في السرير ؟	هل نصح الطبيب بالراحة في السرير ؟	هل نصح الطبيب بالراحة في السرير ؟	هل نصح الطبيب بالراحة في السرير ؟
1 ☐ Yes 2 ☐ No 9 ☐ Not known	1 ☐ Yes 2 ☐ No 9 ☐ Not known	1 ☐ Yes 2 ☐ No 9 ☐ Not known	1 ☐ Yes 2 ☐ No 9 ☐ Not known
هل أخذت علاج للتزيف ؟	هل أخذت علاج للتزيف ؟	هل أخذت علاج للتزيف ؟	هل أخذت علاج للتزيف ؟
1 ☐ Yes 2 ☐ No 9 ☐ Not known	1 ☐ Yes 2 ☐ No 9 ☐ Not known	1 ☐ Yes 2 ☐ No 9 ☐ Not known	1 ☐ Yes 2 ☐ No 9 ☐ Not known
هل شخصت لك اي مشكلة صحية و أعطي لك علاج خلال هذا الحمل ؟	هل شخصت لك اي مشكلة صحية و أعطي لك علاج خلال هذا الحمل ؟		
1 ☐ Yes 2 ☐ No 9 ☐ Not known	1 ☐ Yes 2 ☐ No 9 ☐ Not known	1 ☐ Yes 2 ☐ No 9 ☐ Not known	1 ☐ Yes 2 ☐ No 9 ☐ Not known
إذا كانت الإجابة نعم، صفي لنا المشكلة و العلاج ؟	إذا كانت الإجابة نعم، صفي لنا المشكلة و العلاج ؟		
ما عدا البرد و الأنفلونزا	ما عدا البرد و الأنفلونزا	ما عدا البرد و الأنفلونزا	ما عدا البرد و الأنفلونزا
Please continue onto next pregnancy, or to Question 60 if no more pregnancies	Please continue onto next pregnancy, or to Question 60 if no more pregnancies	Please continue onto next pregnancy, or to Question 60 if no more pregnancies	Please continue onto next pregnancy, or to Question 60 if no more pregnancies

18 March 2003

Study Form Log

Study Number or MRN: _____

Main Study Form	
Consent Form	
Pregnancy Form	6 12
Diabetes Form	
Consanguinity Form	
Cardiac Form (x number)	
Non-Cardiac Form (x number)	
Illness Form	
Registration Form 1	

Interviewer questions

What was the tempo of the interview? Was it leisurely or rushed? Were there people coming and going? Please describe:	
Did the Mother herself sign the consent form or did the Father? Did she offer it to him or did he express a desire to give the signature?	
Did you get a chance to document the consent process in the Medical Chart?	
Did you give a copy of the consent form to the parents?	
Who told you about the interview? Deema, Ahsan, Judi, etc. Was this a missed patient (September - February)? Was it an additional patient (June-August)?	
Where was the patient captured?	
Where was the interview performed?	

مستشفى الملك فيصل التخصصي
ومركز الأبحاث

KING FAISAL SPECIALIST HOSPITAL
AND RESEARCH CENTRE

Title of Proposal:
Consanginity and Disease

عنوان البحث :
زواج الأقارب و الأمراض الوراثية

Part I – Research Participant Information Sheet:

الجزء الأول – معلومات للمشارك في البحث:

A. Purpose of the Research:

الغرض من البحث:

To determine if a population with Congenital Heart Disease (CHD) has a higher or lower rate of Consanginity than a disease free population.

تحديد ما إذا كانت نسبة القرابة لدى المصابين بمرض القلب الخلقي أعلى أم أقل مما هي عليه لدى الأصحاء.

B. Description of the Research:

وصف البحث:

Case control study to assess the impact of consanguinity on CHD

دراسة حالات مقارنه لتقيم دور صلة القرابة في التشويه الخلقي لأمراض القلب

C. Potential Risks and Discomforts:

جـ المخاطر والانزعاجات المحتملة:

None

لا يوجد

D. Potential Benefits:

الفوائد المحتملة:

لا يوجد

None

E. Alternative to Participation (where applicable):

هـ البدائل عن المشاركة (إن وجدت):

لك الخيار في عدم المشاركة في هذه الدراسة.

You have the right not to participate

F. Cost/s Reimbursements:

التكاليف / التعويضات المالية:

You will bear no addition cost

مشاركتك في هذه الدراسة لن تتحمل أي تكاليف إضافية .

G. Termination of Participation (where applicable):

You are free to withdraw your data at any time.

ز. إنهاء المشاركة (إذا أمكن):
بإمكانك سحب المعلومات الخاصة بك في أي وقت تشاء

ORA
A
C

(ORA 5.1.5.2)
23Oct.2000

For ORA Official Use Only
INFORMED CONSENT FOR RESEARCH WITH NO DIRECT BENEFITS TO PARTICIPANT
This Consent Document is approved for use by the Research Ethics Committee of KFSH&RC
From: 28 September 2004
TO: 28 September 2005
991 031

إقرار بالموافقة على بحث
بدون فائدة مباشرة للمشاركين

RECEIVED
06 SEP 2003

H. Compensation / Treatment:

In the event of injury resulting from participation in the research study, hospitalization and professional attention, if these are required, will be provided at KFSH at no cost to you. Financial compensation from KFSH&RC is not available.

ح. التعويضات / المعالجات:

في حالة حدوث أي ضرر – لا قدر الله – من جراء المشاركة في هذه الدراسة سيتكفل مستشفى الملك فيصل التخصصي ومركز الأبحاث بتقديم الرعاية الطبية اللازمة أو التزويم بالمستشفى إذا لزم الأمر ولكنه لا يلتزم بمنح أي تعويضات مالية بديلة.

I. Voluntary Participation:

Participation in this study is voluntary. You will suffer no penalty nor loss of any benefits to which you are otherwise entitled should you decide not to participate. Withdrawal from this research study will not affect your ability to receive alternative methods of medical care available at KFSH&RC.

Significant new findings developed during the course of the research study which might be reasonably expected to affect your willingness to continue to participate in the research study will be provided to you.

ط. المشاركة التطوعية:

المشاركة في هذه الدراسة طوعيه وإذا قررت عدم المشاركة فانك لن تتعرض لأي مضايقات أو لفقدان حقك المشروع في المعالجة. كما أن قرارك بالانسحاب من الدراسة لن يؤثر على تلقيك لخدمة علاجية بديلة متوفرة في مستشفى الملك فيصل التخصصي ومركز الأبحاث.

سيتم إبلاغك بأي نتائج هامة جديدة تظهر خلال تطورات البحث مما قد يؤثر بطريقة معقولة على رغبتك في الاستمرار بالمشاركة في هذه الدراسة.

2. I acknowledge that I have read, or had explained to me in a language I understand, the attached Research Participant Information of this study and, the possible attendant discomforts, symptoms, side effects and risks reasonably to be expected

٢. أقر بأنني قد قرأت – أو شرح لي بلغة مفهومة لدي – هذه المعلومات المتعلقة بمشاركتي في هذا البحث وقد أوضح لي طبيعة وأهداف هذه الدراسة ومدي كونها تجريبية (إن كانت كذلك) والآثار الجانبية أو الانزعاجات أو الأعراض أو المخاطر المتوقع حدوثها وجميع المضاعفات الممكنة إن وجدت والناتجة عن أسباب معروفة أو غير معروفة مرتبطة بالدراسة كما أقر بأنه قد أتيحت لي الفرصة لتوجيه جميع الأسئلة المتعلقة بموضوع الدراسة وتلقيت الإجابات الشافية.

3. I understand that this study is not intended to be of any direct therapeutic benefit to me and I voluntarily accept the risks and discomforts associated with this study.

٣. أفهم بأن هذه الدراسات ليست لها أي فائدة علاجية مباشرة لي ومع ذلك أتطوع بالمشاركة فيها مع علمي بالمخاطر والانزعاجات الناتجة عنها.

4. I understand that I am entitled for reimbursement for expenses incurred as a result of my participation in this study

٤. من المفهوم لدي بأنني استحق استرداد المصروفات التي نتجت عن مشاركتي في هذه الدراسة.

5. I understand that I am free to withdraw this authorization and discontinue participation in this study at any time. I understand that such withdrawal will not affect my ability to receive any medical care made necessary by the performance of this studies or to which I might be otherwise entitled.

٥. وأفهم بأن لي مطلق الحرية بسحب هذا التفويض وإنهاء مشاركتي بهذه الدراسة في أي وقت أشاء مع علمي بجميع العواقب والمخاطر المترتبة على انسحابي من الدراسة (إن وجدت). كما أفهم بأن انسحابي من هذه الدراسة لن يؤثر على حقي في تلقي العناية الطبية اللازمة والتي تمنح للمشاركين بالدراسة أو استحقها في الأحوال العادية.

6. I grant this consent as a voluntary contribution in the interest of medical research.

6. أوافق على أن يكون هذا الإقرار كمشاركة طوعيه في هذا البحث الطبي

7. I confirm that I have read, or had read to me, the foregoing authorization and that all blanks or statements requiring completion were properly completed before I signed.

7. كما أؤكد بأنني قد قرأت – أو قرأ لي هذا التفويض وأن كل المعلومات اللازمة قد تمت تعبئتها بدقة قبل توقيعي عليه.

Patient/Surrogate Signature: _____

Date: _____

Print name: _____

Relationship: _____

(If signed by Surrogate)

توقيع المريض أو ولي الأمر: _____

التاريخ : _____

الاسم : _____

صلة القرابة : _____

8. I confirm that I have accurately translated and/ or read the information to the subject:

8. أقر بأنني قد قرأت / أو ترجمت للمشارك بدقة هذه المعلومات

Witness: _____
Signature

Print name: _____

شاهد: _____
التوقيع

الاسم (طباعة): _____

مركز الأبحاث

KING FAISAL SPECIALIST HOSPITAL
AND RESEARCH CENTRE

KFSH&RC ID#:_____

رقم البطاقة : _____

I have fully explained to the above volunteer/ relative/ surrogate the nature and purpose of the above-mentioned research program (including the fact that the study will not result in any direct therapeutic benefit).
I have offered to answer any questions relating to this study and have fully and completely answered all such questions.

أقر بأنني قد شرحت للمتطوع/ لقريبه/ أو ولي أمره المذكور أعلاه بصورة كاملة طبيعة وأهداف مشروع البحث المذكور والمتضمن عدم وجود فائدة مباشرة على المشارك والي أي مدي (إن وجد) هي دراسة تجريبية. كما قد شرحت للمضاعفات المحتمل حدوثها من جراء هذه الدراسة سواء كانت لأسباب معروفة أو غير معروفة. والعواقب والمخاطر المترتبة (إن وجدت) إذا قرر المتطوع إنهاء مشاركته بالدراسة . كما إنه من المفهوم لدي بأنه قد فهم طبيعة الدراسة والغرض منها والمخاطر الناتجة عنها وذلك قبل توقيعه على الموافقة بالمشاركة ، ولقد قمت بتوضيح استعدادي للإجابة على أي أسئلة متصلة بهذه الدراسة ، وقمت فعلا بالإجابة الشافية على جميع أسئلته المتعلقة بالدراسة.

Signature of Principal Investigator/ Delegate:

_____

(Print Name): _____

Date: _____

توقيع الباحث الرئيسي:

_____

الاسم (طباعة): _____

التاريخ: _____

ORA
A
C

For ORA Official Use Only
INFORMED CONSENT FOR RESEARCH WITH NO DIRECT BENEFITS TO PARTICIPANT
This Consent Document is approved for use by the Research Ethics Committee of KFSH&RC

(ORA 5.1.5.2)
23Oct 2000

From: 28 September 2004
TO: 28 September 2005
991 031

إقرار بالموافقة على بحث
بدون فائدة مباشرة للمشاركين

Consanguinity and Disease

Departments of Biostatistics, Epidemiology & Scientific Computing, Cardiovascular Diseases, Pediatrics and Obstetrics and Gynaecology

CARDIAC FORM

Study Number or MRN: .....

Participants's name: _____

1	Question number from questionnaire رقم السؤال في الاستمارة		

Questions	Coding Categories		SKIP TO
2 Identify Subject (1) Mother الام (2) Father الاب (3) Mother's mother اخت من الام (4) Mother's father اخت من الاب (5) Father's mother اخت من الام (6) Father's father اخ من الاب (7) Mother's full sister or full brother (8) Father's full sister or full brother لا شقيقات او اشقاء الام. لا شقيقات او اشقاء الاب	(9) Mother's half sister or half brother - Paternal (10) Mother's half sister or half brother - Maternal (11) Father's half sister or half brother - Paternal (12) Father's half sister or half brother - Maternal (13) Cousin (14) Other		
3 If other, please specify اذا احصائي اخرى يرجى التوضيح	_____		
4 What did the doctor(s) call this heart condition? ماذا اطلقة الاطباء على الحالة ؟	_____ _____ _____		

5 ما هي الامراض أو الصعوبات الغير طبيعية الملاحظة ؟ What symptoms, difficulties or physical findings were noted?	Symptom	Yes	No	Unknown
	a. Murmur			
	b. Shortness of breath			
	c. Blue lips			
	d. Blue nail beds			

6 How old were you (was he/she) when the diagnosis of this condition was made? كم كان عمر المفحوص عند تشخيص حالته ؟	_____ _____ _____		
7 Were you (he/she) taken care of by a هل كان المفحوص يعالج من قبل ؟	Heart specialist	1	
	Regular physician	2	
	Unknown	9	
8 Is the condition still present? هل مازالت الحالة قائمة ؟ *If "murmur went away", "innocent", "functional" or "normal", stop here*	Yes	1	
	No	2	
	Unknown	9	

اخت أو اخ الام من الاب
اخ او اخت الام من الام
" " " الاب من الاب
" " " الاب من الام
اشقاء الصحيحة او الخال
غير ذلك .

Consanguinity and Disease

Departments of Biostatistics, Epidemiology & Scientific Computing, Cardiovascular Diseases, Pediatrics and Obstetrics and Gynaecology

9	Were any of thse tests done to diagnose this condition? هل اجريل اي من هذة الفحوصات لتشخيص الحالة؟	Diagnostic Test	Yes	No	Unknown
		a. Electrocardiogram			
		b. Echocardiogram			
		c. Cardiac catheterization			
10	Were you (was he/she) admitted to a hospital for this condition? هل ادخلت المستشفى بسبب هذة الحالة؟	Yes	1		
		No	2		
		Unknown	9		
11	Did you (he/she) have a heart operation? هل اجريت له عملية قلب؟	Yes	1		
		No	2		
		Unknown	9		
12	If yes, please specify اذا كانت الاجابة نعم وضح	_____	⌊⌋		
13	Were you (was he/she) given any heart medicine such as digitalis? هل اعطيت بعض ادوية القلب مثل:	Yes	1		
		No	2		
		Unknown	9		
14	If yes, please specify اذا كانت الاجابة نعم وضح	_____	⌊⌋		
15	Were you (was he/she) advised to take any special precautions because of your (his/her) heart, such as taking penicillin before dental work? هل نصحت بالاخذ اي احتياطات بسبب قلبك مثل	Yes	1		
		No	2		
		Unknown	9		
16	If yes, please specify اذا الاجابة نعم وضح	_____	⌊⌋		
17	Is _____ living now? هل المقصود مازال على قيد الحياة؟	Yes	1		
		No	2		
		Unknown	9		
18	If no, اذا الاجابة لا	How old was he/she at the time of death? كم كان عمر المقصود عند حدوث الوفاة؟	____		
19	Cardiac Disease Code (0) No heart disease (1) Looping abnormaliites (2) Major septation/conotruncal (3) Atresia/hypoplasias (4) Stenotic/valve lesions (5) Septal defect/ductus (6) Other great vessel, coronary (7) Miscellaneous (8) Non-study lesion (9) Unknown	_____	⌊⌋		

١- تخطيط القلب
٢- اشعة صوتية
٣- قسطرة

Consanguinity and Disease

Departments of Biostatistics, Epidemiology & Scientific Computing, Cardiovascular Diseases, Pediatrics and Obstetrics and Gynaecology

Non-CARDIAC FORM

Study Number or MRN: .....

Identification
Participants's name: _____

1	Question number from questionnaire رقم السؤال في الاستماره ؟		⌊⌊

Questions	Coding Categories		SKIP TO
2 Identify Subject حدد الشخص أو المقصود بالسؤال ؟	Mother الأم	1	
	Father الأب	2	
	Mother's mother الجده من الأم	3	
	Mother's father الجد من الأب	4	
	Father's mother الجده من الأب	5	
	Father's father الجد من الأب	6	
	Mother's full sister or full brother شقيق أو شقيقة الأم	7	
	Father's full sister or full brother شقيق أو شقيقة الأب	8	
	Mother's half sister or half brother Paternal أخ أو أخت الأم من الأب	9	
	Mother's half sister or half brother Maternal أخ أو أخت الأم من الأم	10	
	Father's half sister or half brother Paternal أخ أو أخت الأب من الأب	11	
	Father's half sister or half brother Maternal أخ أو أخت الأب من الأم	12	
	First cousin أبناء عمومة أو أخوال	13	
	Other علاقة أخرى	14	
3 If other, please specify إذا أجابة ضمن علاقة أخرى الرجاء الترتيب	_____	⌊⌊	
4 What did the doctor(s) call this condition? ماذا أطلق الأطباء على هذه الحالة	_____ _____ _____	⌊⌊	
5 How old were you (was he/she) when the diagnosis of this condition was made? كم كان عمر الشخص بالسؤال عندما تشخص المرض ؟	_____ _____ _____	⌊⌊	

Consanguinity and Disease

Departments of Biostatistics, Epidemiology & Scientific Computing, Cardiovascular Diseases, Pediatrics and Obstetrics and Gynaecology

Questions	Coding Categories		SKIP TO
6 Describe any symptoms or difficulties due to this condition وضحي لنا الاعراض او الصعوبات المتعلقة بهذه المشكلة			
7 Were you (he/she) taken care of by a هل كان (المعني بالسؤال) يعالج من قبل	Specialist أخصائي	1	
	Regular physician طبيب عام	2	
	Unknown لا أعرف	9	

8 Were any of these tests done to diagnose this condition? هل أجريت أي من هذه الفحوصات لتشخيص الحالة؟	Diagnostic Tests Performed	Yes	No	Unknown
	a. Chromosome (genetic, cytogenetic) اختبار الجينات			
	b. Blood test for clotting problem, abnormal hemoglobin			
	c. Other: x-ray, CT scan, MRI, ultrasound			

اختبار تخثر الدم ← نسمة صدر، أشعة مقطعية للرأس →

9 Were any special treatments given هل اعطيت اي العلاج خاص؟	Diagnostic Tests Performed	Yes	No	Unknown
	a. Surgery عملية			
	b. Cast or braces ...			
	c. Special education تعليم خاص (تربية)			
	d. Medication(s) أدوية			
	e. Special diet نظام غذائي خاص			

10 Is _____ living now? هل المتوفى ما زال على قيد الحياة؟	Yes نعم	1	
	No لا	2	
	Unknown غير معروف	9	

11 If no, اذا كانت الاجابة لا	How old was he/she at the time of death?	____	

لا كم كان عمر المتوفى عند الوفاة؟

12 Malformation Code (1) (2) تشوه خلقي			

Diabetes Supplement

Study Number or MRN: .....

Questions	Coding Categories		SKIP TO
1s How well is your diabetes controlled? كيف كانت عملية ضبط السكر ؟	Good جيد	1	
	Poor ضعيف	2	
	Unknown غير معروف	9	
2s Did you have any hypoglycemic attacks during the pregnancy with this child? هل عانيت من انخفاض السكر مما يصل إلى حالة اغماء اثناء فترة الحمل بهذا الطفل؟	Yes نعم	1	
	No لا	2	73
	Unknown غير معروف	9	
3s If yes, try to remember the very first time this occurred during this pregnancy. What week was it? اذا كانت الاجابة نعم تذكري أول حالة اغماء خلال هذا الحمل في أي اسبوع ؟	Week (Don't know = 98)	⌊⌊⌋⌋	
4s Or, try to remember the month of pregnancy أو حاولي تذكر اي شهر حمل ؟ *Interviewer:* Ask only if 3s unknown otherwise Interviewer to complete بيان في حالة الاجابة غير معروفة (اترك فارغ)	Month (Don't know = 98)	⌊⌊⌋⌋	
5s Or, try to remember the trimester of pregnancy حاولي تذكر فترة الحمل ؟ *Interviewer:* Ask only if 3s and 4s unknown otherwise Interviewer to complete بيان اذا كانت الاجابة غير معروفة (اترك فارغ)	Trimester (Don't know = 98)	⌊⌊⌋⌋	
6s Did you have any hyperglycemic attacks during the pregnancy with this child? هل عانيتي من ارتفاع في السكر مما تم وصفه كحالة اغماء في فترة الحمل ؟	Yes نعم	1	
	No لا	2	79
	Unknown غير معروف	9	
7s If yes, try to remember the very first time this occurred during this pregnancy. What week was it? اذا كانت الاجابة بنعم .. تذكري أول حالة اغماء خلال هذا الحمل في أي اسبوع)	Week (Don't know = 98)	⌊⌊⌋⌋	
8 Or, try to remember the month of pregnancy أو حاولي تذكر اي شهر حمل ؟ *Interviewer:* Ask only if 7s unknown otherwise Interviewer to complete	Month (Don't know = 98)	⌊⌊⌋⌋	
9 Or, try to remember the trimester of pregnancy حاولي تذكر فترة الحمل *Interviewer:* Ask only if 7sand 8s unknown otherwise Interviewer to complete	Trimester (Don't know = 98)	⌊⌊⌋⌋	
10 How old were you when you were diagnosed with diabetes? كم كان عمرك عندما شخص السكر ؟	Record age at diagnosis	⌊⌊⌋⌋	

Diabetes Supplement

Questions	Coding Categories		SKIP TO
11 If you have diabetes, what type is it? اذا كان عندك سكر، من اي نوع	Type I المعتمد على الانسولين	1	
	Type II غير المعتمد على الانسولين	2	
	Gestational (only when pregnant) سكر حمل	3	
	Unknown لا اعرف	9	
12 How was your diabetes controlled during your pregnancy? خلال فترة الحمل كيف كانت عملية ضبط السكر؟	Diet حمية	1	
	Tablets حبوب	2	
	Insulin injections ابر انسولين	3	

Other Illnesses

—	For each of the following ask a. Have you ever had _____ ؟ هل اصبت بأي مرض b. If yes, did you receive any treatment for this? ؟ اذا كانت الاجابة نعم ، هل تناولت علاج If yes, complete the following table below: اذا كانت الاجابة نعم ـ أكمل الجدول التالي : c. Did you have _____ in the 6 months before or during your pregnancy. هل اصبت بـ ... ـــ If yes, في الـ ٦ أشهر السابقة لحملك d. Did you take medication during that time period? If yes, enter in drug table, p. 18 هل استعملت دواء أثناء تلك الفترة ؟

		Ever مطلقاً					Reference period مرجع				
		Illness مرض		Treatment دواء			Illness مرض		Medication دواء		
		Yes	No	NA	Yes	No	Yes	No	NA	Yes	No
1	Thyroid Disease امراض الغده الدرقيه specify _____										
2	Epilepsy (seizures) امراض الصرع										
3	Systemic lupus (SLE) الذئبه الحمراء										
4	Scleroderma وذمه صلبه (خزب سقلب)										
5	Cancer سرطان specify _____										

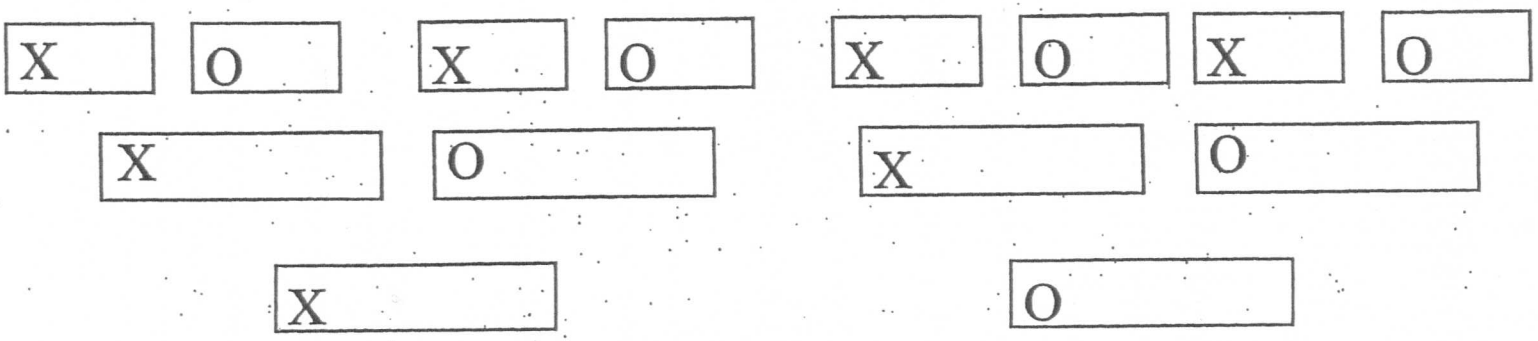
		Age at onset العمر عند البدء	Duration in years فترة استمرار المرض
—	How old were you when you were diagnosed with كم كان عمرك عندما تأكد اصابتك بـ ؟ _____?		
—	How old were you when you were diagnosed with _____?		

Study Number

Pedigree Supplement

X - Fathers

O - Mothers



Study Participant

Informant: 1=Mother, alone

Consanguinity code:

18 March 2002/Sandridge/EDU/BESC/KFSH&RC

Statistica, anno LX, n. 4, 2000

COLLECTING PEDIGREE INFORMATION IN AN EPIDEMIOLOGICAL CONTEXT

Amy L. Sandridge

1. INTRODUCTION

There is evidence which suggests that the custom of endogamy contributes a negative influence on population morbidity. Jaber *et al.* (1992) found that 16% of the offspring resulting from first cousin marriages had major malformations as compared with 4% of offspring of marriages where the spouses were from different villages and therefore unlikely to be related. It was reported in 1995 that the prevalence of inbreeding of parents of patients with multiple handicaps was 66% versus 50% among patients without multiple handicaps (Abu-Rezq HAS *et al.*). An increase was found among consanguineous couples in prenatal and neonatal losses although these were not statistically significant (Al-Awadi, 1986). In Saudi Arabia at least four studies have been conducted. Two descriptive studies have looked at rates of consanguinity (Tabbara *et al.*, 1988; MOH, 1996) and two have looked at differences in disease rates (Chalebey and Tuma, 1987; Panter-Brick, 1991). The Chalebey and Tuma study looked at the rate of positive family history of schizophrenia in a group of consanguineous schizophrenics and a group of non-consanguineous schizophrenics and found a higher rate among the consanguineous schizophrenics. The Panter-Brick study found that of the 36 parents of children with neuro-metabolic disorders studied 32 of them were consanguineous.

Despite the perceived dangers, consanguineous marriages still occur. Various hypotheses have been suggested for this preference which include property (both bridewealth and inheritance), ease of arrangement of pre-nuptial agreements and a belief that compatibility between husband and wife and bride and mother-in-law will be enhanced (Dronamraju and Meera Khan, 1963; Khlat *et al.*, 1986). With respect to property considerations the suggestion has been made that patrilineal cousin marriage is preferred because it is the property of the grandfather which is being preserved (Granqvist, 1931; Rosenfeld, 1957). Political support has also been suggested as an explanation of the practice (Barth, 1954). Another reason found has been the conviction that by marrying within the extended family there is less uncertainty regarding health and other unfavorable family characteristics (Bittles *et al.*, 1991; Al Rowais, personal communication, 1998).

As a development of the concept of increased political support arising from

patrilateral parallel cousin marriage, Murphy and Kasdan (1959) have argued that this practice is an essential component of the structure of Arabian society. Musil (1928) found that if there is no suitable patrilateral parallel cousin available then the marriage of a woman will be to the nearest kinsman descended from the brothers of the paternal grandfather or great-grandfather. Ayoub's finding (1957) that mother's sister's daughter marriage occurs among Lebanese peasants can be understood to be similar in effect if the dominant preference within the system is patrilateral parallel cousin marriage. Where a cross cousin marriage has been constructed often there is also a second degree patrilateral parallel cousin marriage (PP2C) and this may in fact be the reason for the choice (Murphy and Kasdan, 1959).

If there is underlying danger associated with marriage between relatives it is not well documented. Adverse health effects are believed to be the result of the expression of rare, recessive genes inherited from a common ancestor that when contributed from both the mother and the father will result in the defect. This implies coincidence rather than determinism. While this area of genetics, mapping of the human genome, is still in its infancy, the absolute risks of abnormal offspring for marriages between first cousins is less than double the overall population risk for marriages between unrelated persons. Consanguinity at the level of third cousins or more remote relationships is not considered genetically significant (Thomson *et al.*, 1991). As Al Awadi *et al.* (1985) discuss, in populations where such marriage traditions have existed for a long time there might in fact be an increase in the normal homozygotes, due to natural selection.

Descriptive evidence of the prevalence of first cousin marriages within human populations is limited. In particular, no one has investigated whether some pairings carry more danger than others. Anecdotally, in Arabian society it is a belief that it is less risky in terms of health outcomes for a man to marry his child to his brother's child than for a woman to marry her child to her sister's child. The Saudi Arabian health service recognizes that first cousin marriage may contribute negatively to the health of the people specifically if it is a phenomenon repeated generation after generation within a closed sub-set of the larger society (Al Rowais, personal communication, 1998). The hypothesis that there may be more danger for some pairings is a novel one and relevant research is quite limited. Only one team previously has counted the occurrences of specific first cousin pairings (Al-Awadi *et al.*, 1985).

The King Faisal Specialist Hospital and Research Centre (KFSH&RC) inaugurated a Congenital Heart Disease Registry (CHDR) in 1998 (KFSH&RC, 1999). For the first year of the registry (January, 1998-January 1999) data was collected on consanguinity limiting the codes to 'first cousin', 'second cousin' and 'other related'. Two problems were exposed and then addressed by an expansion of codes and a detailed documentation of the pedigree. The first problem was related to basic use of kinship terminology and the second to multiple consanguineous marriages for a single descendent.

Kinship terminology has long been the province of anthropology and ethnography. Anthropologists have determined that societies tend to be endogamous or ex-

ogamous manifested by preferential marriage patterns. These marriage patterns lead to referencing one group of people with the same kinship term as would be used for a specific relationship (Parkin, 1997). For example, it might be common to refer to the women of a woman's peer group as her 'sisters' when in fact some of them are the daughters of her mother's sisters and others are not related to her at all or for a man to refer to all the women of his mother's peer group as his 'mothers'.

In Saudi Arabia kinship terms are used loosely, a tendency which may be exacerbated when the native Arabic speaking person is being interviewed in a language foreign to him/her. An older male relative may be referred to as an 'uncle' when in fact that man is a cousin. During the first year of data collection for the CHDR, a misunderstanding in this expression of affinity led to marital relationships being wrongly classified as 'uncle-niece' – an arrangement which is not embraced by Islam.

A second problem with kinship terminology is that informants may know that they are related by blood to their spouses but may not know what to call that relationship. For example, the distinction between 'first cousin once removed' and 'second cousin' is not facilely describable (figure 1).

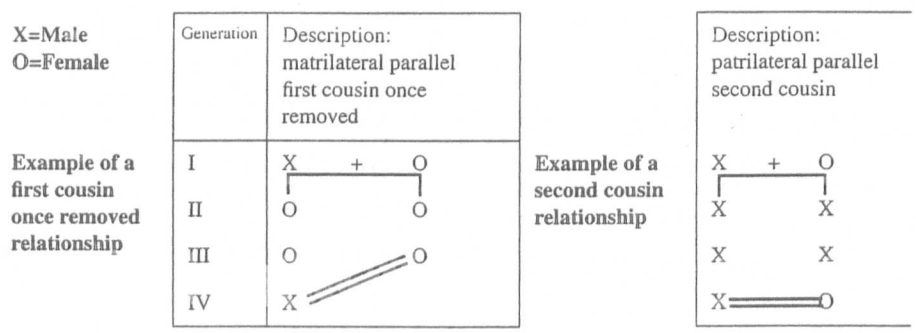


Figure 1 – Diagrams of first cousin once removed and second cousin.

Secondly, an erroneous kinship term may be applied from a demonstration of affinity rather than a definition of consanguinity. An example of this would be if a person married the first cousin of his brother's wife (if that wife were unrelated to the brother) but referred to her as his 'cousin' as well as his wife. Thirdly, the use of the word 'cousin' when it means that two of a couple's parents took at least five breast feeds (meals) from the same woman must be weeded out from the category of consanguinity (i.e., *milk cousins*).

The second difficulty in collecting information on consanguinity is that a husband and a wife are able to be both first cousins and second cousins at the same time depending on the reference relative (figure 2). Relationships of this complexity do not have simple descriptive names such as 'first cousin'. However, if they are identified through a chart then they can be defined and grouped into coefficients of relationship.

Example of simultaneous first cousin (mothers are sisters) and patrilateral parallel second cousin (PP2C) marriage

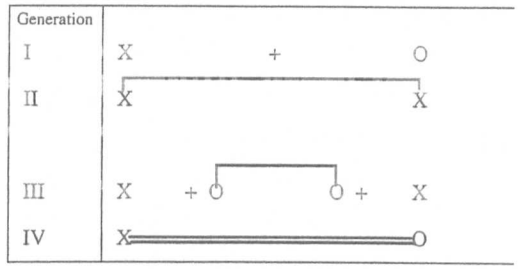


Figure 2 – Diagram of first cousin simultaneous with second cousin.

2. METHOD

The mother or father of the child is asked by a native Arabic speaking interviewer if s/he is related by blood to the co-parent of the child. If the answer is "yes" then the interviewer will work with the informant(s) to record the ancestry until the relation is identified. The informant will be encouraged to explain double relationships where they exist as in figure 2. If the relationship is an easily defined first cousin relationship then it is assigned a code. If it is complex then the pedigree is brought to the investigator's attention for code assignment. Half-sibling relationships are routinely sought. For first cousins, the anthropological concepts of parallel, cross, matrilineal and patrilineal have been used with the expansion of 'cross-cousin' into the two possible types as well as the use of double first cousin and double cross first cousin giving a total of 6 marital patterns resulting in offspring who will be true first cousins.

3. RESULTS

Of 1491 CHD patients registered since the introduction of the new method of pedigree collection 815 sets of parents stated that they were non-consanguineous (55%) (Two of the non-consanguineous parents stated they were *milk cousins*); and 676 stated they were consanguineous. Of the 676, 509 described relationships identified as first cousins (34%); 20 (1%) described double first cousins; 63 (4%) described relationships which are identified as first cousins once removed or first degree step cousins; 77 (5%) described second cousin relationships and 7 (< 1%) described relationships less close than second cousins. The largest pattern of consanguinity found was patrilateral parallel first cousin ($n = 282$; 42% of 676). This was followed by cross cousin of the type where a woman marries her son to her brother's daughter ($n = 104$; 15%). The third largest category was cross cousin of the type where a woman marries her daughter to her brother's son ($n = 67$; 10%). The fourth most common type was patrilateral parallel second cousin (PP2C) ($n = 58$; 9%). Of the 676 consanguineous marriages 374 of them were conducted on patrilateral lines or did not deny patrilaterality even if there was another relationship as well. Examples of patrilaterality would be simple first cousin patrilateral parallel, patrilateral parallel first cousin once removed, patrilateral parallel second, third or fourth cousin. Com-

plex relationships included cross cousin (first) with PP2C; and matrilateral parallel first cousin with PP2C. The number of different patterns documented was 42 with 13 patterns of first cousin once removed and 10 patterns of second cousin.

4. DISCUSSION

This investigation, initiated to address a concern over the classification of first cousins once removed, found less total consanguinity than other studies conducted in Saudi Arabia (table 1). Except for the Bedouin population studied by Tabbara ([1]) the percentage of first cousin marriages appears consistent from study to study but a smaller percentage of 'other consanguineous related' couples was found in the CHD data (around 11% as compared to 25, 30 and 21).

There are several motivating factors for the development of this method. KFSH&RC is interested in collecting data on genetic relationships however the resources are not available as of yet to collect this data routinely. Nevertheless with this method in specific studies it is possible to collect the data which may lead to hypothesis generation. Secondly, this method's precision and lack of ambiguity should be a contribution to other researchers. Thirdly, this method allows for testing the hypothesis that some marriage patterns hold more risk than others with respect to congenital heart disease.

A study to compare this population with a population without CHD is in preparation.

TABLE 1

Comparison of Saudi Arabian Consanguinity Statistics

Description of Consanguinity	KFSH&RC		Tabbara *et al.*		MOH	
	CHD Data		General	Bedouin	SAFHS	
	N	%	% (*)	% (*)	N	%
Non-consanguineous	815	55	47	11	6095	48
First cousin	509	34	28	59	3936	31
Double cousin or closer	20	1				
First cousin once removed	63	4				
Second cousin	77	5	5	7		
Less close than second cousin	7	< 1				
Other, not otherwise specified			20	23	2667	21
Total Consanguinity		45	53	89		52
Total	1491	100	100	100	12698 (**)	100

(*) *N* not reported.
(**) Ever-married women under 50 years of age

Department of Biomedical Statistics and Scientific Computing,
King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia
AMY L. SANDRIDGE

([1]) Identification of the *Bedouin* community at this point of Saudi Arabia's history is not straightforward (Al Rowais, personal communication, 1998) and therefore constitutes an unknown fraction of both the CHD data and the SAFHS data.

ACKNOWLEDGEMENTS

The author would like to acknowledge the contribution of Mr. Waieeh Mitri, Scientific Computing, BSSC as the Project Leader for the web based CHD Registry, Dr. Corazon Molina and Mrs. Nadya Khafagah, Research Data Management, BSSC for their implementation of the method and collection of the data, and Mr. Abdallah Al Rowais, Epidemiology, BSSC (formerly MOH) for his comments regarding this work. The KFSH&RC Congenital Heart Disease Registry Committee was very kind to supply access to the data.

REFERENCES

H.A.S. ABU-REZQ, A.A.H. AL-TARKAIT, N.I.K. HUSIEN, B. QASRAWI, Z. RADOVANOVIC (1995), *Multihandicap and consanguinity in Kuwait: a case-control study (letter)*, "Annals of Saudi Medicine", 15, 2, pp. 189-91.

S.A. AL-AWADI, M.A. MOUSSA, K.K. NAGUIB, T.I. FARAG, A.S. TEEBI, M. EL-KHALIFA, L. EL-DOSSARY (1985), *Consanguinity among the Kuwaiti population*, "Clinical Genetics", 27, pp. 483-486.

S.A. AL-AWADI, K.K. NAGUIB, M.A. MOUSSA, T.I. FARAG, A.S. TEEBI, M.Y. EL-KHALIFA (1986), *The effect of consanguineous marriages on reproductive wastage*, "Clinical Genetics", 29, pp. 384-388.

A. AL-ROWAIS, ABDULLAH (1998), *Personal Communication. Epidemiologist*, Ministry of Health, Kingdom of Saudi Arabia.

M. AYOUB (1957), *Endogamous marriage in a Middle Eastern village*, PhD dissertation, Harvard University, cited in Murphy and Kasdan, 1959.

F. BARTH (1953), *Principles of social organization in Southern Kurdistan*, Universitetets Etnografiske Museum Bulletin n. 7, Oslo, cited in Murphy and Kasdan, 1959.

A.H. BITTLES (1991), *Reproductive behavior and health in consanguineous marriages*, "Science", 252, pp. 789-794.

A.H. BITTLES (1994), *The role and significance of consanguinity as a demographic variable*, "Population and Development Review", 20, 3, pp. 561-584.

K. CHALEBY, T.A. TUMA (1987), *Cousin marriages and schizophrenia in Saudi Arabia*, "British Journal of Psychiatry", 150, pp. 547-549.

K.R. DRONAMRAJU, P. MEERA KHAN (1963), *The frequency and effects of consanguineous marriages in Andhra Pradesh*, "Journal of Genetics", 58, pp. 387-401, cited in Bittles, 1994.

H. GRANQVIST (1931), *Marriage conditions in a Palestinian village*, Helsingfors, Commentationes Humanarum, Scietas Scientarium Fennica, 3, cited in Murphy and Kasdan, 1959.

L. JABER, P. MERLOB, X. BU, J.I. ROTTER, M. SHOHAT (1992), *Marked parental consanguinity as a cause for increased major malformations in an Israeli Arab community*, "American Journal of Medical Genetics", 44, pp. 1-6.

M. KHLAT, S. HALABI, A. KHUDR, V.M. DER KALOUSTIAN (1986), *Perception of consanguineous marriages and their genetic effects among a sample of couples from Beirut*, "American Journal of Medical Genetics", 25, pp. 299-306.

KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE (KFSH&RC) (1999), *Congenital heart disease registry preliminary report*, Biomedical Statistics and Scientific Computing, Research Data Management technical report.

MINISTRY OF HEALTH (MOH) (1996), *Kingdom of Saudi Arabia, Saudi Arabia family health survey 1996, preliminary report*, edited by T.A. KHOJA, S.M. FARID.

R.F. MURPHY, L. KASDAN (1959), *The structure of parallel cousin marriage*, "American Anthropologist", 61, pp. 17-29.

A. MUSIL (1928), *The manners and customs of the Rwala Bedouins*, New York, American Geographical Society. Oriental Explorations and Studies, n. 6, cited in Murphy and Kasdan, 1959.

C. PANTER-BRICK (1991), *Parental responses to consanguinity and genetic disease in Saudi Arabia*, "Social Science and Medicine", 33, 11, pp. 1295-1302.

R. PARKIN (1997), *Kinship: an introduction to the basic concepts*, Blackwell, London.

H. ROSENFELD (1957), *An analysis of marriage statistics for a Moslem and Christian Arab village*, International Archives of Ethnography, 48, pp. 32-62, cited in Murphy and Kasdan, 1959.

TABBARA *et al.* (1988), *Unpublished research King Khalid Eye Specialist Hospital national survey*, cited in C. Panter-Brick, 1991.

M.W. THOMPSON, R.R. MCINNES, H.F. WILLARD (1991), *Thompson and Thompson Genetics in Medicine*, Fifth edition, W.B. Saunders Company.

RIASSUNTO

La raccolta di informazioni sull'albero genealogico in contesto epidemiologico

Viene sviluppato un metodo che documenta le relazioni di consanguineità in una data popolazione. I risultati ottenuti da dati raccolti sui genitori di pazienti registrati presso il Congenital Heart Disease Registry a KFSH e RC, Riyadh, Arabia Saudita, mostrano un numero atteso di genitori che sono primi cugini ma un numero minore di quello noto in letteratura di matrimoni tra consanguinei con altra parentela.

SUMMARY

Collecting pedigree information in an epidemiological context

A method has been developed which documents consanguineous relationships in any population. Results from data collected from parents of patients registered in the the Congenital Heart Disease Registry at KFSH&RC, Riyadh, Saudi Arabia show an expected number of parents who described a pattern of relationship consistent with a first cousin relationship but fewer numbers of 'other related' than previously reported in the literature. Further studies are in preparation.

Royal Statistical Society

JOURNAL OF THE ROYAL STATISTICAL SOCIETY

Series B (Statistical Methodology) Volume 62, Part 4, 2000

CONTENTS

RIVISTA DI POLITICA ECONOMICA

Anno XC - Serie III - Dicembre 2000 Fascicolo XII

SOMMARIO