The effect of overweight and obesity on fecundity and pregnancy outcome amongst women in Sub-Saharan Africa

Jennifer Anne Cresswell

March 2011

Thesis submitted for the degree of Doctor of Philosophy

Faculty of Epidemiology and Population Health

London School of Hygiene and Tropical Medicine

I, Jennifer Anne Cresswell, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Background: Obesity is an emerging public health concern in Sub-Saharan Africa and adult women are the population group most likely to be obese. Previous research conducted in high-income countries has demonstrated that high body mass index (BMI) has an adverse effect on a large number of reproductive outcomes; however no study has investigated this in Sub-Saharan Africa.

Methods: Cross-sectional data of women (15-49 years) from twenty-seven countries in Sub-Saharan Africa, collected through the Demographic and Health Surveys, were used to examine the effect of BMI on female fecundity and adverse pregnancy outcomes. Underweight women (BMI <18.5kg/m^2) were excluded. Multivariable regression models were used to examine four outcomes: (i) subfertility; (ii) time to first conception; (iii) caesarean delivery; (iv) neonatal death. The fecundity results were supplemented with a systematic review on the effect of BMI on waiting time to conception.

Results: Increased BMI was associated with significantly increased odds of subfertility (Obese OR: 1.51; 95% CI: 1.35-1.69). Five years after first marriage, 17% of non-contracepting obese (BMI ≥30kg/m^2) and 12.5% of pre-obese women (BMI 25-29.9kg/m^2) had yet to conceive compared to 9.3% of optimal women (BMI 18.5-24.9kg/m^2); however this difference was not statistically significant (p=0.5378).

Each unit increase in maternal BMI (kg/m^2) was significantly associated with a 7% increase in the odds of caesarean delivery (OR: 1.07; 95% CI: 1.06-1.08). Maternal obesity was significantly associated with increased odds of neonatal death (OR: 1.52; 95% CI: 1.18-1.97). The association was strongest for deaths occurring in the first week of life to infants delivered vaginally (OR: 2.43; 95% CI: 1.43-3.88).

Conclusions and Implications: Increased BMI is associated with adverse reproductive outcomes in the Sub-Saharan context. The risk is particularly strong for outcomes occurring around the intrapartum period. Overweight/obesity should be recognised as a risk factor for adverse reproductive outcomes in Sub-Saharan Africa.

Acknowledgements

I am very grateful to the Economic and Social Research Council for the financial support provided throughout my MSc and PhD.

I would like to thank my supervisor Véronique Filippi for all of her encouragement, insights and advice. Véronique has been a fantastic supervisor and I could not have completed this thesis without her.

Many thanks to Mary De Silva for her helpful support and guidance and to Emma Slaymaker for her invaluable help with the intricacies of the DHS data. I would also like to thank Julian Gardiner for his advice on statistical issues. Thank you to all the staff and students in the Centre for Maternal Reproductive and Child Health at LSHTM, in particular Oona Campbell for her encouragement, helpful comments and suggestions throughout my PhD.

I would like to thank all my friends at LSHTM, especially Wei (for her endless patience in answering my many statistical questions!) Chris and Sue. Finally and most importantly I am most grateful to my parents, brother and all my family for their love and encouragement. Thank you everyone.

Table of Contents

List of Tables

List of Figures

Abbreviations Commonly Used in this Thesis

BMI	Body mass index
CI	Confidence interval
DHS	Demographic and Health Surveys
GDM	Gestational diabetes mellitus
GNP	Gross national product
NOS	Newcastle-Ottawa scale
OR	Odds ratio
WHO	World Health Organization

Underweight	BMI <18.5 kg/m^2
Optimal weight	BMI 18.5-24.9 kg/m^2
Overweight	BMI ≥25 kg/m^2
Pre-obese	BMI 25-29.9 kg/m^2
Obese	BMI ≥30 kg/m^2
Morbidly obese	BMI ≥40 kg/m^2

Chapter 1

INTRODUCTION

This thesis brings together the important public health issue of reproductive health with the emergence of overweight/obesity as a health concern in low-income countries.

Low-income countries are currently undergoing a nutrition transition. Overweight and obesity are emerging as a significant public health issue, particularly in urban areas. Adult women of reproductive age are more likely to be overweight than men. As obesity is a risk factor for a large number of adverse reproductive outcomes, the rise in average population BMI has key implications for reproductive health.

Sub-Saharan Africa is currently at an early stage of transition, nevertheless by 2030 the prevalence of obesity is projected to be 17.2% [1]. No published study has yet estimated the effect of overweight/obesity on reproductive health in Sub-Saharan Africa; this thesis uses existing secondary data sources to make a contribution towards filling this knowledge gap.

1.1 Reproductive Health in Sub-Saharan Africa

"Within the framework of WHO's definition of health as a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity, reproductive health addresses the reproductive processes, functions and system at all stages of life. Reproductive health, therefore, implies that people are able to have a responsible, satisfying and safe sex life and that they have the capability to reproduce and the freedom to decide if, when and how often to do so."

World Health Organization (2011)[2]

Sub-Saharan Africa has the highest burden of reproductive ill-health in the world. In 2008 there were an estimated 358,000 maternal deaths globally, of which more than half occurred in Sub-Saharan Africa (204,000 deaths) despite the region accounting for only 13% of the global population [3]. Women in Sub-Saharan Africa have a 1 in 31 lifetime risk of dying from a maternal cause, 139 times higher than that in developed regions (1 in 4300) [3]. Sub-Saharan Africa is the only region where the absolute number of maternal deaths has increased from 1990, the baseline for the Millennium Development Goals; although trends in the maternal mortality ratios (MMR) do show some evidence of a declining trends in central and eastern Africa if deaths from HIV/AIDS are excluded [4]. Both sets of estimates of maternal mortality published during 2010 agree that Sub-Saharan Africa currently has the greatest burden of maternal mortality in the world [3-4].

The major causes of maternal death in Africa are thought to be haemorrhage (34%), sepsis/infections (10%), hypertensive disorders (9%), HIV/AIDS (6%) and obstructed labour (4%) [5]. Most deaths occur around the time of delivery, due to intrapartum obstetric complications [6]. However, a maternal death merely represents the extreme end of the distribution of poor reproductive outcomes; a further estimated 10-20 million women develop physical or mental disabilities each year as a result of pregnancy and childbirth [7].

Many women who suffer severe obstetric complications will experience ongoing adverse physical, psychological and social consequences, which may persist for an extended period of time after the birth itself [8-10]. The economic costs of a complicated delivery also often place a considerable burden upon households; observational data from Benin has shown that complicated deliveries can cost between 8-34% of annual household cash expenditure

compared to 2-5% for a spontaneous vaginal delivery; whilst in Ghana delivery complications represented between 3-8% of average annual household cash expenditure compared to just 1% for a normal delivery [11]. The proportional economic burden for the poorest households will be even greater than this. Women may subsequently attempt to compensate by carrying out heavy physical work before they are fully recovered, or delaying necessary medical treatment [12].

Obstetric complications also have adverse consequences for the infant. The most recent modelling estimates suggest that there were 3.1 million neonatal deaths during 2010 [13] and that intra-partum complications are an important cause of neonatal mortality [14]. In general, risk factors such as obstructed labour, eclampsia and ruptured membranes are associated with a greater increase the risk of neonatal death than pre-existing maternal characteristics such as age or parity [15]. Overall, intra-partum related neonatal deaths are thought to account for 9% of all deaths in children under the age of five [14].

Poor reproductive health is not limited to those women who suffer adverse pregnancy outcomes; the World Health Organization (WHO) definition of reproductive health, which opened this chapter, also states that women should have the *"capability to reproduce and the freedom to decide if, when and how often to do so"* [2]. Hidden morbidities, such as infertility, present a substantial and often un-recognised burden to women of reproductive age. Such issues have historically been neglected as UN organisations, governments and non-governmental organisations (NGOs), who have been focused on high average fertility rates in low-income countries, issues of over-population and unmet contraceptive need.

Sub-Saharan Africa is thought to have some of the highest rates of infertility in the world, predominantly due infections or injuries sustained in previous childbirths, in addition to a high burden of sexually transmitted infections in some countries [16-18]. Many cases of infertility are thought to go unrecorded; many women will not seek health care since they perceive treatment to be too expensive, ineffective, or are afraid to reveal their problem to others due to concerns over stigmatisation [19]. In the Sub-Saharan context, where childbearing often forms an essential part of a woman's identity, infertility can have severe social and psychological ramifications [20-23] .

The burden of poor reproductive health is unacceptably high in Sub-Saharan Africa. However, obesity is now emerging as a public health issue in the region. Research in high-income settings has shown that obesity has an adverse effect on numerous reproductive outcomes

including infertility and delivery complications [24-25]. Yet, evidence from low-income settings is limited and research from Sub-Saharan Africa is nearly non-existent. This thesis will address this gap by exploring the association between BMI and (i) reduced fecundity, (ii) adverse pregnancy outcomes amongst women of reproductive age (15-49 years) within Sub-Saharan Africa.

1.2 Obesity is an Emerging Public Health Issue in Low Income Countries

Obesity, defined by the WHO as *"abnormal or excessive fat accumulation that may impair health"* [26], is a serious threat to global public. At the most fundamental level, obesity is caused by an excess energy balance, i.e. calories consumed exceed the amount of energy expended. Dramatic and ongoing global shifts in diet towards the consumption high-fat and high-sugar foods coupled with urbanisation and an increasingly sedentary lifestyle for many populations mean that obesity will be one of the major health challenges of the 21st century. If recent secular trends continue then by 2030 a projected 38.1% of the global adult population will be overweight and 19.7% will be obese, which equates to 2.16 billion overweight 1.12 billion obese people in absolute terms [1].

Obesity has been viewed as a problem of affluent high-income settings. However, levels of overweight and obesity are now rising rapidly in low and middle income countries [27-28]. In Sub-Saharan Africa, prevalence of obesity is currently low by global standards; age-standardised prevalence in 2005 was 3.1% amongst men and 10.7% amongst women [1]. This is projected to increase rapidly to a combined prevalence of 17.5% obese by 2030 [1]. Many low-income countries now face a "double burden" of disease as they deal with the emerging issue of chronic diseases, such as obesity, cardiovascular disease and diabetes, simultaneous with the unresolved burden of infectious diseases and under-nutrition [29-30]. Obesity and under-nutrition may even co-exist within the same household [31-32]

Obesity and associated diet-related factors, are estimated by the WHO to currently cause 18.1% of deaths and 6.5% of disability-adjusted life years (DALYs) lost in low and middle income countries [33]. The burden is felt amongst adults of economically-active working age: in South-East Asia and Africa 41% of deaths caused by overweight occur amongst the under 60s [33].

1.3 Obesity is Associated with Poor Reproductive Health Outcomes

In low-income countries, adult women are the population group most likely to be overweight or obese [1, 34-35]. In Sub-Saharan Africa reproduction plays a central role in women's lives. The average number of births per woman is 5.2, albeit with a large range between 2.4 births per woman in South Africa to 7.4 births in Niger [36]. Thus, the increasing prevalence of an exposure associated with poor reproductive outcomes is of immense concern.

Research from high-income countries has shown that obesity has a deleterious effect on reproductive and maternal health. Obesity has a detrimental effect on fecundity, primarily through (i) ovulatory disorders, such as anovulation, polycystic ovary syndrome and amenorrhea [24, 37], and (ii) increase in the risk of spontaneous pregnancy loss [38-39]. Maternal obesity has also been associated increased congenital malformations in the foetus [40]. Maternal obesity is associated with a number of adverse pregnancy outcomes, including both elective and emergency caesarean delivery [41-42], induction of labour and pre-eclampsia [25]. Furthermore, it is to be expected that a rising population BMI will be accompanied by an increase in related conditions, such as type II diabetes, gestational diabetes and hypertension [43-46]. All of which are known to have important independent effects on adverse reproductive outcomes.

Obesity is inherently a modifiable risk factor for both reduced fecundity and adverse pregnancy outcomes; therefore it can be targeted by public health interventions if sufficient information is known about the risk. Sub-Saharan Africa already has one of the highest burdens of infertility in the world [18, 47]; a frequently highlighted unmet need for skilled obstetric care, including caesarean delivery [48-49], and in 2008 had the highest neonatal mortality rate globally (41 deaths per 1000 live births) [50]. An estimated 23% of neonatal deaths are thought to be due to birth asphyxia and 7% are related to congenital abnormalities [15], both of which are associated with maternal obesity. However, there is currently no epidemiological evidence quantifying the effect of obesity in Sub-Saharan Africa.

Quantitative estimates of the effect of obesity are needed to monitor and assess the scale of the problem as it develops, and to act as baseline data for future research. Such estimates can be useful to inform the development and design of future prevention and intervention studies. The results will also be useful for advocacy purposes. Several authors have advocated implementing early preventive measures to combat the emerging epidemic of

obesity and related chronic diseases in low-income settings [51-52]; the findings of this thesis should be valuable for this purpose.

1.4 Thesis Aims and Objectives

Therefore, the overall aim of this thesis is to investigate the effect of obesity on reproductive health in Sub-Saharan Africa. This thesis utilises the existing data source of the Demographic and Health Surveys (DHS) to investigate the following research questions:

1. Is high body mass index (BMI) a risk factor for reduced female fecundity in the low-income, high-fertility setting of Sub-Saharan Africa?
2. Is high BMI a risk factor for adverse pregnancy outcomes in Sub-Saharan Africa?
    a. What is the effect of increased maternal BMI on the odds of delivery by caesarean section in Sub-Saharan Africa?
    b. What is the effect of increased maternal BMI on the odds of neonatal death in Sub-Saharan Africa?

Since the DHS are standardised, nationally-representative surveys it will be possible to compare national trends and effect estimates. The results of this thesis represent the first nationally-representative results on the impact of obesity on reproductive health in Sub-Saharan Africa.

The specific objectives of this thesis are to:

1. Describe the current prevalence of overweight and obesity in the twenty-seven Sub-Saharan countries for which data are available.
2. Estimate the typical weight trajectory and rate of weight change of women during the reproductive ages in this setting; in order to estimate the extent of any potential misclassification bias arising from the cross-sectional design of the DHS.
3. Conduct a systematic review of the existing epidemiological literature to quantify the association between overweight/obesity and reduced fecundity, as measured by waiting time to pregnancy or conception.

4. Quantify the effect of increased BMI on reduced female fecundity in Sub-Saharan Africa

5. Quantify the effect of increased maternal BMI on caesarean delivery in Sub-Saharan Africa.

6. Quantify the effect of increased maternal BMI on neonatal mortality in Sub-Saharan Africa.

1.5 Thesis Outline

This thesis begins by providing general background information pertinent to the research topic (Chapter 2). The background chapter is organised into three sections. The first describes what is currently known about reduced fecundity and infertility in Sub-Saharan Africa; this is followed by a section on adverse pregnancy outcomes (caesarean delivery and neonatal death). Chapter 2 concludes by providing background information relating to the nutrition transition process, and diet and physical activity levels in Sub-Saharan Africa. In this section I demonstrate that obesity has negative consequences for reproductive health and is an emerging public health concern in low-income settings, likely to be of increasing importance throughout the twenty-first century.

Chapter 3 presents the methods used in this thesis. I begin by describing the main data source, the DHS, including providing information on sampling and survey design. I then describe the analytic frameworks used in each analyses and the construction of each of the outcome variables in turn. The same primary exposure (BMI) was used throughout this thesis; in Section 3.3 I provide information relating to the quality of height and weight data in the DHS and the BMI categorisations scheme used in the thesis. Chapter 3 concludes with a description of the statistical methods used in the thesis.

In Chapter 4 I describe the national BMI distribution for each of the twenty-seven Sub-Saharan countries included in this thesis. I then identify risk factors for being overweight in this setting. I decided to present a descriptive analysis of BMI as a distinct chapter in order to avoid excessive repetition later in the thesis, as each of my different outcomes share the same primary exposure.

Chapter 5 presents an investigation into potential exposure misclassification due to temporal changes in BMI. As will be discussed, one of the most important methodological limitations of this thesis is that the DHS are cross-sectional surveys; therefore I am implicitly assuming that BMI has remained constant throughout the reference period used in the study (usually the five years preceding data collection.) As there is no one suitable data source available in order to quantify this misclassification I combine three different strategies: (i) a literature review; (ii) an investigation of age-specific changes in median weight and BMI in three African countries (Ghana, Kenya and Zambia) where there have been four consecutive DHS collecting anthropometric data; (iii) an analysis of a prospective cohort of women recruited as part of a study into health after severe obstetric complications in Burkina Faso. These findings are then triangulated to estimate the extent of any potential exposure misclassification in my thesis.

The main findings are presented in Chapter 6, Chapter 7 and Chapter 8.

Chapter 6 presents a systematic review to assess the effect of overweight/obesity on waiting time to pregnancy or conception (TTP). This leads into Chapter 7, which is a quantitative assessment of the effect of BMI on reduced female fecundity in Sub-Saharan Africa using DHS data. In Chapter 7 I investigate two different outcomes: first of all logistic regression is used to investigate the effect of BMI on the odds of subfertility (a variable constructed to proxy clinical infertility); this is followed by a survival analysis on the time between first marriage and the month of the first conception.

Chapter 8 investigates maternal BMI and adverse pregnancy outcomes in Sub-Saharan Africa. I focused on (i) odds of caesarean delivery; (ii) neonatal death, due to constraints imposed by the available variables collected in the DHS. Multivariable logistic regression models are presented quantifying the effect of maternal BMI; subsequently a more in-depth analysis of the timing of death within the neonatal period is conducted using a discrete-time survival model.

The thesis concludes with a discussion, presented in Chapter 9, of the main findings of the thesis. This is followed by an overview of the strength and limitations of the work and recommendations for future research.

Chapter 2

BACKGROUND

The aim of Chapter 2 is to present the background information needed to understand the context of my thesis and to interpret the main findings.

Chapter 2 is organised into three parts. In Section 2.1 I discuss the background literature relevant to my first research question investigating obesity and reduced fecundity. The evidence relating to infertility in Sub-Saharan Africa is reviewed and the methodological difficulties in measuring infertility using population-based survey data briefly discussed.

Section 2.2 looks at the background to obesity and adverse pregnancy outcomes; specifically caesarean delivery and neonatal deaths in Sub-Saharan Africa.

The background chapter concludes in Section 2.3 with information relating to the emerging public health importance of overweight/obesity in Sub-Saharan Africa. This section emphasises the topical relevance of this thesis, and explains how the findings presented are timely and fill a clear research gap.

2.1 Reduced Fecundity and Infertility in Sub-Saharan Africa

2.1.1 Definitions & Measurement Issues

In this thesis the term 'fecundity' is used to refer to the potential physiological capacity of an individual to reproduce, this is distinct from the term 'fertility' which is used in the demographic sense of describing the actual number of (live born) children that a woman has previously given birth to [53]. Fecundity is therefore a hidden, underlying and somewhat intangible construct. It consists of the absence of an outcome (i.e. a recognisable conception or birth) rather than an observable event and therefore presents a specific set of methodological challenges. The term 'fecundability' is also used in this thesis, meaning the average probability of conception in a given menstrual cycle during which a woman is engaged in sexual intercourse and no contraception is used [54].

The term 'infertility' is defined in this thesis as the total inability to reproduce; representing the extreme manifestation of reduced fecundity. Infertility can be sub-categorised as primary infertility where a woman has never achieved a pregnancy, and secondary infertility where she has previously been successful in achieving pregnancy but is no longer able to do so. However, infertility is also difficult to measure in a population-based study. Usually a woman has no obvious manifestations of any underlying clinical pathology and will probably be unaware of her condition until she attempts to conceive. Even after a full medical investigation around 25-30% of couples presenting for infertility treatment will never have a specific medical cause for their problem diagnosed [55]. Infertility may be due to either or both partners in a relationship, and each may potentially be able to conceive with an alternative partner.

Given that reduced fecundity and infertility are represented by the absence of a conception or birth an important consideration in the measurement of these outcomes is the length of the reference period used to determine that this event is not going to occur [56-57]. Many clinical studies define a couple as infertile if they fail to conceive after twelve months of attempting to do so [55, 58]. However, although about 80% of couples conceive within six menstrual cycles and 90% take place within the first twelve cycles; about half of the remaining 10% will nonetheless spontaneously conceive without any medical treatment [58]. Epidemiological studies typically use a longer reference period than twelve months, in order to reduce the number of false positive cases: the WHO has recommended using a cut-off of twenty-four months [59]. Demographic studies often define the endpoint as a live birth (cf. a recognisable conception) because of the difficulties in collecting reliable data on abortions, still births and

miscarriages in a retrospective questionnaire [17-18]. Simulation studies have suggested that in this scenario a reference period of five years may be needed to measure primary infertility and seven years to measure secondary infertility [60-61].

The analyses presented throughout this thesis lie on the border between epidemiology and demography, and aspects from each approach will be utilised in the outcome measurement; a full discussion of the operationalisation of the fecundity variables is presented in the methods section in Chapter 3.

2.1.2 Infertility in Sub-Saharan Africa

Historically research on infertility has been neglected in Sub-Saharan Africa, primarily due to political focus on the threat of over-population, high fertility rates and an unmet need for contraception. Nevertheless, infertility may have severe social and psychological repercussions for those women who are unable to reproduce on the individual level.

Data on the prevalence of infertility in Sub-Saharan Africa is very poor. Work by Ulla Larsen has attempted to infer age-specific infertility status using birth history data has suggested wide variation from country to country [18, 62]. In general, Central Africa has high levels of infertility, about 25% in Cameroon and 29% in the Central African Republic; whilst Togo (7%), Rwanda (8%) and Burundi (8%) have relatively low levels of infertility [18]. The proportion of women designated to have primary infertility (those who remain childless after seven years since first marriage) ranges between 1-4% [18]. Infertility rates in Sub-Saharan Africa, although still high by global standards, are thought to have declined since the 1970s; although temporal trends are difficult to measure adequately using birth history data because of the difficulty in adequately controlling for contraceptive use [62]. This hypothesis is supported by Rutstein & Shah (2004) who used DHS and World Fertility Survey (WFS) data to calculate the proportion of women aged 25-49 who have been married five years but have no live birth in successive surveys [47]. There are no up-to-date estimates of the prevalence of infertility in Africa; the data used in the Larsen study spanned the years to 1977-1997 and the Rutstein & Shah report looked at surveys conducted between 1995-2000 [18, 47].

Estimates of infertility in Sub-Saharan Africa are high by global standards. Although data are again limited, it has been suggested that a substantial proportion (estimates ranging between 50-80% of female infertility) may be due to tubal factors [63]. A major cause of damage to the fallopian tubes is pelvic inflammatory disease (PID) which often originates from an infection in

the cervix [63]. An estimated 20-30% of infertile women are thought to suffer from ovulatory disorders in Sub-Saharan Africa. Damage to the uterus or cervix, often caused by a previous childbirth or induced abortion in the Sub-Saharan context, contributes to 10-20% of infertility cases [63]. However, all of these estimates were generated from clinical studies where the patient had presented for medical treatment for her infertility; which is likely to have caused a degree of selection bias. Many women with infertility in Sub-Saharan Africa will be unable to access treatment for infertility either due to the high economic cost or fear of stigmatisation, and of those who do many may prefer to visit traditional healers rather than use the Western medical system [64].

A case-control study of women referred to the gynaecology clinic at Gweru Provincial Hospital, Zimbabwe, and control women recruited from the delivery ward found that history of a caesarean section was much more frequent among the infertile patients than the fertile women (17.9% versus 8.5%) [65]. Women in the infertile group were much more likely to have had a previous caesarean section with post-operative sepsis (OR: 11.5; 95% CI: 3.44-38.42) [65]. Participants were matched on age, parity, education and height but the odds ratio was not adjusted for any further factors in the analysis [65].

In the Sub-Saharan context infertility can be a particularly devastating condition with severe social and psychological consequences. However, there is an important distinction between primary infertility where a woman has no child, and secondary infertility where a woman is unable to conceive but does have one or more previous births. Women with at least one previous birth tend to suffer considerably less discrimination[20]. In-depth qualitative interviews from Tanzania have described widespread stigmatisation and disrespect for infertile women [20]. Women may be known as *utasa*, a Swahili term meaning "completely barren" which is a "*terrible and painful word*" [20]. Infertile women may be neglected, divorced or abandoned by their husband [21-23].

2.1.3 Obesity and Reduced Fecundity

There are three major biological pathways through which female fecundity may be impaired:

1. **Disorders of the female reproductive tract**; mainly tubal obstruction or endometriosis
2. **Ovulatory disorders**; including amenorrhea, anovulation and polycystic ovarian syndrome
3. **Spontaneous pregnancy loss**

However, obesity is associated with ovulatory disorders and spontaneous pregnancy loss.

Ovulatory Disorders

An absence of menstrual cycles (amenorrhoea) or irregular menstrual cycles (oligomenorrhoea) may indicate anovulation. An anovulatory cycle is one in which ovulation does not take place; it is usually caused by hormonal imbalance, but can occasionally be due to a blockage or absence of ova [66].

Obesity primarily reduces female fecundity through creating hormonal imbalances. Obese women are disproportionally affected by hyperandrogenism (the excess production of male hormones known as androgens) which commonly leads to ovulatory disorders [67]. Polycystic ovarian syndrome (PCOS) is also commonly associated with anovulatory infertility and has increased prevalence amongst the obese; although the direction of causation is unclear as PCOS also leads to weight gain [68-69]. PCOS is one of the most common reproductive disorders in high-income countries, but is poorly understood and both the symptoms and the severity vary between women [66, 70]. Prevalence in low-income settings is unknown.

Menstruation is an important consideration for the purposes of this thesis, because women have one window of opportunity in which they can conceive per menstrual cycle. The number of menstrual cycles a woman experiences in her lifetime will be affected by (i) age at menarche; (ii) age at menopause; (iii) frequency and length of cycles during the reproductive years.

In high-income countries, girls who are overweight or obese tend to experience puberty earlier than those of optimal weight, and thus may become exposed to the risk of conception at an earlier age [71]. There is also evidence to suggest that obesity increases the age at menopause [72-73] so the number of years a woman is menstruating and therefore potentially able to become pregnant is increased amongst obese women.

However, conversely increased body mass has been found to be associated with increased menstrual cycle length (>30 days) amongst pre-menopausal women less than 45 years of age [74]. An analysis of data from the British Cohort Study has shown that obesity at both age seven years and age twenty-three years to be independently associated with irregular menstrual cycles at age 33 years [75]. Irregular menstrual cycles or longer cycle length would have the effect of decreasing the total number of menstrual cycles experienced. Thus, obesity could be hypothesised to act in both directions in terms of influencing conception opportunities; however as relatively few women attempt pregnancy at very young or very old ages I expect it to have an overall negative effect on my fecundity outcomes in this thesis.

Spontaneous Pregnancy Loss

The spontaneous loss of a clinically recognised pregnancy in the first 20-24 weeks of gestation is known as either a spontaneous abortion or a miscarriage. An estimated 25% of pregnancies are lost before they become clinically detectable, around the time of implantation [76].

Studies of miscarriage rates after infertility treatment have provided useful information on the effect of obesity; studies of miscarriage in the general population are methodologically difficult due to biases in the gestational age at which a woman recognises and reports her pregnancy [77]. There is a growing body of evidence to suggest that overweight women have an increased miscarriage rate after infertility treatment [78].

A statistically increased risk of miscarriage has been reported amongst obese, but not amongst pre-obese women, compared to optimal weight women in both a nested case-control [79] and prospective cohort study [39], possibly suggesting that the threshold of adiposity required for an observable negative effect on miscarriage is higher than the overweight cut-off of 25kg/m^2. A large study of 126 080 deliveries in the Soraka University Medical Center, Israel over a ten year period, found that obese women had 40% increased odds of suffering two or more consecutive miscarriages (OR: 1.4; 95% CI 1.2-1.7) compared to non-obese patients after socio-demographic and medical factors were adjusted for in the analysis; women with known hypertensive disorders or diabetes mellitus were excluded from this study [80]. However, evidence for an association is mixed; another prospective study of 1200 women enrolled after a sonogram in the first trimester (mean 9.9 weeks gestation) there was no significant increase in miscarriage rates amongst the obese [81].

Data from the Danish National Birth Cohort (n=54,505) which interviewed women during the second trimester found that pre-pregnancy obesity was associated with an increasing excess risk of foetal death as gestation advanced [82]. An effect of borderline statistical significance was observed at 14-19 weeks gestation (HR: 1.6; 95% CI: 1.0-2.5). However, this study suggested that maternal obesity is more important as a risk factor at later gestational ages of 37-39 weeks (HR: 3.5; 95% CI: 1.9-6.4) and 40+ weeks (HR: 4.6; 95% CI: 1.6-13.4) when the event would be classified as a still birth rather than a miscarriage [82].

A systematic review of sixteen studies found that overweight patients had significantly higher odds of miscarriage regardless of whether conception was spontaneous or assisted, but there was insufficient evidence to compare the risk amongst different subgroups [38].

Obesity and Male Infertility

Obesity is associated with increased male infertility, both directly and indirectly. Most males who seek infertility treatment are observed to have a decreased ratio of testosterone to oestogen, due to over activity of the aromatase enzyme[83]. High oestrogen levels have been shown to have a deleterious effect on spermatogenesis in animal models [84]. Obese men further exhibit reduced androgen and sex hormone-binding globulin (SHBG) levels [85].

Obesity may also be associated with male infertility indirectly, through changes in sexual behavior. Obese men report increased erectile dysfunction and a lower libido [84].

Male infertility will not be investigated in this thesis. I will be constructing a subfecundity variable as a proxy for infertility on the basis of each woman's birth history (see section 3.2.1). Although DHS collects anthropometry data on a subsample of male participants, it will not be possible to adequately attribute paternity to the birth history for such a hypothesis to be tested.

2.2 Adverse Pregnancy Outcomes in Sub-Saharan Africa

2.2.1 Caesarean Delivery in Sub-Saharan Africa

The most recent DHS data available for Sub-Saharan Africa (displayed in Table 2.1) suggests there is substantial variation in caesarean delivery rates. Overall caesarean rates range from a low of 0.4% (Chad, 2004) to a high of 13.4% (Namibia, 2006-07) [86].

Table 2.1 Caesarean deliveries in Sub-Saharan Africa

Country, year	Deliveries by Caesarean Section in the 3 years Preceding Survey									
	Relative Wealth Quintile (%)					Ratio	Residence (%)		Ratio	Total (%)
	Poorest	2	3	4	Richest		Urban	Rural		
Burkina Faso, 2003	0.2	0.5	0.2	0.9	2.2	**11.0**	2.6	0.4	**6.5**	0.7
Cameroon, 2004	0.6	0.5	1.7	4.1	4.5	**7.5**	3.7	0.7	**5.3**	2.0
Chad, 2004	0.0	0.0	0.3	0.0	1.6	**n/a**	1.6	0.1	**16.0**	0.4
Congo-Brazzaville, 2005	1.6	1.9	2.9	4.3	7.1	**4.4**	4.5	2.1	**2.1**	3.2
DRC, 2007	2.7	3.9	3.9	6.4	6.3	**2.3**	5.3	4.0	**1.3**	4.5
Ethiopia, 2005	0.0	0.4	0.2	0.2	6.1	**n/a**	10.5	0.3	**35.0**	1.1
Ghana, 2008	0.9	4.8	9.1	6.6	14.5	**16.1**	9.5	4.4	**2.2**	6.4
Guinea, 2005	0.2	0.5	0.9	2.0	7.5	**37.5**	5.2	0.8	**6.5**	1.8
Kenya, 2008-09	2.4	4.2	5.3	8.4	14.8	**6.2**	12.3	5.4	**2.3**	6.7
Lesotho, 2004	2.3	4.6	6.2	6.7	8.2	**3.6**	7.7	5.1	**1.5**	5.5
Liberia, 2007	0.9	1.9	5.1	6.0	8.3	**9.2**	6.1	3.1	**2.0**	4.0
Madagascar, 2008-09	0.1	0.3	0.7	1.2	7.4	**74.0**	6.1	0.9	**6.8**	1.5
Malawi, 2004	3.6	2.3	2.2	3.6	4.8	**1.3**	4.3	3.0	**1.4**	3.2
Mali, 2006	1.0	0.7	0.6	1.5	5.4	**5.4**	4.0	0.8	**5.0**	1.7
Mozambique, 2003	0.4	0.3	0.6	2.7	9.3	**23.3**	6.2	0.6	**10.3**	2.2
Namibia, 2006-07	3.8	4.7	9.9	18.6	35.1	**9.2**	22.3	7.3	**3.1**	13.4
Niger, 2006	0.2	0.4	0.3	0.3	3.9	**19.5**	4.5	0.3	**15.0**	1.0
Nigeria, 2008	0.2	0.4	0.8	2.7	6.4	**32.0**	3.7	1.1	**3.4**	1.9
Rwanda, 2005	1.2	1.8	1.9	2.6	8.3	**6.9**	7.5	2.2	**3.4**	3.0
Senegal, 2005	0.7	1.3	2.4	7.2	8.1	**11.6**	7.1	1.4	**5.1**	3.5
Sierra Leone, 2008	0.6	0.8	1.1	0.9	6.1	**10.2**	3.6	0.9	**4.0**	1.6
Swaziland, 2006-07	7.1	6.3	9	8.5	8.5	**1.2**	7.6	7.9	**1.0**	7.9
Tanzania, 2004-05	1.1	2.9	3.5	2.5	9.3	**8.5**	8.2	2.4	**3.4**	3.6
Zambia, 2007	1.2	1.5	1.7	5.7	8.9	**7.4**	6.8	1.8	**3.8**	3.3
Zimbabwe, 2005-06	1.4	2.7	4.4	6.9	11.4	**8.1**	10	2.9	**3.4**	4.9

Data extracted from the DHS StatCompiler: http://www.statcompiler.com/ [86]

However, national rates of caesarean delivery conceal very large urban/rural gradients. In nearly half of the countries included in this thesis there were over 10 times as many caesarean

deliveries in the richest quintile as in the poorest [86]. Urban-rural gradients were smaller in magnitude, although still substantial. In four countries (Mozambique, Niger, Chad and Ethiopia) caesarean delivery rates were over 10 times higher amongst urban residents, compared to those living in rural areas [86].

Caesarean rates in Sub-Saharan countries are very strongly associated with both urban/rural and socio-economic status [48]. The size of this difference is much larger than that reported for antenatal or skilled delivery care [48].

Data from seventeen Sub-Saharan countries has shown that the annual rate of change (%) in the proportion of deliveries carried out by caesarean section varied substantially between countries between ~1991 and ~1998 [87]. In most countries there was little or no change; however, in some areas notably Cote d'Ivoire (+8.2%), Benin (+9.3%) and Senegal (+11.4%) there were large increases in the proportion of women delivering by caesarean; whilst in some countries such as Niger (-4.8%) and Burkina Faso (-6.3%) overall caesarean rates declined [87]. However, the DHS is not adequately powered to detect small changes in caesarean rates so care should be taken in interpreting the trend data [87-88].

In Sub-Saharan Africa the circumstances of a caesarean operation is usually different to that of high-income countries. A systematic review of studies involving caesarean sections done in health facilities in Sub-Saharan Africa between 1970-2000 found that about 75% of caesareans were carried out for severe maternal indications [89]. Nearly all were due to one or more of the following: prolonged labour, previous caesarean, malpresentation, abruptio placentae, placenta praevia or eclampsia [89]. There is substantial unmet need for caesarean delivery care throughout most of Sub-Saharan Africa [90]. However amongst the very richest elite social groups, childbirth may be over-medicalised and unnecessary caesareans, which also carry an excess risk to maternal outcomes, may be carried out [91-92].

Associations between Caesarean Delivery and Obesity Reported in Sub-Saharan Africa

Only a limited number of studies specifically relating to maternal overweight and caesarean delivery have been conducted in any low-income setting [93-95], particularly in Sub-Saharan Africa. A search for relevant studies from Sub-Saharan Africa using PubMed and Web of Science using the search terms displayed in Table 2.2 and with no restrictions on dates

retrieved a handful of results, but none that had an adequately rigorous design or provided any detailed analysis.

Table 2.2 Search terms used to identify studies on maternal overweight/obesity and caesarean delivery in Sub-Saharan Africa

Database	Search Terms
PubMed	("Overweight"[Mesh] OR "Obesity"[Mesh] OR "Body Mass Index"[Mesh] OR overweight OR obes* OR body mass index OR BMI) AND ("Cesarean Section"[Mesh] OR caesarean OR caesarean OR pregnancy outcome) AND ("Africa"[Mesh] OR Sub-Saharan)
Web of Science	(overweight OR obes* OR body mass index OR BMI) AND (c$esarean OR pregnancy outcome) AND (Africa OR Sub-Saharan)

This search located three papers; two from Benin and one from South Africa. All three were retrospective analyses of routine hospital records and none provided any effect estimates adjusted for confounding factors.

A retrospective review of hospital records (n=323) from Cotonou, Benin [96] found that a larger proportion of those who were overweight delivered by caesarean section compared to women of optimal weight (32.3% of pre-obese women and 34.5% of obese women had a caesarean compared to 21.1% of optimal weight women). No further analysis was presented; however I calculated that this would correspond to an unadjusted odds ratio of 1.79 (95% CI: 0.99-3.24) for pre-obese women and 1.97 (95% CI: 1.00-3.91) amongst obese women, both estimates being of borderline statistical significance.

Unfortunately only a very limited description of the socio-demographic characteristics of the study population is presented, and there is no attempt was made to adjust for any confounding factors. Skilled birth attendance levels are very high in Cotonou, according to the Benin DHS (2006) 21.2% of women were assisted by a doctor during delivery and overall 97.1% were assisted by a health professional [97]; however the characteristics of patients who contribute to the vaginal and caesarean section delivery groups are likely to be quite different, with women in need of emergency caesarean section originating from further away from hospitals. Therefore there is likely to be a strong selection bias operating on the in-patient population. Furthermore, no information is given regarding the timing of the anthropometric measurements; if weight was measured around the time of delivery a substantial amount of exposure misclassification will have taken place.

The second study from Benin [98] looked at the prevalence of obesity and occurrence of operative complications amongst 300 patients scheduled for a caesarean delivery at the University Teaching Hospital. The authors report that in this particular hospital 50.7% of caesarean deliveries were to obese women. Pre-obese women were combined with optimal weight women in this study and so the only comparisons that can be made are between women with a BMI less than 30kg/m^2 and women with a BMI of 30kg/m^2 or more. The medical indications for the caesarean appeared to be similar between the groups but no statistical tests of this are provided and overall this study provides very little useful information.

A retrospective study of 752 deliveries in Johannesburg, South Africa found that a slightly higher proportion of morbidly obese women (BMI >40 kg/m^2) delivered by caesarean section (55.3% vs. 48.3%) or required an assisted delivery (5.3% vs. 1.4%) compared to optimal weight women, but this difference was not statistically significant (p=0.15) [99]. The paper does not report any key demographic information such as age and parity of the patients or make adjustments for any confounding factors. The authors furthermore mention poor documentation in the hospital record system as a major limitation of their study.

Therefore, although a very small number of studies looking at the maternal overweight-caesarean relationship in sub-Saharan Africa do currently exist there is a lack of robust evidence adequately controlling for confounding factors.

2.2.2 Obesity and Adverse Maternal Outcomes

This section provides some details on the biological mechanisms behind the obesity-caesarean delivery association, organised by maternal outcome.

Pregnancy-Induced Hypertension and Pre-eclampsia

Hypertension and pre-eclampsia can present serious complications for the mother, but also to her baby. A well-conducted systematic review of thirteen cohort studies published prior to June 2002 found that the risk of pre-eclampsia approximately doubled with each 5-7 kg/m^2 increase in pre-pregnancy BMI [100]. A national, population-based study of Swedish women who had two consecutive singleton births between 1992 and 2001 (n=151 025) showed that substantial weight gain (≥ 3 kg/m^2) during the inter-pregnancy interval was associated with a

significantly increased risk of pre-eclampsia and gestational hypertension, independent of whether women were overweight or had an optimal BMI [101].

Gestational Diabetes Mellitus

Again, gestational diabetes is a risk for both the mother and the baby. Women with gestational diabetes are known to be at increased risk of going on to develop type 2 diabetes mellitus [102]. Foetal risks, including macrosomia (large for gestational age) and birth defects are discussed further in the section on adverse neonatal outcomes (Section 2.2.5) below.

A systematic review of 70 studies (59 cohorts and 11 case control studies) found that the risk of developing gestational diabetes mellitus (GDM) is positively associated with BMI [103]. The review included a meta-analysis of unadjusted ORs which found that pre-obese women had nearly double the odds (OR: 1.97; 95% CI 1.77-2.19) of developing GDM and this increased to over five times the odds (OR: 5.55; 95% CI: 4.27-7.21) amongst the morbidly obese; overall prevalence of GDM increased by 0.92% for each 1 kg/m^2 increase in BMI [103].

Dystocia

Maternal overweight and obesity are associated with abnormal labour (dystocia). In the absence of medical intervention this can cause severe maternal morbidities including damage to the reproductive organs, fistula and infection or in extreme cases maternal death [7]. Dystocia is also an important risk factor for still birth and neonatal death [14]. The association between maternal obesity and dystocia has been hypothesised to occur through either ineffective uterine contractility, obstructed labour, or a combination of these causes.

Several epidemiological studies, including case-control [104], prospective [105] and retrospective [106-107] cohort designs, have found ineffective uterine contractility to be associated with maternal BMI. An *in vitro* study of the force and frequency of myometrial contractions[1] according to maternal BMI category found there was a marked decline in myometrial activity with increasing BMI (p=0.049) and that the frequency of contractions was decreased in obese women (p=0.0006) [108].

However, it is also well-established that maternal obesity is a risk factor for macrosomia in the infant independent of maternal diabetes [109-110] so it might be expected that obese mothers are also more likely to have difficulties with cephalopelvic disproportion. A retrospective study of 3355 singleton deliveries to primiparous mothers in the USA found that the risk of

[1] The myometrium is the middle layer of the uterine wall; its main function is to contract during labour.

cephalopelvic disproportion was increased for obese women and for those with a large pregnancy weight gain [111]. A study of Danish women (n=4358) with uncomplicated pregnancy found a significantly higher incidence higher incidence of cephalopelvic disproportion in the pre-obese and obese categories, compared to women with optimal BMI [107].

A prospective cohort study of nulliparous women with spontaneous-onset of labour in Sweden [105] attempted to assess whether maternal overweight is associated with non-elective caesarean due to ineffective uterine contractility and/or obstructed labour. The study concluded that caesareans due ineffective uterine contractility were associated with maternal BMI (Pre-Obese OR: 1.50; 95% CI 1.42-1.59; Morbidly Obese OR: 3.98, 95% CI: 3.14-5.04) but caesareans conducted due to obstructed labour were not (Pre-Obese OR 1.09; 95% CI 0.91-1.31; Morbidly Obese OR: 1.79, 95% CI: 0.65-4.92).

However, this conclusion should be interpreted with a great deal of caution; there was a substantial discrepancy in the available statistical power between the two groups (e.g. just 35 morbidly obese women were in the obstructed labour category, compared to 103 women in the corresponding ineffective uterine contractility group). Indeed, a significant association for caesarean due to obstructed labour was observed amongst women with a BMI 30-34.9 kg/m^2 (OR: 1.56; 95% CI 1.14-2.14) whilst the sample sizes in the subsequent 35-39.9 kg/m^2 and ≥ $40kg/m^2$ categories were particularly small. The lack of an association amongst the obstructed labour group could thus be potentially a product of insufficient statistical power rather than being taken to imply, as the author of this study appears to interpret, that a true association does not exist. Indeed, there is evidence to suggest that both ineffective uterine contractility and obstructed labour may play a significant role in the development of delivery complications [107].

Caesarean Delivery

Unsurprisingly, given the increased risk of dystocia and other maternal complications, overweight and obese woman are at increased risk of caesarean delivery. Two comprehensive systematic reviews have been published in recent years examining the association between maternal BMI and risk of caesarean delivery [41-42]; both examined related research questions and reached very similar conclusions. However, none of the studies included in either review were conducted in low-income countries.

The initial Chu *et al.* (2007) [41] review comprised 33 cohort studies and concluded that the crude pooled odds of caesarean delivery are increased amongst pre-obese (OR: 1.46; 95% CI: 1.34-1.60; n=23) obese (OR: 2.05; 95% CI: 1.86-2.27; n=29) and severely obese (OR: 2.89; 95% CI: 2.28-3.79; n=7) women, compared to those of optimal weight. The authors did not conduct a pooled analysis of adjusted results due to differences in study design. However they did carry out a sensitivity analysis using adjusted odds ratios for the obese vs. optimal weight comparison using those studies that reported both crude and adjusted estimates; there was very little change in the magnitude of the association (OR: 2.02; 95% CI: 1.71-2.41; n=9).

The Poobalan *et al.* (2009) [42] review restricted their search strategy to investigate the risk of caesarean delivery solely amongst nulliparous women. It consisted of 11 studies (five of which were also included in the Chu *et al.* meta-analysis) and also found that the crude pooled odds of caesarean delivery amongst pre-obese (OR: 1.53; 95% CI: 1.48-1.58; n=10) obese (OR: 2.26; 95% CI: 2.04-2.51; n=11) and severely obese (OR: 3.38; 95% CI: 2.49-4.57; n=4) are increased relative to optimal weight women. This review further investigated whether there was any difference between the risks of elective or emergency caesarean section in a subgroup analysis. The authors concluded that the increase in risk amongst women who delivered by emergency caesarean (pre-obese OR: 1.64, 95% CI 1.55-1.73, n=3; obese OR: 2.23, 95% CI 2.07-2.42, n=4) is slightly greater than those who had an elective caesarean delivery (pre-obese OR: 1.32, 95% CI: 1.21-1.45, n=3; obese OR: 1.87, 95% CI: 1.64-2.12, n=4).

Although the Chu *et al.* and Poobalan *et al.* reviews used slightly different methodologies in terms of their search strategy and inclusion criteria, study quality assessment and the statistical methods used in the meta-analysis, the similarity of the results both in terms of the magnitude and trend of the effect estimates is immediately obvious: there is a dose-response relationship with increasing maternal BMI and risk of caesarean delivery. Caesarean delivery is also a more risky procedure amongst obese women compared to those of optimal weight because of their higher risk of anaesthetic complications and increased difficulties in performing intubation [112].

Maternal Death

A recent report from the Confidential Enquiry into Maternal and Child Health for 2003 to 2005 showed that 30% of maternal deaths from direct causes and 24% of maternal deaths from indirect causes in the UK during this period were amongst obese mothers; the national

maternal obesity prevalence is 16% [113]. Obesity was particularly prevalence amongst deaths caused by thromboembolism [113].

Maternal death is a very rare event in high-income settings such as the UK so there is insufficient statistical power to conduct any form of adjusted analysis and this statistic is likely to be confounded by socio-economic status and maternal age. However, it does indicate that obese women are over-represented amongst maternal deaths.

2.2.4 Neonatal Mortality in Sub-Saharan Africa

Neonatal mortality is defined by the WHO as the death of a live born infant within the first 28 completed days of life (i.e. day 0 to day 27) [114]. This period is sometimes divided into the early neonatal (day 0 to day 6) and late neonatal (day 7 to day 27) periods [114]. Just under 40% of all child deaths occur in the neonatal period; around 75% of neonatal deaths occur during the early neonatal period [15].

The neonatal mortality rate for Sub-Saharan Africa is estimated to be 44 neonatal deaths per 1000 live births [114]. The neonatal mortality rate is higher in Eastern Africa (42 deaths per 1000 live births), Middle Africa (46 deaths per 1000 live births) and Western Africa (49 deaths per 1000 live births) compared to Southern Africa (23 deaths per 1000 live births) [114].

Neonatal mortality decline between 1990 and 2010 in Sub-Saharan Africa, although annual declines were not so substantial as observed in Asia, Latin America and North African countries; across Sub-Saharan Africa neonatal mortality declined at between 1-2% per year [13]. The rate of decline accelerated in the period 2000-2010 compared to 1990 -2000, which is encouraging [13]. However, much less progress has been made in reducing neonatal mortality, compared to under-five mortality in the region [13].

Data on neonatal deaths in low-income countries, where most such deaths occur, is very limited due to the lack of vital registration systems [14-15, 115]. Most estimates rely on estimates based on DHS data [115]. Neonatal deaths are less likely to be recorded if they occur in the first few hours after birth, and in many settings misclassification as a still birth occurs [15]. However, it is thought that between 25-50% of neonatal deaths occur in the first twenty-four hours after birth [15].

The most common causes of neonatal death are thought to be infections (sepsis/pneumonia, 26%; neonatal tetanus, 7%; diarrhoea, 3%), pre-term births (27%) and intrapartum birth

injuries (23%) [15]. However, this varies according to the overall level of neonatal mortality: countries with a low level of neonatal deaths tend to have proportionally more deaths due to prematurity and congenital abnormalities which are the most medically difficult to prevent; whereas countries in Sub-Saharan Africa which have a high overall neonatal mortality rate there is a high proportion of deaths due to infections and birth injuries sustained during the intrapartum period [15, 49]. Intra-partum related neonatal deaths can ultimately be avoided by providing timely access to skilled obstetric care, including caesarean delivery [116]. However, family community care programmes which have promoted clean delivery kits and the referral of complications to a health facility have also been demonstrated to be effective in reducing neonatal mortality [117].

No studies have previously investigated neonatal death according to maternal obesity in low-income settings.

2.2.5 Obesity and Adverse Neonatal Outcomes

Particularly in the Sub-Saharan context where many neonatal deaths are caused by intrapartum injuries, many of the mechanisms detailed in the previous section on maternal outcomes will also act to impact neonatal health. However, maternal obesity is also known to also act directly on the health of the neonate; these mechanisms are discussed in this section.

Structural Birth Defects and Congenital Malformations

Malformations that develop *in utero* are an important risk for neonatal and infant death. Increased risk of neural tube defects and congenital heart defects are most commonly associated with maternal obesity. However data from the National Births Defects Prevention Study in the USA showed have that in fact a large number of other structural birth defects such as spina bifida, limb reduction defects and rectal malformations are additionally associated with maternal obesity [118].

A systematic review by Stothard *et al.* (2009) of thirty-nine studies which included a meta-analysis of eighteen studies found that both pre-obese and obese mothers were significantly at risk of pregnancy affected by neural tube defects [40]. The odds of spina bifida more than doubled (OR: 2.24; 95% CI 1.86-2.69) amongst obese mothers; and the odds of anencephaly

were also significantly increased (OR: 1.39; 95% CI 1.03-1.87) although the magnitude of the effect was smaller [40].

A separate systematic review of twelve studies published between January 2000 and January 2007 showed a increasing trend of in the unadjusted odds of neural tube defects amongst pre-obese (OR: 1.22; 95% CI 0.99-1.49), obese (OR: 1.70; 95% CI 1.34-2.15) and severely obese (OR: 3.11; 95% CI 1.75-5.46) women, compared to those of optimal weight [119].

As obesity and diabetes both cause similar metabolic disturbances including insulin resistance and hyperglycaemia; this is a likely biological explanation for the observed effect and it is likely that some of the observed association may be accounted for by undiagnosed diabetes [40]. Maternal obesity has also been associated with reduced folate levels which could be a potential mechanism [40]. In a large cross-sectional study of 41,902 pregnancies there was no association between BMI and a major defect independent of pre-gestational diabetes and the multivariable model showed the odds of a major congenital abnormality to be nearly 4-fold greater amongst diabetic mothers (OR: 3.8; 95% CI: 2.1-6.6) [120].

Macrosomia

An infant is defined as macrosomic if they weight ≥4000g at birth. There is a substantial body of evidence in the epidemiological literature indicating an association between maternal obesity and macrosomia [110, 121-123]. In part, this is due to the strong association between gestational diabetes and macrosomia but overweight women are also more likely to give birth to a macrosomic infant independent of maternal diabetes [109].

Pre-term delivery

A population-based study of 167,750 women in Sweden found that nulliparous women who are obese have increased odds of very preterm (<32 weeks of gestation) compared to those with a BMI <20 kg/m^2 (OR: 1.6; 95% CI 1.1-2.3) after adjustment for a number of confounding factors including maternal age, parity, education and smoking; no association was observed between maternal BMI and delivery between 33-36 weeks gestation [124]. However, amongst parous women the odds of preterm delivery were decreased in all BMI categories compared to lean women with a BMI <20 kg/m^2 as the baseline group [124].

Other Severe Neonatal Morbidity

Maternal obesity is associated with increased admission to a neonatal intensive care unit; although these infants also require less oxygen and have a shorter average stay in intensive care than infants born to obese mothers [110].

An analysis of 58,089 women from the Maine State Birth Records database, USA, found that infants born to obese mothers were more likely to have low Apgar scores (score of 4-6) compared to those whose mother was optimal weight (OR: 1.43; 95% CI: 1.1-1.7) after adjusting for socio-demographic confounders [125]. The risk was further increased amongst morbidly obese mothers (OR: 2.03; 95% CI: 1.5-2.7) [125]. However, this study did not find an association between maternal BMI category and very low neonatal Apgar score (score of 0-3) [125] and other studies have reported no association, despite being adequately powered [80].

Neonatal Death

A large cohort study (n=24,505) of singleton pregnancies at Aarhus University Hospital, Denmark, between 1989 and 1996 found that maternal obesity more than doubled the odds of stillbirth (OR: 2.8; 95% CI: 1.5-5.3) and neonatal death (OR: 2.6; 95% CI: 1.2-5.8) compared to optimal weight women, although no statistically significant effect was observed amongst the pre-obese category [126]. This study adjusted for a large number of confounding factors including maternal age, parity, gender of the child, maternal intake of caffeine, alcohol and smoking behaviour, diabetes mellitus and hypertensive disorders.

Results from the Danish National Birth Cohort study have also found that infants born to overweight mothers are at increased risk of neonatal death (Pre-Obese HR: 1.7, 95% CI: 1.2-2.5; Obese HR: 1.6, 95% CI: 1.0-2.4) [127]. Similarly, a case-control study from the USA found infants born to obese mothers to be at increased risk of neonatal (OR: 1.57; 95% CI: 1.30-1.90), post-neonatal (OR: 1.28; 95% CI: 1.02-1.61) and overall infant (OR: 1.46; 95% CI: 1.23-1.73) death once adjusted for a range of socio-demographic confounders including age and maternal smoking [128]. A very large scale population-based cohort study of 167,750 births from Sweden is the only published study to-date to investigate the risk of death within the neonatal period [124]. The authors found no significant association between early neonatal death and obesity (OR: 1.2; 95% CI 0.7-1.7) but did find a strong association between maternal obesity and late foetal death (OR: 2.7; 95% CI: 1.8-4.1) [124]. The reported effect estimates were adjusted for maternal age, parity, education, smoking behaviour, height and whether the mother was living with the father.

2.3 The Nutrition Transition

The final part of this background chapter presents information relating to the nutrition transition in Sub-Saharan Africa, and specifically to rising levels of overweight and obesity currently occurring in the region. This section makes the case that obesity is an emerging public health issue in Sub-Saharan Africa, and is one that is likely to become of increasing importance throughout the twenty-first century.

2.3.1 Outline of the Nutrition Transition Theory

Historically, public health and development professionals have been concerned with under-nutrition; one of the targets of the first millennium development goal is to reduce by 50% the proportion of people who suffer from hunger [129-130]. Nevertheless, it is possible for an individual to be malnourished yet still have an adequate, or even excessive, calorie intake for what is required to meet their daily energy requirements [130]. It is now well-established that average BMI is increasing in almost every country in the world [131]. Whilst this is a positive development in areas that suffer from chronic food shortages, it also means that an increasing number of individuals are defined as overweight or obese.

Overweight/obesity and the corresponding burden of chronic non-communicable diseases such as hypertension, diabetes and cardiovascular problems are an emerging problem in low-income settings as well as high-income countries [44, 132-135]. Indeed, the prevalence of women who are overweight now exceeds the prevalence of women who are underweight in over half of all developing countries [136] and cardiovascular conditions and diabetes are increasing throughout Africa [43-46]. A number of authors, most notably Popkin [28, 137-140]; have documented a major shift in global human dietary and behaviour patterns since the middle of the twentieth century. This has become known as the "nutrition transition".

The nutrition transition is closely related to two other population-level trends: the demographic and epidemiological transitions. Whilst the demographic transition describes a change from a pattern of high levels of both fertility and mortality to one of low mortality and low (or even below replacement) fertility, and the epidemiological transition describes the shift from high levels of infectious disease and periodic famines to one of low levels of infectious disease but high levels of chronic disease [141], the nutrition transition describes a

shift in diet. The nutrition transition usually occurs either simultaneously with, or shortly after the demographic and epidemiological transitions [142].

The nutrition transition is hypothesised to take place over five stages, outlined in Table 2.3. This framework presents a simplified version of what is a complicated and multifaceted process, but it is a useful tool for thinking how about large-scale shifts in the diet and behaviour of a population over time.

There are, of course, many exceptions to this framework. The pattern that has been followed the most frequently to-date is the Western high-income country model, characterised by a rapid increase in consumption of high-fat, sweetened and processed foods combined with a decrease in physical activity levels associated with economic development and increasing personal wealth and disposable income [137]. However, more recent examples from the former Soviet Union, China, Korea and Latin American countries have repeatedly shown that it is possible for overweight/obesity rates to rise to high levels whilst individual incomes remain comparatively low [137, 143-145]. In part, this is due to the spread of vegetable oilseed-based fats which are relatively cheap compared to animal-based alternatives [29, 140].

Most countries in Sub-Saharan Africa are currently in the third stage of the nutrition transition but in some countries, particularly in Southern Africa and parts of Western Africa, and many urban populations are starting to exhibit many of the characteristics of Pattern Four. Obesity rates greater than 30% have been reported amongst women in squatter settlements in Johannesburg, Cape Town and rural Zulu populations [146] whilst a recent systematic review and meta-analysis of 28 studies from Western Africa showed that the obesity prevalence in urban West Africa had more than doubled in fifteen years, from 7% to 15% [35]. However, the expected transition in Africa is likely to present a number of fundamental differences to the previous experiences of current high-income countries; issues specific to the nutrition transition contemporary low-income countries are explained in the next section.

Table 2.3 The Nutrition Transition

Transition Profile	Pattern One Collecting Food	Pattern Two Famine	Pattern Three Receding Famine	Pattern Four Degenerative Disease	Pattern Five Behavioural Change
Diet	Plants, low-fat wild animals; varied diet	Cereals predominant; diet less varied	Fewer starchy staples; more fruits, vegetables, animal protein; low variety continues	More fat (especially from animal products), sugar and processed foods; less fibre	Less fat and processing; increased carbohydrates, fruits and vegetables
Nutritional Status	Robust, lean, few nutritional deficiencies	Women & children suffer most from low fat intake; nutritional deficiency diseases emerge; stature declines	Continued maternal & child health problems; many deficiencies disappear; weaning diseases emerge; stature grows	Obesity; problems for the elderly (e.g. bone health); many disabling conditions	Reduced body fat levels and obesity; improved bone health
Food Processing	Non-existent	Food storage begins	Storage process (drying, salting); canning and processing technologies; increased food refining	Numerous food transforming technologies	Technologies create foods and food constituent substitutes (e.g. macronutrient substitutes)
Economy	Hunter-gatherer	Agriculture & animal husbandry begins; shift to monocultures	Agricultural revolution (e.g. crop rotation, fertilisers). Industrial revolution.	Increased mechanisation & service sector expansion	Service sector mechanisation; industrial robotisation
Demographic Profile	Low fertility, high mortality; low life expectancy; young population	High natural fertility; low life expectancy; young population	Mortality rates fall; fertility static then starts to decline; relatively young population that gradually starts to age	Rapid fertility decline (may be some fluctuations); substantial increases in life expectancy; rapid increase in elderly population	Life expectancy extends, disability-free period increases; increasing proportion of the population >75 years
Epidemiological Profile	Infectious diseases; no epidemics	Epidemics occur; endemic diseases (plague, smallpox, tuberculosis); starvation common	Tuberculosis, smallpox and other infectious diseases and weaning diseases (e.g. diarrhoea) expand and later decline	Chronic diseases related to diet (e.g. cardiovascular disease); infectious diseases decline	Increased health promotion (preventive & therapeutic); rapid changes in cardiovascular disease; slower change in age-specific cancer profile

Adapted from Popkin (1993)[137]

2.3.2 Transition in Contemporary Low-Income Countries

Popkin (2002) [147] has suggested that the nutrition transition, as currently being experienced by low and middle income countries, will differ from that previously observed in high income countries in several important ways, namely:

1. The transition is now occurring at much lower levels of economic development and much more rapidly than previously
2. The dual existence of under-nutrition and over-nutrition as competing public health issues are creating unique challenges.
3. The socio-cultural and political context of obesity in contemporary low-income countries is different.

1. <u>The Nutrition Transition and Economic Development</u>

The start of the nutrition transition process now appears to be commencing at much lower levels of economic development than previously occurred in the USA and European countries [142]. The rate at which levels of overweight/obesity are rising in contemporary developing country populations rapid, especially amongst adult women [142].

An ecological-level analysis by Ezzati *et al.* (2005) [148] clearly demonstrated the association between prevalence of overweight/obesity and economic development. The authors compared age-standardised mean BMI to national income (measured by GDP per capita in International dollars[2]) using data from 69 countries of varying levels of economic development. Mean BMI was shown to increase until GDP reached around I$12,500 (for females) or I$17,000 (for males); subsequently a slow decline in mean BMI was observed once national income reached around I$20,000 [148]. The fastest rate of increase in mean BMI was seen in countries with the lowest GDP [148]. A similar trend to this was also was observed in a separate cross-national analysis by Martorell *et al.* (2000) [27].

The Ezzati *et al.* study also looked at whether there is an association between the proportion of household income spent on food and mean BMI. They found that an inverse association exists, but only in settings where the proportion of household income spent on food is more

[2] The international dollar (I$) is a hypothetical unit of currency which adjusts local currency for purchasing power and inflation using the US dollar as the standard.

than 30-40%; below this cut-off there is no significant relationship between the two factors [148]. Food purchases take up a greater proportion of income in low-income groups; therefore cost-effectiveness becomes relatively more important. The 1995 Income and Expenditure Survey from South Africa found that households defined as in food poverty (those who spent less money on food than the cost of a basic, nutritionally-adequate food basket) spent a mean of 49.4% (±0.9%) of their income on food, compared to 30.8% (±0.3%) of food secure households [149].

Low cost, commercially available foods (as may often be purchased by poorer families living in urban areas) are often energy-dense but nutrient-poor [150]. Healthier foods, such as wholegrain starches, fruits and vegetables are more expensive; furthermore if cost per joule of energy content is taken into account the difference can rise to over 1000% [151-152]. In rural environments grains and vegetables are grown locally; however in urban areas where all or nearly-all food must be purchased cost-energy ratio becomes an important consideration. Surveys of food stores in South Africa have noted that healthy food choices are nearly always available, but are less affordable [153]. By calculating the calorie content and cost of typical South African diets, and then calculating the cost of replacing items with a healthier option (for example lean hamburger meat replacing standard hamburgers; bran flakes replacing corn flakes ; wholemeal starches replacing white starches) a healthier diet was estimated to cost Rand 10.2 more per day (a 69% increase in cost) [153].

As any given country progresses through the nutrition transition the relationship between socio-economic status and overweight/obesity changes [136]. A recent review of the association between obesity and socio-economic status amongst adults in developing countries between 1989 and 2003 concluded that obesity is no longer solely a problem of the higher socio-economic groups [144]. Cross-sectional studies from fourteen individual countries were included (Albania, Brazil, Chile, China, Cuba, India, Lithuania, Peru, the Russian Federation, Samoa and South Africa) in addition to two multi-country studies [27, 154] which are discussed below. The review concluded that the association between socio-economic status and obesity differed according to gender: half the studies found a positive association between socio-economic status and obesity amongst men (the other half found no significant association); in contrast, amongst women most studies (10/14) obesity was most prevalent in the lower socio-economic groups (two studies found a positive association and the remaining two found no association)[144]. However, it should be noted that the definition of a developing country used in this review was any country with a GNP below US $9,075, which includes countries defined as middle-income by the World Bank [144]. Thus of the countries included in the review, only India (GNP US $390) and China (GNP US $710) would be classified

as a low-income setting [144]. There is a noticeable paucity of research originating from very low income countries.

An analysis of 38 nationally-representative nutrition surveys by Martorell *et al.* (2000) [27] used a binary education variable as a proxy for socioeconomic status. All of the data in this analysis was cross-sectional, mostly DHS data. They showed that the magnitude of the association between education and obesity was related to GNP. For example in Sub-Saharan Africa, after adjusting for age, the odds of being obese were much larger amongst women who had been educated to above primary school level compared to women with low education (for example Burkina Faso OR: 10.69, $p<0.001$; Malawi OR: 13.04, $p<0.001$; Niger OR: 13.67, $p<0.001$) whilst in Latin America the odds ratios were closer to one or even inverted (for example Mexico OR: 0.59, $p<001$; Dominican Republic OR: 0.82, $p<0.01$; Peru OR 1.67, $p<0.001$) [27]. Unfortunately, the analysis only included age, area of residence (urban/rural) and education as covariates so these results may be biased by residual confounding.

Similarly, Monteiro *et al.* (2004)[154] also used education as a proxy for socioeconomic status in their analysis of 37 nationally-representative surveys (18 of the surveys from the Martorell *et al.* and the Monteiro *et al.* study are the same). They found that the age-adjusted prevalence of obesity was significantly higher amongst the most educated quartile compared to the least educated quartile in most (26/37) countries, no statistically significant difference in three surveys and a higher risk of obesity amongst the least educated quartile in the remaining counties (8/37) [154]. The authors also found there to be a significant interaction between education and national GNP and estimated that the point where the probability of obesity in the lower educated group exceeding the probability in the highest educated group occurred when a country reached around US $ 2,500 [154]. This is approximately the current level of economic development in Swaziland; most countries in Sub-Saharan Africa are currently at a lower level of development [155].

2. The 'Dual Burden' of Underweight and Overweight

The emergence of the phenomena of dual burden households has been noted by several authors but the underlying processes are not clear [150, 156]. These are households containing at least one underweight individual and one overweight individual (very often a mother and child).

It has been hypothesised that, in all but the very poorest countries or fragile states, food scarcity is no longer the main factor in malnutrition [150]. Particularly in urban areas, a dominant part of the diet has become energy-dense cheap foods which are low on nutritional

content but may be highly processed and contain relatively high levels of fats and sugars. The nutritional content of food is very important to the growth patterns of young children [157].

A rare example of a longitudinal nutrition study in Sub-Saharan Africa is the "Birth-to-Twenty" cohort of urban South African children born in 1990. The first food-frequency questionnaire for this cohort was conducted in 1995 and collected data for 1096 children; however by 2003 only 143 children remained in the cohort. Amongst these 143 children the mean daily calorific intake in 2003 (when they were thirteen years old) was 2127 kcal (95% CI: 1994-2260 kcal) but 93% of individuals did not appear to be getting the recommended daily allowance (RDA) of calcium, 74% were not receiving their iron RDA and 78% were below the RDA for vitamin A [158]. This cohort study suffers from very substantial losses to follow-up so few conclusions can be drawn from the data.

Dual burden households are not relevant to the research questions in this thesis and will not be discussed further here. But they serve to demonstrate some of the unique challenges posed by rising obesity levels in countries at a low level of economic development.

3. Different Socio-Cultural Context to Obesity

The double burden of over-nutrition and under-nutrition, combined with an existing burden of infectious disease and poor health infrastructure; all taking place over a relatively short timeframe compared to that experienced by contemporary high-income countries means that the political environment to combat obesity is very different. Government and donors priorities are not focused on issues of non-communicable diseases and it is seen as a problem concerning only the elite members of the population [52, 159].

Furthermore, in many countries in Sub-Saharan Africa obesity does not have the negative image attached to it that exists in many high-income countries, so some of the incentives to diet and lose weight are absent. Qualitative research from South Africa [160] and Senegal [161] has suggested that being overweight may be perceived as a sign of good health, prosperity and happiness, so there may be little social pressure to maintain an optimal body weight.

Evidence from the few diabetes programmes currently in place in Africa have reported that it is difficult to persuade patients of the importance of maintaining a healthy weight; weight loss may be stigmatised due to its association with AIDS [162].

2.3.3 Increasing BMI in Sub-Saharan Africa

Obesity is caused by energy imbalance; energy intake exceeds physical activity levels and the excess energy is stored in the body as fat. This section will discuss the literature relating to diet and physical activity in Sub-Saharan Africa; however I will begin by describing urbanisation in the region. Urbanisation is a key correlate of rising BMI; although not causally related, it is closely associated with behavioural and lifestyle shifts which are associated with the two immediate determinants of weight gain: energy intake (i.e. diet) and energy expenditure (i.e. level of physical activity.) An analysis of DHS data from seven Sub-Saharan countries between 1992 and 2005 found that the prevalence of overweight and obesity increased by 35.5% amongst urban residence in this period [163].

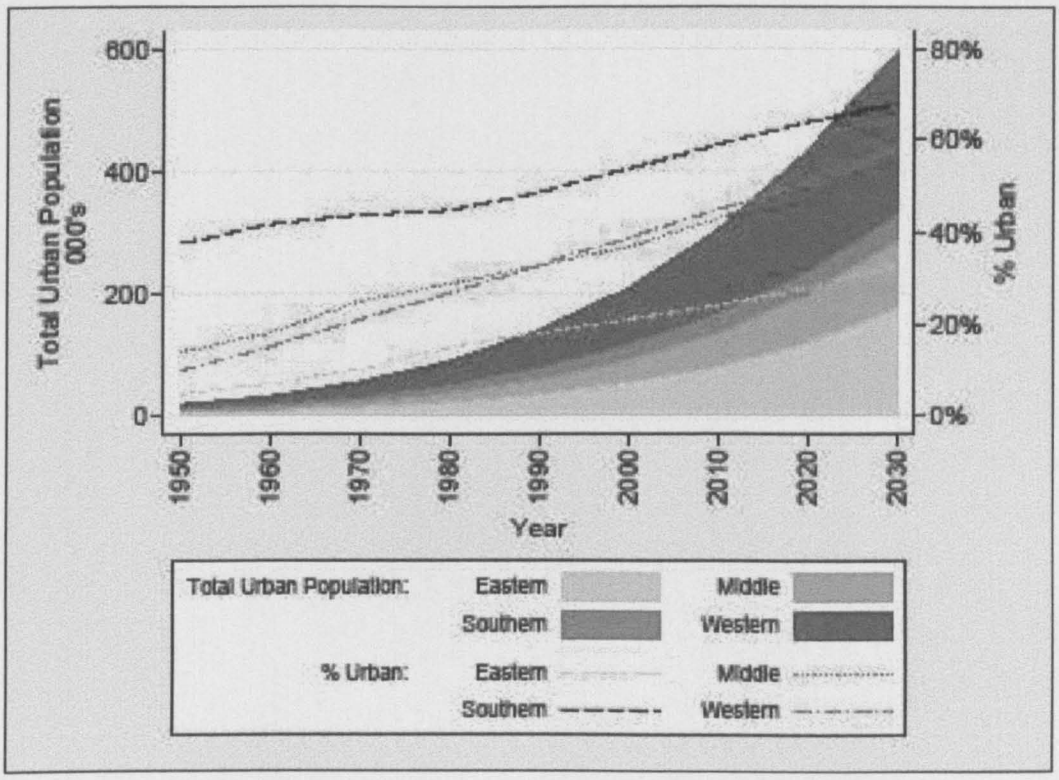
Urbanisation

Globally, the number of people living in urban areas increased from 220 million to 2.8 billion over the twentieth century, and by 2008 half the world's population (3.3 billion people) were living in urban areas [164]. Both the absolute number and proportion of the global population living in urban areas are expected to continue increasing in the 21st century, the number of urban-dwellers is projected to reach around 4.9 billion by 2030 [164]. In 2009 the total population of Africa reached one billion, with 395 million (nearly 40%) living in urban areas.

The total population of Africa is expected to increase by around 60% between 2010 and 2050, whilst the urban population is set to triple to 1.23 billion over the same period [165].Within Sub-Saharan Africa, Eastern Africa is currently the least urbanised region on the continent (around 23.5% urban) and Southern Africa is the most urbanised (58.7%) but a similar increasing trend can be observed across the entire continent [165] (see Figure 2-A).

Further rises in urbanisation are expected to continue at least in the medium-term in Sub-Saharan Africa, which suggests that the proportion of overweight/obese should be expected to rise.

Figure 2-A Urbanisation Trends in Sub-Saharan Africa



Data extracted from UN-HABITAT (2010) [165]

Living in urban areas is a key risk factor for increasing BMI because urban populations tend to include more polished grains, high-fat, high-sugar and processed foods in their diet, and are more likely to eat convenience foods prepared away from home [137, 166-167]. Urban dwellers are furthermore less likely to be engaged in an energy-intensive form of employment than those living in rural areas [166, 168-169] and are also less likely to engage in physical leisure activities, especially if they live in a poorer neighbourhood [170-172]. Urban residence was found to be an independent risk factor for being overweight amongst adult women in Mozambique in a nationally-representative cross-sectional survey, after adjustment for age, income and education (OR: 2.75; 95% CI 1.82-4.18) [34]. A similar survey from Ouidah, Benin found that urban-rural differentials in obesity were mainly explained by differences in socio-economic status and physical activity levels [168]; although, this study did not investigate dietary intake which is also likely to be an important contributory factor.

Shifts in Diet Structure

As previously outlined, the development of vegetable oil-based fats has meant that fat-based diets have become available to those at lower income levels than previously. According to the

nutrition transition theory, typical diet in countries yet to undergo or early in the transition will primarily consist of starchy foods with little variety, low fat and high fibre content; these are replaced by increased fat and sugar content as the transition progresses [142]. However, there will be many geographic and cultural variations on this theme, particularly in the early stages of the transition when much food will be locally produced. In particular urban versus rural diets are likely to differ.

It is very difficult to assess shifts in African diet structure due to the lack of robust evidence available. Methods to assess dietary intake in such settings are still being developed and any historical data are likely to be even less robust. One attempt to describe temporal trends in dietary intake by measuring fat and carbohydrate intake amongst adults in Johannesburg, South Africa, showed a 10.9% relative reduction in the proportion of energy intake from carbohydrates (from 63.3% to 61.7%) in 1990 compared to 1940 and a relative 59.7% increase in energy intake from fats over the same period (from 16.4% to 26.2%) [173]. The review found that in absolute terms, carbohydrate intake shifted from an average of 334 g/person/day to 245 g/person/day and fat consumption increased from 34 g/person/day to 54 g/person/day [173]. Nevertheless, insufficient methodological detail was provided by the authors to draw any strong inferences from these results.

Whilst trend data are lacking, more recent cross-sectional studies have provided somewhat more detailed information on some aspects of contemporary dietary intake. A cross-sectional survey of 1011 households in two areas of Nairobi, Kenya (Korogocho: a low income slum, and Dandora: a low-middle income area) found that food purchased from street vendors plays an important part in the diet of poor households [174]. On average households in Korogocho consumed street foods 3.6 days per week with 40% reporting consuming street foods nearly every day; in the low-middle income area, Dandora, on average household s consumed street foods 2 days per week and 20% of households reported near-daily consumption [174].

A more detailed questionnaire containing open-ended responses was administered to a stratified sample of 73 households from the main study [174]. This found that the most commonly bought street food was *mandazi*, deep-fried dough similar to a doughnut, which in many households was bought from a street vendor but eaten inside the home by the whole family as a breakfast meal. Overall, 42 out of 73 households (58%) said that they bought street food because they were cheap; nevertheless 57 households (78%) reported that home-prepared foods tasted better and 59 households (81%) reported street foods to have a "very bad" or "a little bad" effect on health; although sufficient contextual was not provided to

suggest whether participants were likely to be meaning from a general healthiness or food hygiene perspective [174].

A subsequent study conducted in 302 out of the original households measured the nutritional content of foods consumed over three 24-hour recall periods per individual [175]. The contribution of non-home prepared foods to daily fat intake was higher than the contribution to daily energy intake, whilst the contribution to iron, vitamin A and calcium intake was lower ($p<0.001$) [175]. Nevertheless, total energy intake was still relatively low and all groups consumed fewer calories than their recommended daily intake. Energy and nutrient intake was similar amongst those who reported consumed street foods and those who only consumed home-prepared foods, suggesting that the types and quantities' of foodstuffs consumed were similar [175].

The importance of street foods to the urban diet was also observed in Western Africa [176]. A recent study of adolescents in *Seconde* grade in Cotonou, Benin (mean age 16.3 years) found that out-of-home prepared foods contributed more than 40% of their average daily energy intake. The dietary diversity of low-consumers of out-of-home foods was similar to high consumers in terms of the number of different types of foods eaten, but low-consumers were seen to include more fruit and vegetables in their diet. Both low-consumers and high-consumers of out-of-home foods had a high daily fat intake, getting 30% of their energy intake from fats [176].

Evidence relating to temporal trends in dietary intake in Sub-Saharan Africa is very weak, so it is not possible to attribute current diets to any form of transition. However, there is clear evidence in urban areas that convenient "take-away" and cheap foods were of substantial importance even to the poorer income groups.

Shifts in Physical Activity Levels

Urbanisation is usually linked to declining physical activity levels because employment options in towns and cities are often more sedentary than in rural areas and less distance typically needs to be travelled to obtain food or water. However, the evidence available to evaluate temporal trends in physical activity is even more limited than reviewed in the previous section on diet. Many studies use some form of self-reported measure to report on activity during the previous week. However, such studies are methodologically limited; there are many cultural differences inherent in the relevance and phrasing of questions; and what is considered to be meaningful exercise differs according to context [177-178].

Despite these limitations, some physical activity studies do exist for Sub-Saharan Africa, which give a broad indication of urban/rural and gender differentials in physical activity levels. A systematic review and meta-analysis of the prevalence of physical activity in adult West African populations retrieved ten sub-national population-based studies and five nationally-representative but unpublished studies (World Health Surveys for the assessment of cardiovascular risk factors [179].) Overall, 75% of urban West African adults were described as having "sedentary occupations" [179]. However, there was substantial variation between studies in both estimates and the definitions used to classify physical inactivity. Comparing the World Health Surveys, which used a standardised questionnaire, estimates of inactivity amongst urban women ranged between 11.4% in Burkina Faso to 30.9% in Mali; the range amongst rural women ranged between 6.2% in Cote d'Ivoire 20.5% in Senegal [179]. A pooled analysis of the World Health Survey data found that 13% (95% CI: 9-18%) of West African populations were inactive, and that inactivity was highest amongst urban women. Inactivity increased with age amongst both sexes [179].

A cross-sectional study of non-pregnant, apparently healthy (no previous diagnosis of hypertension, diabetes or coronary heart disease) urban adults (25-60 years) living in Cotonou, Benin found substantial gender differentials in physical activity levels [169]. Prevalence of obesity in this study population was nearly four times higher in women than in men (28% vs. 8%) [169]. Participants were asked to recall all physical activity within three 24-hour periods; 70% of women reported less than 30 minutes of moderate physical activity a day compared to just 14% of men. Conversely 39% of men reported vigorous physical activity for 20 minutes or more compared to just 1% of women [169].

Women also had a much lower level of physical activity than men in Ethiopia [180]. A cross-sectional sample of adults aged 25-64 years living in Addis Ababa, Ethiopia surveyed using the WHO STEPS instrument with a probability-based sampling strategy, for collecting data on socio-demographic characteristics and lifestyle behaviours, associated with chronic diseases found that 10.5% (95% CI: 6.46-12.11%) of women were obese compared to 2.0% (95% CI: 1.30-2.70%) of men [180]. Overall, 31.2% (95% CI: 29.25-33.15%) of women had a low level of physical activity (sedentary) compared to 16.9% (95% CI: 15.0-18.7%) of men [180].

One South African study of rural, black adult women attempted to objectively measure the association between adiposity and physical activity by using pedometers to measure mean steps per day [181]. They found that BMI decreased by 1.4 kg/m^2 for each additional 5000 steps per day ($p=0.035$), after adjusting for age, motor vehicle access, education, tobacco use and self-reported co-morbidities [181]. Unfortunately the analysis in this study was not

extended further to investigate important questions such as what characteristics were associated with the different activity levels.

In conclusion, prevalence of overweight/obesity and related chronic diseases are rising in low and middle income countries; this process is known as the "nutrition transition". Although prevalence is currently low by global standards, overweight/obesity is expected to rise rapidly in Sub-Saharan Africa over the next few decades. Much of this process may be attributable to the changes in physical activity levels and diets associated with urbanisation.

Chapter 3
Methods

The purpose of Chapter 3 is to describe the data and statistical methods used throughout this thesis.

The chapter begins by describing the data source of the Demographic and Health Surveys (Section 3.1). Information relating to the survey design and the structure of key questionnaire modules is provided. Section 3.2 outlines how the four main outcome variables used in this thesis were operationalised and discusses the considerations and decisions that were made in variable construction. This process is then repeated for the primary exposure variable, BMI, which is common to all analyses throughout the thesis (Section 3.3). In Section 3.4, I provide details regarding the statistical methods used in my thesis, including an explanation of how the complex survey design of the DHS was accounted for in the analyses and a discussion of methodological issues related to data clustering.

3.1 Data Source: the Demographic & Health Surveys

3.1.1 Survey Design

The Demographic and Health Surveys (DHS) are nationally-representative surveys, implemented by ICF Macro and funded by USAID, which were originally designed to focus on fertility, child health and family planning in low-income countries but have since been expanded to include modules on nutrition, anthropometry and HIV/AIDS. Work on the first DHS began in 1984, and anthropometry was included for the first time in 1987 (in Sri Lanka). DHS has now carried out over 240 surveys in 85 countries, and in many countries in Sub-Saharan Africa the surveys are carried out regularly, at approximately five yearly intervals. The data are made freely available to registered users for bona fide research purposes, and is widely used in demographic, epidemiological and social science research. Extensive documentation is available online, including methodological reports into some known data quality issues [182].

DHS use consistent sampling designs and the same core questionnaire modules, in order to facilitate comparisons between countries and time points. Surveys are implemented by a national in-country agency with technical training and support from ICF Macro. The sample is designed to be representative at the national level, the residence level (urban or rural) and the regional level [183]. In most of the countries included in this study a two-stage cluster design was used.

Typically, the entire country is divided up into non-overlapping enumeration areas (EAs) based on a pre-existing sampling frame, often developed from a previous national census [183]. If the EA is too large to be accurately mapped then it may be split into more manageable segments. Clusters (also known as primary sampling units, PSUs) are selected from within this sampling frame; a "take" of households is then systematically selected from within each PSU [183].

Most surveys (the exceptions in this thesis are Burkina Faso, DRC and Sierra Leone) used some form of stratification. Stratification has three advantages over simple random sampling: (i) precision may be increased (i.e. the standard errors are reduced); (ii) it is possible to obtain stratum-specific estimates with specified precision which is useful if results need to be produced on a regional level or for specific population sub-groups; (iii) administratively and logistically stratified sampling has advantages over generating a simple random sample over an entire country [184].

Although the DHS states that ideally survey samples should be self-weighting with all eligible women having an equal probability of selection [183], in practice sample weights are usually necessary for analysis. This is because certain areas or groups are often over-sampled in order to allow findings for a particular population subgroup to be reported, a weight therefore has to be introduced to allow for the unbalanced sampling in whole population analyses.

Table 3.1 Survey design

Survey	Year	No. of Primary Sampling Units (PSUs)	Total Households Selected	Household Response Rate	Eligible Women Response Rate
Benin	2006	750	17,982	99.1%	94.4%
Burkina Faso	2003	400	9,470	99.4%	96.3%
Cameroon	2004	446	11,556	94.3%	94.3%
Chad	2004	196	5,512	99.4%	97.2%
Congo-Brazzaville	2005	225	6,012	99.2%	94.8%
Democratic Rep. of Congo	2007	300	9,002	99.3%	96.7%
Ethiopia	2005	540	14,645	98.5%	95.6%
Ghana	2008	412	12,323	99.1%	96.5%
Guinea	2005	297	6,480	99.2%	97.2%
Kenya	2008-09	400	9,936	97.7%	96.3%
Lesotho	2004	405	9,903	95.2%	94.3%
Liberia	2007	300	7,471	97.2%	95.2%
Madagascar	2008-09	600	18,985	98.8%	95.6%
Malawi	2004	522	15,041	97.8%	95.7%
Mali	2006	410	13,695	98.8%	96.6%
Mozambique	2003	858	14,475	94.8%	90.9%
Namibia	2006-07	500	9,970	97.8%	94.7%
Niger	2006	345	8,418	97.9%	95.6%
Nigeria	2008	888	36,298	98.3%	96.5%
Rwanda	2005	462	10,644	99.7%	98.1%
Senegal	2005	377	7,859	98.5%	93.7%
Sierra Leone	2008	353	7,758	97.6%	94.0%
Swaziland	2006	275	5,500	95.2%	94.1%
Tanzania	2004	475	10,312	98.8%	97.3%
Uganda	2006	368	9,864	97.5%	94.7%
Zambia	2007	320	7,969	97.8%	96.5%
Zimbabwe	2005-06	400	10,752	95.0%	90.2%

The household and eligible women's response rate by survey are also provided in Table 3.1. All women aged 15-49 years who usually live in the household and guests who stayed there the previous night are eligible to participate. The household response rate is the proportion of households where an interview was held out of those that were found to be occupied (some structures identified in the sampling selection were found to be vacant or destroyed). The

eligible women's response rate is the proportion of successful interviews out of those women identified as eligible during the household questionnaire.

Both the household and eligible women response rates are relatively high in the DHS. All surveys had a household response rate greater than 94%. The eligible women response rate ranges from 90.2% (Zimbabwe, 2005-06) and 98.1% (Rwanda, 2005) in this study. The main reason for non-response for eligible women was failure to locate the women at home. In the case of the desired respondent not being at home, interviewers are generally required to call back on at least three occasions at different times of day before abandoning an interview attempt [185-186].

3.1.2 Data Editing and Imputation Procedures

The questionnaire used in the DHS has a complex system of checks and skips to ensure that the data collected during fieldwork is as complete and accurate as possible [187]. However, it is inevitable some errors do occur. During the data entry stage a range of consistency checks are made and implausible values flagged for further checking and imputation. The DHS does not allow certain variables to have missing or implausible values; this includes key dates (for example, birth date of the respondent, date of first union, birth dates of children.) If a plausible value was not collected during fieldwork then this information is imputed. This is done in a four step process [188]:

1. An unconstrained range is initially calculated from the data available, for example, if the year but not the month of an event is available then this range will span twelve months.

2. The range is adjusted using other relevant variables, for example the year for respondent's date of birth could be inferred from her current age and the date of the interview.

3. The range is adjusted to fit with neighbouring constraints where events must form a logical sequence. For example the birth date of a child must be separated by the minimum required time from conception to delivery from births on either side (deemed to be seven months to allow for premature births).

4. A value is randomly imputed within the final logical range.

The proportion of missing or implausible data for each survey is displayed in Table 3.2. In general, this figure is relatively low; imputation was required for a mean of 5.2% of months for

the respondent's date of birth, but in only 0.1% of cases was the imputation of both the month and year required. However, there were a few notable exceptions to this, in particular in Benin (13.5%), Niger (15.1%) and Guinea (46.6%) of the month of birth values were missing. This is not necessarily an indication of poor fieldwork quality, it is possible that women in these cultures are less likely to attach importance or remember such information or that the interviewers were less willing to probe or guess a date. Data on age at first union was generally fairly complete and less than 2% of women had missing or implausible data for this variable in all countries.

Table 3.2 Proportion of data coded as 'missing' or 'implausible'

Survey (year)	Birth Date		Age at First Union	Child Births with a Complete Date		
	Month Only	Month & Year		Living	Dead	Total
Benin (2006)	13.5%	0.1%	0.3%	84.2%	70.9%	82.2%
Burkina Faso (2003)	5.2%	0.0%	0.1%	93.8%	86.1%	92.3%
Cameroon (2004)	6.2%	0.2%	0.7%	92.9%	83.0%	91.2%
Chad (2004)	1.8%	0.0%	0.4%	98.1%	97.1%	97.8%
Congo-Brazzaville (2005)	2.6%	0.0%	0.4%	97.7%	87.9%	96.5%
Democratic Rep. of Congo (2007)	2.1%	0.1%	1.0%	98.6%	91.8%	97.4%
Ethiopia (2005)	1.2%	0.1%	0.2%	98.7%	96.8%	98.4%
Ghana (2008)	3.4%	0.1%	0.3%	96.3%	89.0%	95.5%
Guinea (2005)	46.6%	0.0%	0.0%	48.6%	25.5%	43.4%
Kenya (2008-09)	1.7%	0.1%	0.5%	97.9%	94.8%	97.6%
Lesotho (2004)	0.7%	0.2%	1.1%	99.3%	95.8%	98.9%
Liberia (2007)	2.9%	0.1%	1.9%	97.0%	94.7%	96.6%
Madagascar (2008-09)	1.6%	0.0%	0.9%	98.4%	92.4%	97.8%
Malawi (2004)	1.0%	0.1%	0.9%	99.2%	96.4%	98.7%
Mali (2006)	7.0%	0.1%	0.0%	92.7%	84.8%	90.8%
Mozambique (2003)	2.9%	0.1%	1.8%	97.2%	91.0%	95.9%
Namibia (2006-07)	0.5%	0.2%	0.9%	99.4%	95.0%	99.1%
Niger (2006)	15.1%	0.1%	0.0%	83.3%	74.5%	81.1%
Nigeria (2008)	2.5%	0.2%	2.0%	97.4%	92.7%	96.5%
Rwanda (2005)	2.4%	0.1%	0.1%	97.1%	91.4%	96.0%
Senegal (2005)	9.4%	0.2%	0.6%	89.4%	78.6%	87.8%
Sierra Leone (2008)	2.7%	0.7%	0.8%	96.7%	89.1%	95.3%
Swaziland (2006)	0.5%	0.2%	0.0%	99.4%	96.2%	99.1%
Tanzania (2004)	1.6%	0.0%	0.1%	98.4%	93.9%	97.7%
Uganda (2006)	2.7%	0.0%	0.1%	96.8%	89.4%	95.6%
Zambia (2007)	0.8%	0.0%	0.8%	99.5%	96.7%	99.0%
Zimbabwe (2005-06)	0.4%	0.1%	0.4%	99.5%	97.5%	99.3%

The final column of Table 3.2 provides the proportion of child births with a complete date. As might be expected, complete recall was uniformly higher for those children who were still alive at the time of the interview than for those who had died. Only four countries had more than 10% of child births without a complete recorded date; these were Senegal (12.2%), Benin (17.8%), Niger (18.9%) and Guinea (56.6%). It is perhaps concerning that the countries with the highest proportion of missing data for both respondent and child dates of birth were the same. Guinea in particular appears to have had substantial difficulties.

The data which the DHS makes publically available is in the form of a standardised recode file. Standard variables (for example age, education and the birth history) are in one section and country-specific variables are in another. As far as possible, variable names and definitions are kept consistent between different surveys.

3.1.3 Structure of the DHS Questionnaire

Throughout this thesis most of the variables I have used were collected in the women's questionnaire, which is administered to women aged 15-49 years. Women's height and weight measurements were recorded in the household questionnaire, as was information on household assets, which was used to construct the wealth quintile variable.

The DHS questionnaire follows a standardised format from country to country to enable cross-country and temporal comparisons to be made [187]. A carefully designed system of skips and checks is used to ensure completeness. Here I describe the design of two questionnaire modules used throughout the thesis: the DHS birth history module and the reproductive calendar.

DHS Birth History Module

In the DHS women are asked detailed questions about their birth history, displayed below. Responses are available in the standard recode file for up to the last twenty live births. The DHS also asks a series of probes and checks relating to the number of sons versus daughters born, the number still alive, and the number who still live with the woman, which are summed by the interviewer and used to prompt the respondent to minimise the chance that births will be forgotten by the respondent.

Table 3.3 Birth history questions (1)

QUESTION WORDING (AS PER MODEL QUESTIONNAIRE)	POSSIBLE RESPONSES
#212. What name was given to your first/next baby?	
#213. Were any of these births twins?	Single/Multiple
#214. Is (NAME) a boy or a girl?	Boy/girl
#215. In what month and year was (NAME) born? (Probe: What is his/her birthday?)	Month and year recorded
#216. Is name still alive?	Yes/no
#217. (IF ALIVE) How old was (NAME) at his/her last birthday?	Age in completed years recorded
#218. (IF ALIVE) Is (NAME) still living with you?	Yes/no
#220. (IF DEAD) How old was (NAME) when he/she died?	The interviewer probes to record the age at death in days if less than one month; months if less than two years; or years
#221. Were there any other live births between (NAME OF PREVIOUS BIRTH) and (NAME) including any children who died after birth?	Used as a prompt to check that no births are accidentally omitted.

Thus the birth history is not only be used to determine the respondent's total parity but also to provide information such as multiple births, birth intervals and infant and child mortality. The respondent is subsequently asked a few further questions relating to current pregnancy status and menstruation. This section will later be used to construct both the subfertility and time to first birth variables, and also the neonatal mortality outcome.

The DHS contains very detailed data on previous live births. Unfortunately the data are not so complete for stillbirths, abortions or miscarriages. The main question asked on the subject: "Have you ever had a pregnancy that miscarried, was aborted, or ended in a stillbirth?" makes it impossible to differentiate between the events. A few countries have introduced additional questions, for example if a still birth was macerated or fresh; however in this thesis I needed to focus on data that was available over a large number of countries in order to allow me to gain sufficient statistical power by pooling.

Table 3.4 Birth history questions (2)

QUESTION WORDING (AS PER MODEL QUESTIONNAIRE)	POSSIBLE RESPONSES
#229. Have you ever had a pregnancy that miscarried, was aborted, or ended in a stillbirth?	Yes/no
#230. When did the last such pregnancy end?	Month and year recorded

If the date provided in response to question #230 is within the previous five full calendar years (i.e. the period covered by the reproductive calendar, described below) then the month of the pregnancy termination and the duration of pregnancy prior to termination are recorded in the calendar. And the interviewer further probes for additional pregnancy terminations within this five year period. The respondent is then asked the equivalently worded questions to above.

Table 3.5 Birth history questions (3)

QUESTION WORDING (AS PER MODEL QUESTIONNAIRE)	POSSIBLE RESPONSES
#235. Did you have any miscarriages, abortions or stillbirths that ended before (DATE REPRODUCTIVE CALENDAR COMMENCES)	Yes/no
#236. When did the last such pregnancy that terminated before (DATE REPRODUCTIVE CALENDAR COMMENCES) end?	Month and year recorded

Therefore, information is collected in the DHS on all terminations in the five full calendar years preceding the survey, subject to disclosure and recall by the respondent. However, if the respondent reports having a termination prior to the start of the calendar we do not know the total number (only that it was one or more).

DHS Reproductive Calendar

The DHS reproductive calendar was introduced in countries with a high contraceptive prevalence and collects monthly data on births, pregnancies and terminations, contraceptive use and marital unions in the five full calendar years preceding data collection. It has primarily been used to analyse topics such as contraceptive switching and discontinuation [189-191]. As this module is used in countries deemed to have high contraceptive use, few countries in Sub-Saharan Africa have had this collected. However, in more recent DHS a reduced calendar, containing just one column (information on pregnancies and contraceptive use) has been

introduced. Datasets in my study which do contain contraceptive data in the reproductive calendar are:

- Ethiopia (2005)
- Ghana (2008)
- Kenya (2008-09)
- Madagascar (2008-09)
- Malawi (2004-05)
- Namibia (2006-07)
- Nigeria (2008)
- Sierra Leone (2008)
- Swaziland (2006-07)
- Tanzania (2004-05)
- Uganda (2006)
- Zambia (2007)
- Zimbabwe (2005-06)

The module is carefully designed to minimise recall bias in as far as is possible. This is done by building up information in stages throughout the interview. For example, at the end of the birth history section (described above) the interviewer is carefully instructed:

> *"For each birth since <January XXXX> enter 'B' in the month of birth in the calendar... Ask the number of months the pregnancy lasted and record 'P' in each of the preceding months according to the duration of pregnancy. (Note: the number of 'P's must be one less than the number of months that the pregnancy lasted."[187]*

A similar process is then followed for pregnancies that ended in a termination (miscarriage, abortion or stillbirth). Questions are then asked relating to which contraceptive methods the respondent has ever heard of, and of these which she has ever used. For women who have ever-used contraception the interviewer is instructed:

> *"Use calendar to probe for periods of use and non-use, starting with most recent use, back to <January XXXX>. Use names of children, dates of birth and periods of pregnancy as reference points. Enter method use code of '0' for non-use in each blank month.*
>
> *Illustrative questions:*
>
> - *When was the last time you used a method? Which method was that?*
> - *When did you start using that method? How long after the birth of (NAME)?*
> - *How long did you use the method then?"[187]*

This probing continues until the calendar is completed. In this PhD thesis, the reproductive calendar has primarily been used for the analysis of the interval between first marriage and first conception.

3.1.4 Regional Groupings Used in this Thesis

Throughout this thesis, I shall be presenting my results according to geographic sub-region, according to according to the UN Geographical Sub-Region Classification Scheme [192]. As several of my outcomes (in particular caesarean delivery and neonatal death) are rare, and obesity prevalence in Sub-Saharan Africa is low by global standards (see Chapter 4) I would have insufficient statistical power to examine this association in a multivariable model without pooling national datasets.

I decided to do this according to UN geographic sub-region in order to increase the comparability of my results with those from other study; furthermore grouping according to UN Sub-region also, to some extent, groups countries according to shared culture (for example much of Western Africa are Francophone countries, whilst a substantial proportion of countries in the Eastern Region use either Swahili or English as a lingua franca.) Shared language has been shown to be influential in the demographic transition [193], and conceivably could also influence the nutrition transition.

The country classification system is shown in Table 3.6.

.

Table 3.6 UN Sub-Region geographic classification system

UN Sub-Region	Country
Eastern Africa	Ethiopia (2005) Kenya (2008-09) Madagascar (2008-09) Malawi (2004) Mozambique (2003) Rwanda (2005) Tanzania (2004) Uganda (2006) Zambia (2007) Zimbabwe (2005-06)
Middle Africa	Cameroon (2004) Chad (2004) Congo-Brazzaville (2005) Democratic Republic of Congo (2007)
Southern Africa	Lesotho (2004) Namibia (2006-07)
Western Africa	Benin (2006) Burkina Faso (2003) Ghana (2008) Guinea (2005) Liberia (2007) Mali (2006) Niger (2006) Nigeria (2008) Senegal (2005) Sierra Leone (2008)

3.2 Construction of the Outcome Variables

This section explains how each of the main outcome variables used in this thesis: (i) subfertility; (ii) time to first conception; (iii) caesarean delivery; and (iv) neonatal death, were constructed. The measurement of height and weight in the DHS and the construction of the primary exposure variable (BMI) and other explanatory variables are subsequently discussed in Section 3.3 and Section 3.4.

3.2.1 Subfertility

The DHS is a very rich source of fertility data; however it focuses on children already born and unmet need for contraception in line with the priorities of most governments and NGOS, rather than women who desire a child but are unable to conceive. The DHS does not contain any question specifically relating to whether a woman is currently attempting to conceive, or the length of any pregnancy attempt.

Conceptual Framework

Figure 3-A presents the conceptual framework used in this thesis to inform the analyses on reduced fecundity, which will be presented in Chapter 7. The outcome (reduced underlying fecundity) is shown in red; the primary exposure (excess adiposity) is shown in blue; confounding factors are shown in green. The white box in the centre of the diagram presents the biological mechanisms through which excess adiposity is thought to act to reduce fecundity; no information relating to these mechanisms is available in the DHS. As explained in Chapter 2, increased adiposity is known to cause hormonal imbalances which may lead to anovulation and furthermore is associated with spontaneous pregnancy loss. HIV status is also presented in a white box as it is not included in the analysis.

The variables in the top green box (age, parity and smoking behaviour) act as confounders in the relationship by acting on both obesity and one or more of the biological mechanisms. Female fecundity is highest when a woman is in her twenties and declines thereafter, slowly until around age 35 years and then more rapidly thereafter [66]. Parity may act in either direction; on one hand a woman with one or more previous births has demonstrated her fecundity previously, on the other hand in the Sub-Saharan context increased parity increases the risk of birth injuries or infection from a previous delivery which may impair future fecundity [7]. Smoking has been demonstrated to have a detrimental effect on fecundity in high-income countries [194]; nicotine has been detected in the uterine cervix of female

smokes, it is also hypothesised to decrease oestrogen stimulus and contribute to an earlier menopause [195].

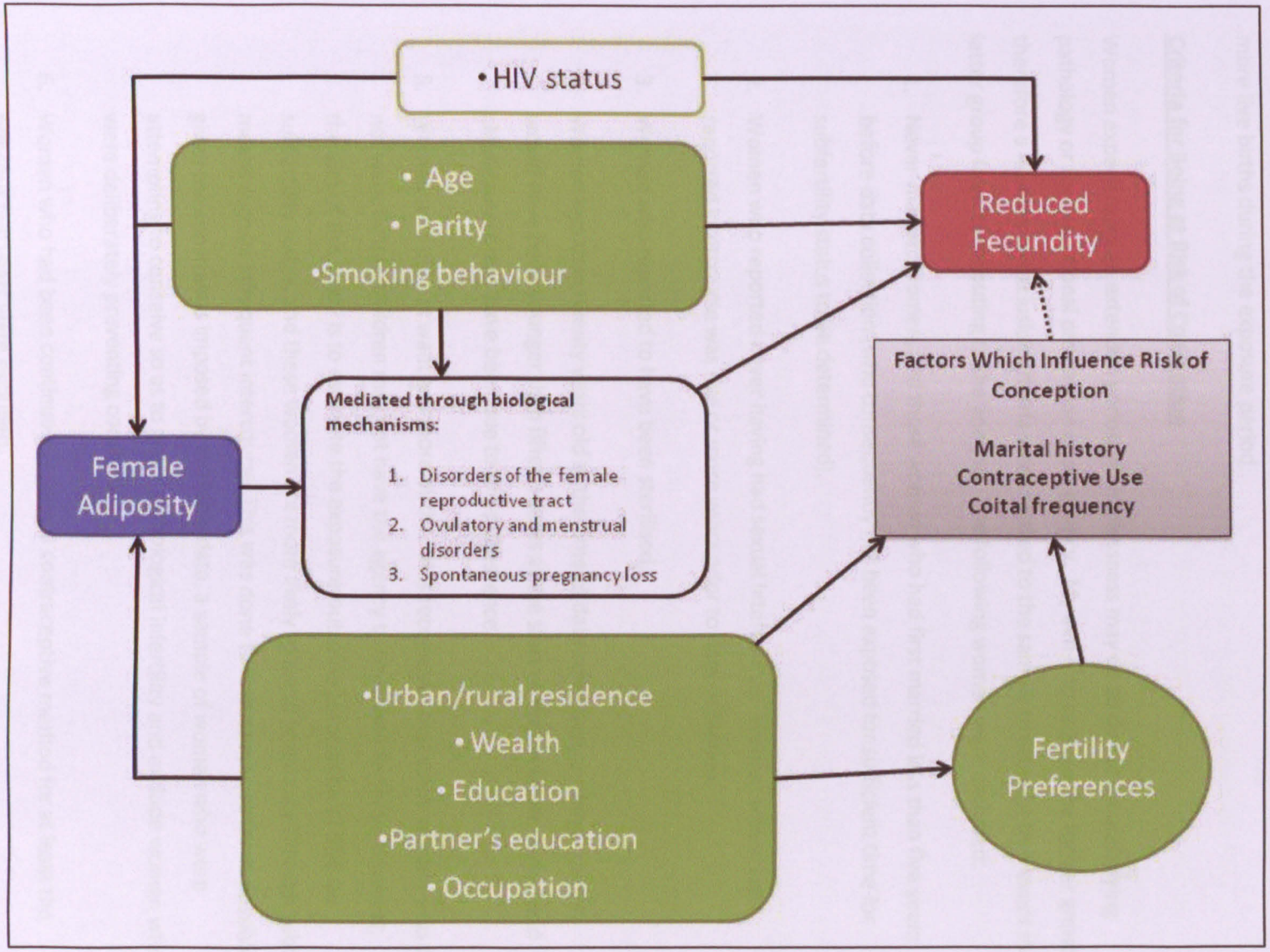
The confounders in the bottom green box also influence risk of obesity; in Sub-Saharan Africa obesity is primarily a characteristic of the elite socio-economic groups [144, 154]; this will be investigated more fully in Chapter 4. However, the way in which they most likely act on fecundity is primarily by influencing a woman's fertility preferences and/or her ability to act on those preferences. Women in the elite socio-economic groups in Sub-Saharan Africa generally prefer smaller family sizes and have lower overall fertility than the national average [196-197]. As previously outlined, underlying fecundity is an intangible construct; in this thesis I will be constructing my fecundity outcome by observing women's child-bearing patterns, i.e. the length of time elapsed without a birth or conception (see Chapter 3). I therefore need to adjust for intentional control of fertility in my analyses.

Age and parity are also associated with a woman's fertility preferences [197]. However, this relationship has been omitted from the conceptual framework for added clarity of the diagram. Age, parity and fertility preferences are all confounders in my analysis and I did not investigate confounder-confounder interactions [198].

The factors in the grey box (marital status, contraceptive use and coital frequency) represent additional considerations that influence the risk (opportunity) of conception. A woman will only be able demonstrate her fecundity if she has intercourse during the fertile period of her menstrual cycle.

HIV status is a potentially important confounder that it will not be possible to control for in this analysis. HIV infection is associated with lower fecundity due to factors such as menstrual irregularity, anovulation and increased miscarriage rates [199-201]. Knowledge of HIV infection may furthermore influence patterns of sexual intercourse and fertility intentions due to psychological or emotional distress, stigmatisation or concerns about infecting a sexual partner [202]. Conversely, amongst younger women, HIV infection is associated with increased sexual activity [203]; as my proxy measure of fecundity is based on birth history, this could paradoxically lead to the appearance of increased fecundity. HIV infection is associated with low body weight, particularly in the absence of timely access to highly active antiretroviral therapy [204]; prospective data from the USA has shown that obesity is associated with a decreased risk of disease progression [205-206].

Figure 3-A Reduced fecundity conceptual framework



I created a binary variable called 'subfertility'. This variable is intended to proxy infertility, in so far as is possible within the limits of the available data. Subfertility will be defined in this thesis as women who have been without a live birth for a minimum of 60 months, despite being at risk of conception during this period. They were defined as fertile if they had one or more live births during the exposure period.

Criteria for Being at Risk of Conception

Women experiencing an extended period of childlessness may do so due to an underlying pathology or the intentional prevention of pregnancy. My aim is to capture the former group, therefore a number of exclusion criteria were applied to the sample to attempt to prevent the latter group from contributing to the analysis. The following women were excluded:

1. Never-married women, and those women who had first married less than five years before data collection (who consequently not been exposed for sufficient time for subfertility status to be determined).

2. Women who reported never having had sexual intercourse. Women whose last reported intercourse was five or more years prior to data collection.

3. Women who reported to have been sterilised.

4. Women less than twenty years old at the time of data collection, as these women would have been younger than fifteen years at the start of the exposure period and childlessness may have been due to pre-pubescence.

5. Women who did not want any more births. It is recognised that some women who do not want further children may not have the agency to limit their fertility. However, the aim of this study is to estimate the exposure-outcome association of BMI on subfertility status, and these women are more likely to avoid pregnancy through subtle means such as infrequent intercourse. This was done to maintain, in so far as possible given the constraints imposed by available data, a sample of women who were attempting to conceive so as to proxy pathological infertility and exclude women who were deliberately preventing conception.

6. Women who had been continuously using a contraceptive method for at least the previous five years were excluded.

Women from Chad were not included in this part of the thesis as the Chad DHS (2004) only collected height and weight data to women with children under the age of five years old.

Length of the Exposure Period

As outlined in the background in Chapter 2, infertility in clinical studies is defined as a twelve month period without conception, whilst the WHO has recommended in epidemiological studies a 24 month exposure period is used to reduce the number of false positives [59]. However, a longer reference period is required when using demographic data to allow for unknown variables such as pregnancy terminations and periods of temporary absence by either partner. Previous work on infertility conducted using the DHS has used an exposure period of five years [17-18].

Women are eligible for this analysis if they are ever-partnered and the date of their first marriage is at least 60 months prior to date collection. A sensitivity analysis was conducted varying the exposure time required to 36 months, 48 months and 72 months.

Ever-partnered is a category comprising of both currently and formerly married women; never-married women were excluded. The decision was made to include formerly married (i.e. those women who are divorced, separated or widowed) because in the Sub-Saharan context women who are infertile are more likely to be divorced or separated [18].

Women became eligible for the analysis at the month of first marriage. It is recognised that a sizeable minority do have their first birth prior to this date [207-208]; however I considered the month of first marriage to be preferable to the alternative, age at first intercourse, as a proxy for the start of regular sexual relations with the intention of conception. Month of first marriage in the DHS represents the month in which a woman began cohabiting with her husband, rather than the date of any formal ceremony; the actual questions asked in the survey are *"In what month and year did you start living with your husband/partner?"* and *"How old were you when you first started living with him?"*[187] This is designed to standardise women's responses since in some Africa cultures marriage may be a protracted process lasting several months [209]. Initial exploratory analyses showed that use of age at first marriage versus age at first intercourse made a negligible difference to the results. This is because I am only interested in if a woman has had one or more births in the most recent five year period.

A minimum of 60 months from the date of first marriage were required for women to become eligible for the analysis to allow sufficient exposure time to elapse to determine fertile/subfertile status.

Validity of the Subfertility Variable

I examined the length of the most the most recent closed birth interval for all women in the dataset who have never used any method of contraception; these women were ultimately fertile (since they went on to have a birth); however for some women a long period of time elapsed before the birth took place. The median birth interval length is 34 months (IQR: 25-46). A minority of women have a very long birth interval yet still do go on to have a subsequent live birth: of women known to be fertile who have never-used contraception, 22% of women have a birth interval longer than 36 months, 11.5% of women have a birth interval longer than 48 months 6.5% of women have a birth interval longer than 60 months and 2.4% of women have a birth interval longer than 84 months. Of course, many of these women will have such a long birth interval for a good reason unrelated to their underlying fecundity, for example they have changed partners. The second part of the definition of fecundity will try, in so far as possible, to restrict the analysis to only those women who have been exposed to conception for the exposure period.

A problem that may be particularly important in the subfecundity analyses is birth displacement. In the DHS, a substantial number of questions relating to pregnancy, child health and nutrition are only asked for the births which have occurred in or since the January of the fifth full calendar year preceding data collection. This has the effect of substantially lengthening the time the interview takes to complete, and hence the amount of work for the interviewer, if there are a number of young children in a household. There is a risk that interviewers may record the births of children born close to the cut-off point as having taken place in the previous year, so reducing their workload.

An attempt to assess the extent of this problem is shown in Table 3.7. It is near impossible to detect on an individual-level where births have been displaced by a few months or a year, but on an aggregate-level it is possible to observe clear patterns in the data which suggest a problem.

For each survey included in this study, children born on or since the January of the full fifth year preceding data collection are eligible to be asked a long set of questions relating to their health, nutrition and immunisations. This is denoted as *year x* in Table 3.7 and the number of births in this and the surrounding years have been tabulated. To take Sierra Leone as an example, the survey took place during 2008 and year x is 2003; therefore year x-2 would be 2001, x-1 is 2002 and x+1 is 2004.

It is immediately noticeable looking down the observed births for *year x* that fewer events are recorded in that calendar year than in those years either side. This can be seen in the ratios presented in the next two columns. Whilst in some countries such as Congo, Rwanda and Zimbabwe, there is a negligible difference (small yearly fluctuations in the number of births should be considered normal), in other countries, such as Benin, Liberia, and Sierra Leone, the number of births is considerably lower in *year x* compared to the preceding calendar year suggesting the possibility that births have been displaced.

An method of quantifying the number of "missing births" has been suggested by Pullum (2006)[210]. This method assumes that the only error in reporting is within the second and third intervals (*year x-1* and *year x*) and that the observed births for *year x-2* and *year x+1* are correct. The estimated "true" frequency of births is then calculated as:

$$\hat{c} = (b + c)\frac{(d/a)^{\frac{1}{3}}}{1 + (d/a)^{\frac{1}{3}}}$$

Where *a* is the observed frequency in *year x-2*, *b* is the observed frequency in *year x-1*, *c* is the observed frequency in *year x*, *d* is the observed frequency in *year x+1* and $\hat{c}$ is the estimated frequency of events in *year x*. Pullum (2006) assessed the validity of this method using UN data and found that it worked well in the African context[210].

The findings are presented in Table 3.7. Out of the countries included in this study a third (Benin, Chad, Ethiopia, Ghana, Liberia, Madagascar, Mali, Niger and Sierra Leone) were "missing" 20% or more observed births that would have been expected. A further nine countries had between 10% and 20% fewer observed births than expected. If these births have been displaced back in time they present a threat to outcome misclassification, but only if a displaced birth (i.e. a child that was truly born 4 years prior to the survey but whose birth date was altered to be 5 years previous) was also a respondent's most recent birth.

Sensitivity analyses will be presented in Chapter 7 to show the effect of varying the length of the exposure period for the reduced fecundity analysis.

Table 3.7 Birth displacement

Survey	Year in which Births become Eligible *(year x)*	Observed Number of Births				Ratio (x/x-1)	Ratio (x/x-2)	Estimated "True" Number of Births during year x	Proportion of "Missing Births" from year x
		x-2	x-1	x	x+1				
Benin	2001	3,031	3,663	2,531	3,066	0.69	0.84	3,103	22.6%
Burkina Faso	1998	2,264	2,454	1,829	2,207	0.75	0.81	2,132	16.6%
Cameroon	1999	1,413	1,609	1,385	1,759	0.86	0.98	1,552	12.0%
Chad	1999	1,076	1,365	991	1,227	0.73	0.92	1,204	21.5%
Congo (Brazzaville)	2000	726	919	832	883	0.91	1.15	904	8.7%
DRC	2002	1,737	1,574	1,537	1,816	0.98	0.88	1,567	2.0%
Ethiopia	2000	2,291	2,387	1,669	2,121	0.70	0.73	2,002	20.0%
Ghana	2003	544	671	485	638	0.72	0.89	593	22.3%
Guinea	2000	1,475	1,751	1,254	1,217	0.72	0.85	1,454	16.0%
Kenya	1998	1,105	1,074	1,015	1,179	0.95	0.92	1,056	4.0%
Lesotho	1999	645	699	658	682	0.94	1.02	685	4.1%
Liberia	2001	1,039	1,355	882	1,035	0.65	0.85	1,118	26.7%
Madagascar	1998	1,103	1,321	912	1,020	0.69	0.83	1,102	20.8%
Malawi	1999	1,866	2,173	1,619	2,149	0.75	0.87	1,941	19.9%
Mali	2001	2,712	3,623	2,207	2,851	0.61	0.81	2,939	33.2%
Mozambique	1998	1,935	2,196	1,729	1,977	0.79	0.89	1,970	13.9%
Namibia	2001	959	1,107	885	898	0.80	0.92	985	11.3%
Niger	2001	1,844	2,407	1,459	1,933	0.61	0.79	1,948	33.5%
Nigeria	2003	5,068	6,251	4,933	5,701	0.79	0.97	5,702	15.6%
Rwanda	2000	1,394	1,715	1,696	1,433	0.99	1.22	1,713	1.0%
Senegal	2000	2,018	2,193	1,953	1,977	0.89	0.97	2,066	5.8%
Sierra Leone	2003	1,128	1,516	918	1,068	0.61	0.81	1,206	31.4%
Swaziland	2001	495	618	453	521	0.73	0.92	540	19.2%
Tanzania	1999	1,548	1,519	1,532	1,665	1.01	0.99	1,544	0.8%
Uganda	2001	1,549	1,875	1,399	1,697	0.75	0.90	1,662	18.8%
Zambia	2002	1,350	1,068	1,041	1,260	0.97	0.77	1,042	0.1%
Zimbabwe	2000	867	1,051	1,028	1,012	0.98	1.19	1,066	3.7%

3.2.2 Time to First Conception

One of the notable limitations of my subfertility indicator variable is that I was unable to accurately determine each woman's immediate fertility intention. There is inadequate data on frequency of sexual intercourse, and of the two alternative questions relating to fertility preference: desired family size and when a woman wants her next child; are inadequate. Previous rounds of the DHS did collect data on coital frequency; analysis of this data has suggested that women may have long periods of sexual abstinence within marriage and that couples adjust their coital frequency in line with their fertility preferences [211-212].

In the Sub-Saharan context child-bearing is a very important part of a woman's identity [20, 22-23]. It is therefore, very likely that recently married (as stated previously 'married' here means 'commenced cohabitation') nulliparous women will be attempting to become pregnant. Indeed, <1% of women in the dataset had an ideal family size of zero; and these women were excluded from the analysis.

The reproductive calendar, described in Section 3.1.3, represents a rich data source of contraceptive data and could be used to conduct a discrete-time survival analysis. An additional advantage of this analysis is that I can use conception as the endpoint, rather than live birth.

Time is analysed in month units (representing menstrual cycles). Women enter the analysis the month of first marriage. The failure event is defined as the month of first conception (i.e. the first 'P' recorded in the reproductive calendar) regardless of whether the pregnancy ended in a termination or a live birth. Women were censored at the time of data collection if they had not conceived by this time.

As the calendar period only covers the five years preceding the survey I restricted the analysis to women who married for the first time during this period. As the first birth interval differs from all later birth intervals (due to the lack of a postpartum infecundable period and the complications of lactational amenorrhea) it should be analysed separately. I did not have sufficient numbers of women who were recently married but on a second order or greater birth to repeat the analysis for this group. Therefore women with a pre-marital birth or who were pregnant at the date of marriage were excluded.

3.2.3 Caesarean Delivery

The outcome used in the caesarean analysis was a binary outcome, based on each woman's response to the question *"Was NAME delivered by caesarean section?"* This was the exact wording in most (24 out of 27) surveys used in this thesis; Congo-Brazzaville (2005) and Nigeria (2008) specified that a caesarean was an operation in the question, and Mozambique (2003) asked *"Was the birth of NAME normal, a vacuum-assisted delivery or caesarean?"* (See Appendix A). The design of the questionnaire meant that this question was only asked to those women who reported that the birth had take place in either a public or a private medical facility; home deliveries (either the respondent's or "other home") were automatically coded as vaginal deliveries. Women were eligible for this analysis if they gave birth at least once during the five years preceding data. The most outcome of the most recent delivery was considered.

Figure 3-B describes the conceptual framework used for this analysis. Variables thought to be potential confounders, based on external knowledge and a review of the literature, were age group (15-19 years, 20-24 years, 25-29 years, 30-34 years, 35-39 years, 40-44 years 45-49 years), relative wealth quintile, de facto area of residence (rural/urban), parity prior to the index birth (1st birth, 2-3 previous births, 4-5 previous births, 6 or more previous births), marital status (currently, formerly or never-married), length of the preceding birth interval prior to the index birth (none/1st birth, less than 2 years, 2-3 years, 4-5 years, 6 or more years), respondent's education (no education, primary only, secondary or higher), partner's education (never-married, no education, primary only, secondary or higher), previous miscarriage/abortion (yes/no), attended antenatal care during the index pregnancy (yes/no) and experiences difficulties accessing healthcare (yes/no). All variables were based on the self-report of the respondent.

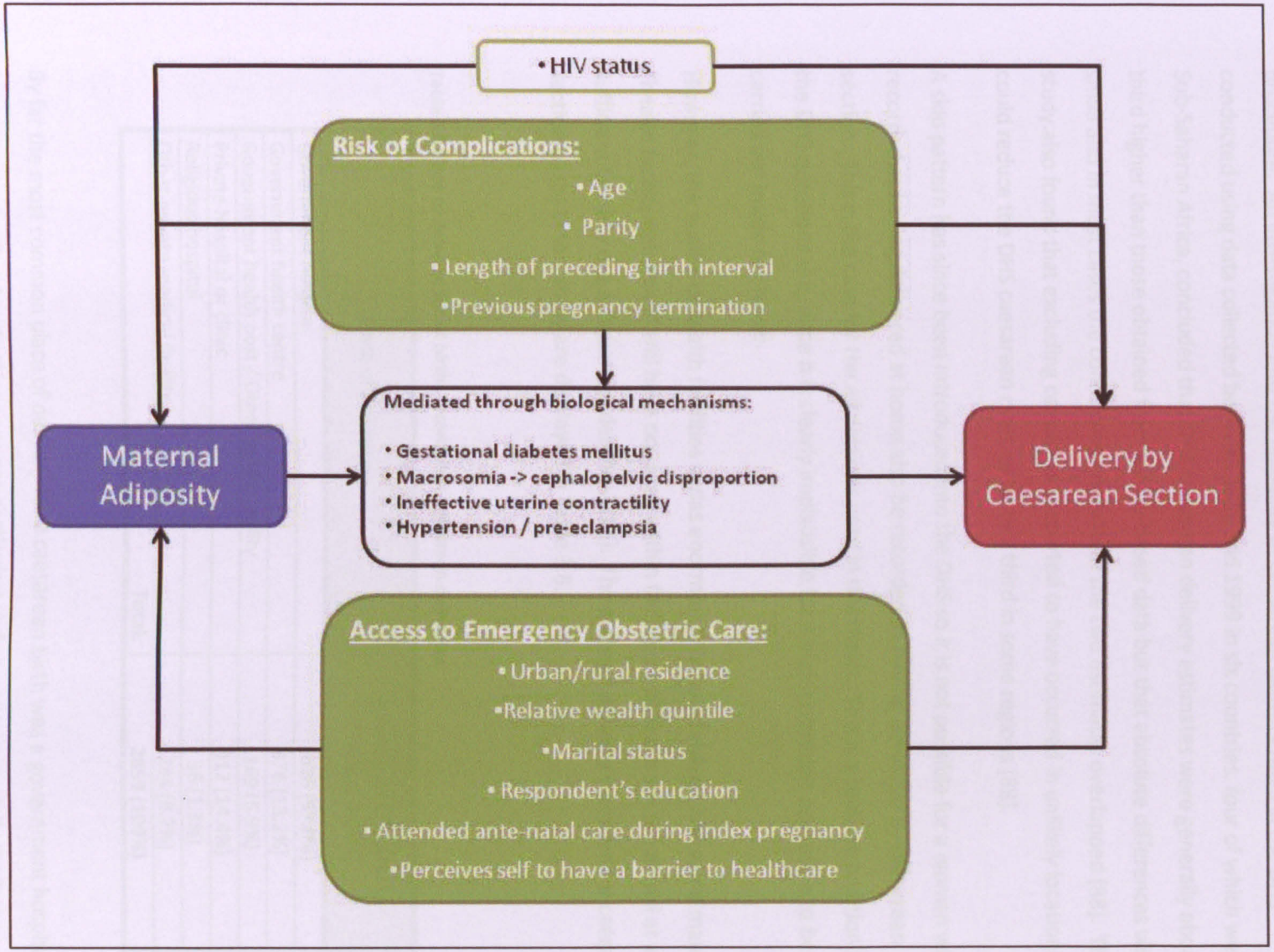
The variable experiences difficulties accessing healthcare was constructed on the basis of the respondent giving one or more affirmative answers to the question "Many different factors can prevent women from getting medical advice or treatment for themselves. When you are sick and want to get medical advice or treatment, is each of the following a big problem or not?" ("Getting permission to go?"/ "Getting money needed for treatment? "/ "The distance to the health facility?" / "Having to take transport?").

HIV status could potentially be an important confounder, which it will not be possible to control for in this analysis. There is strong evidence from a Cochrane review to suggest that elective caesarean delivery prior to the onset of labour reduces the risk of mother-to-child HIV transmission [213]. However, many clinics in low-income settings with relatively high HIV

prevalence, such as in Sub-Saharan Africa, do not have sufficient resources to perform safe caesarean deliveries for all cases, and emphasis has more recently been targeted at the provision of effective antiretroviral therapies for the prevention of mother to child transmission[214]. Nevertheless, practice is likely to have varied according to national policy and individual clinician preferences across the wide geographic and temporal span of the DHS used in this thesis.

Age group, parity, relative wealth and urban/rural residence were deemed to be important confounders *a priori*. In order to determine which other variables to include as confounders in the model the statistical associations in the data were examined. To be acting as a confounder variables needed to be associated ($p<0.05$) with both caesarean delivery and maternal BMI category and not be on the causal pathway [198]. When the unadjusted association between caesarean delivery and BMI category was adjusted sequentially for each potential confounder only respondent's education was found to be acting as a confounder in addition to the *a priori* identified variables of age group, parity, relative wealth quintile and urban/rural residence.

Figure 3-B Caesarean delivery conceptual framework



Validity of the Caesarean Outcome

Validity therefore depends on whether women giving birth in a facility correctly reported their mode of delivery and did not, for example, mistake a caesarean for an episiotomy or other procedure. An investigation into the reliability of caesarean delivery rates in the DHS conducted using data collected between 1989 and 1999 in six countries, four of which were in Sub-Saharan Africa, concluded that DHS caesarean delivery estimates were generally about a third higher than those obtained from facility-based data but that absolute differences were small and in most cases the confidence intervals of the two estimates overlapped [88]. The study also found that excluding caesareans reported to have occurred in unlikely locations could reduce the DHS caesarean rates by up to a third in some regions [88].

A skip pattern has since been introduced into the DHS so it is not possible for a woman who is recorded as having delivered at home also be recorded as having delivered by caesarean section. This is the case for the all datasets used in this thesis. This is a sensible addition to the DHS questionnaire, since it is clearly implausible for a major obstetric operation to be carried out inside the home.

However, the quality of health facilities varies enormously in Sub-Saharan Africa and many "health facility deliveries" will have occurred within facilities which are not functional at a level sufficient to carry out a caesarean delivery [215]. The place of delivery recorded for caesarean section births in this study are displayed in Table 3.8.

Table 3.8 Place of delivery for all births recorded as caesarean deliveries

Place of Delivery	Number of Caesareans Reported (%)
Government hospital	1626 (57.0%)
Government health centre	376 (13.2%)
Government health post / Other public facility	169 (5.9%)
Private hospital or clinic	412 (14.4%)
Religious hospital	36 (1.3%)
Other private medical facility	234 (8.2%)
Total:	**2853 (100%)**

By far the most common place of delivery for a caesarean birth was a government hospital; however, the facility classifications are not particularly informative, especially the large numbers of births listed under "other". These births and those listed as having occurred at a health post, are of particular concern for misreporting. Amongst health professionals working

in any given country there is disagreement about the capabilities of each type of facility; but it is likely that caesarean deliveries are still being reported at facilities function at a low level [216]. The review concluded that the introduction of the skip pattern has improved the internal consistency of the data, but there is still a concern that some caesarean operations are reported to have occurred at facilities unlikely to have the capacity for this procedure to be carried out [216].

3.2.4 Neonatal Death

The neonatal death variable was constructed as a binary variable using the birth history section of the questionnaire, described earlier. A neonatal death was defined in line with the WHO definition of a neonatal death [114], as the death of a live born infant within the first 28 completed days of life (i.e. day 0 to day 27). As with the caesarean outcome, only births which took place during the five years preceding data collection were included in this analysis. The outcome of the most recent delivery was considered. Multiple births at the index delivery were excluded.

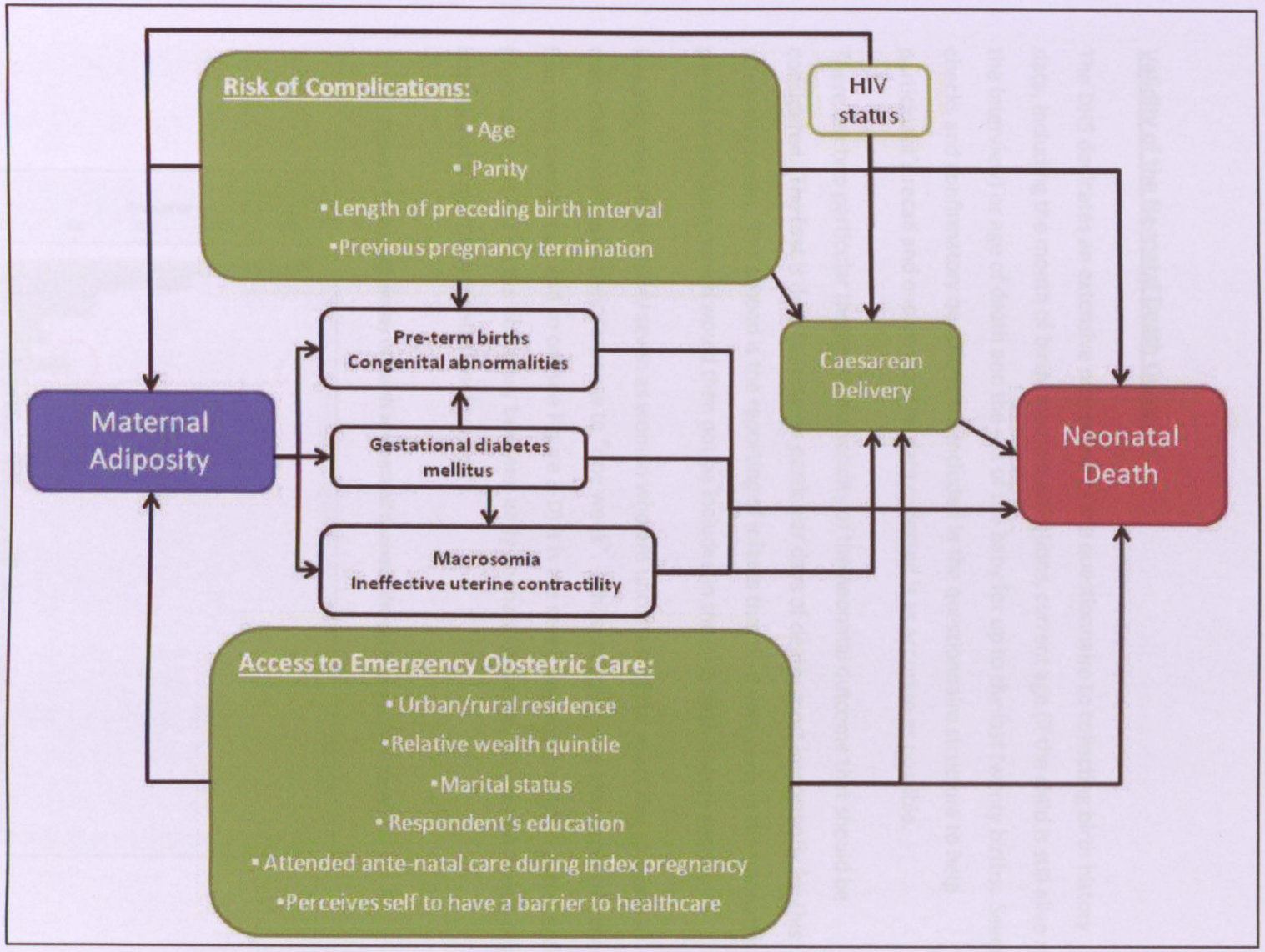
Figure 3-C describes the conceptual framework used for this analysis. Variable selection was carried out in a similar manner to for the caesarean outcome. Variables thought to be potential confounders were age group (15-19 years, 20-24 years, 25-29 years, 30-34 years, 35-39 years, 40-44 years 45-49 years), relative wealth quintile, de facto area of residence (rural/urban), parity prior to the index birth (1st birth, 2-3 previous births, 4-5 previous births, 6 or more previous births), marital status (currently, formerly or never-married), length of the preceding birth interval prior to the index birth (none/1st birth, less than 2 years, 2-3 years, 4-5 years, 6 or more years), respondent's education (no education, primary only, secondary or higher), partner's education (never-married, no education, primary only, secondary or higher), previous miscarriage/abortion (yes/no), attended antenatal care during the index pregnancy (yes/no), experiences difficulties accessing healthcare (yes/no) and mode of delivery at the index birth (vaginal/ caesarean). The variable experiences difficulties accessing healthcare was constructed on the basis of the respondent giving one or more affirmative answers to the question "Many different factors can prevent women from getting medical advice or treatment for themselves. When you are sick and want to get medical advice or treatment, is each of the following a big problem or not?" ("Getting permission to go?"/ "Getting money needed for treatment? "/ "The distance to the health facility?" / "Having to take transport?").

As in previous models, HIV status is a potentially important confounder that it will not be possible to control for in this analysis. HIV infection has been associated with foetal

abnormalities, intrauterine growth retardation, low birthweight and pre-term delivery [217], all of which may contribute to a higher neonatal mortality rate.

Age group, parity, relative wealth and urban/rural residence were deemed to be important confounders *a priori*. In order to determine which other variables to include as confounders in the model the statistical associations in the data were examined.

Figure 3-C Neonatal deaths conceptual framework



When the unadjusted association between caesarean delivery and BMI category was adjusted sequentially for each potential confounder only respondent's education and mode of delivery (caesarean/vaginal) were found to be acting as confounders, so were included in the final model in addition to age group, parity, relative wealth quintile and urban/rural residence.

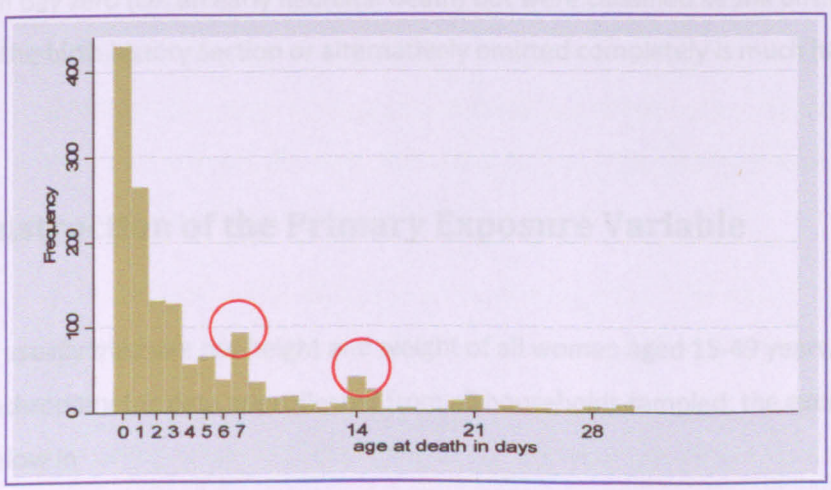
Validity of the Neonatal Death Outcome

The DHS dedicates an extensive proportion of the questionnaire to collecting birth history data, including the month of birth, multiple gestations, current age (if the child is still alive at the interview) or age of death and the sex of the baby for up to the last twenty births. Several checks and confirmatory questions are included in the questionnaire structure to help participant's recall and ensure that the data collected is as accurate as possible.

There are two particular threats to the validity of the neonatal outcome that should be considered. The first is data heaping on particular days of death; most importantly for this study day seven. The second is the reporting of infants that died very early in the neonatal period as stillborn (which would then not be included in the DHS birth history section).

Heaping may occur on day seven as women who are uncertain of the exact day of death of their child may round their response to "one week". Whilst heaping may also occur on day fourteen, twenty-one and so on (see Figure 3-D) it is the seven day point which is particularly important as it lies on the boundary between early neonatal mortality (deaths on days 0-6) and late neonatal mortality (deaths on days 7-27).

Figure 3-D Heaping on day of death amongst all neonatal deaths in the pooled dataset



A simple heaping index can be used to quantify the extent of misclassification by calculating the ratio of excess deaths that occur on day seven compared to days five through to ten[218].

$$Heaping\ Index = \frac{Deaths\ at\ Day_x}{(Deaths\ at\ Day_{x-2} + Day_{x-1} + Day_x + Day_{x+1} + Day_{x+2})/5}$$

This is displayed in Table 3.9, along with some other summary measures of the heaping in the dataset.

Table 3.9 Heaping indicators, calculated using the pooled dataset

Heaping Index at Day 7	1.93
Heaping Index at Day 14	2.59
Heaping Index at Day 21	2.19
Proportion of Deaths on Day 0	0.30
Proportion of Deaths on Day 0 or Day 1	0.49
Ratio of Deaths Day 0: Day 1	1.63

Table 3.9 shows a substantial level of heaping on days seven, fourteen and twenty-one; on each of these days there were close to twice the number of deaths recorded that would be expected if deaths were equally distributed with the adjacent days. This is finding only presents an important misclassification for heaping at day seven (as in the discrete-time survival model deaths between days seven to twenty-seven were included in the same category). Just under a third of all deaths occurred on day zero. The omission of infants who were died on day zero (i.e. an early neonatal death) but were classified as still births and so not recorded in the birth history section or alternatively omitted completely is much harder to detect.

3.3 Construction of the Primary Exposure Variable

Recent DHS usually measure the height and weight of all women aged 15-49 years. In most countries anthropometric data are collected from all households sampled, the exceptions are displayed below in

Table 3.10. Households where women were not designed to be measured under the sampling strategy have been excluded from all analyses in this study.

Table 3.10 Countries where height and weight data was only collected on a sub-sample

Survey (year)	Proportion of Entire Sample where Anthropometric Data Collected
Cameroon (2004)	All eligible women in 50% of households selected
DRC (2007)	
Ethiopia (2005)	
Guinea (2005)	
Lesotho (2004)	
Niger (2006)	
Rwanda (2005)	
Sierra Leone (2008)	
Senegal (2005)	All eligible women in 33% of households selected
Uganda (2006)	

The DHS trains interviewers to measure respondent's rather than relying on self-report. Height is measured using an adjustable wooden measuring board to the nearest 0.1cm; weight is measured using a digital scale accurate to the nearest 100 grams [219].

3.3.1 Quality of the Height and Weight Data

Height is flagged as implausible if the recorded value is greater than six standard deviations above or below the normative median height for that survey [220]. Weight was flagged as implausible if weight was lower than 55% or greater than 240% of the normative weight given height, age and pregnancy status, based on the DHS reference standard [220]. There is no particular "plausible weight cut-off" because what was considered plausible depended on the respondent's height value. Once implausible values had been excluded from the pooled dataset used in this thesis the range of weights remaining varied between a minimum of 26kg (to a woman 1.39m tall and a very low BMI of 13.55 kg/m^2) and 176.2kg (to a woman 1.88m in height and who was morbidly obese with a BMI of 49.85 kg/m^2).

The proportion of implausible values varied by survey, see Table 3.11. In total, 0.68% of women were judged to have an implausible value for height and/or weight. Proportions ranged from just 0.1% (Uganda, 2006) to 6.07% (Sierra Leone, 2008), most likely related to factors such as the quality of interviewer training and supervision, as well as adverse conditions or disruption in the field such as equipment difficulties. Nevertheless, overall the

anthropometric data seems to show a relatively low level of implausible values for such large-scale surveys from low-income settings.

Overall, 3.23% of women had a missing value for height and/or weight; of these the vast majority (90.8%) were missing data for both values. The proportion of missing data varied by survey, ranging from 0.93% (Tanzania, 2004) to 9.29% (Senegal, 2005).

Table 3.11 Proportion of women with missing anthropometric data

Survey	Proportion of Sample Implausible Height and/or Weight Value	Proportion of Sample Missing Height and/or Weight Value
Benin (2006)	0.53%	5.90%
Burkina Faso (2003)	0.22%	1.76%
Cameroon (2004)	0.11%	3.90%
Chad (2004)	0.26%	1.85%
Congo-Brazzaville (2005)	0.81%	2.67%
Democratic Rep. of Congo (2007)	1.21%	4.62%
Ethiopia (2005)	0.51%	2.35%
Ghana (2008)	0.81%	1.89%
Guinea (2005)	0.49%	2.87%
Kenya (2008-09)	0.20%	5.92%
Lesotho (2004)	0.28%	3.45%
Liberia (2007)	0.86%	1.82%
Madagascar (2008-09)	0.83%	1.45%
Malawi (2004)	0.33%	4.80%
Mali (2006)	0.40%	2.09%
Mozambique (2003)	0.30%	5.73%
Namibia (2006-07)	0.43%	2.68%
Niger (2006)	0.15%	2.97%
Nigeria (2008)	1.05%	2.76%
Rwanda (2005)	0.54%	1.50%
Senegal (2005)	0.40%	9.29%
Sierra Leone (2008)	6.07%	5.40%
Swaziland (2006)	2.83%	2.59%
Tanzania (2004)	0.28%	0.93%
Uganda (2006)	0.10%	2.32%
Zambia (2007)	0.53%	1.37%
Zimbabwe (2005-06)	0.34%	1.99%

3.3.2 BMI Classification Used in this Study

Women who were missing either a height or a weight value were necessarily excluded from the study, since it was impossible to calculate a BMI score for these individuals. In addition, women were excluded if they were pregnant or less than three months postpartum at the time of data collection due to the artificial inflation of their weight at this time. A systematic review on postpartum weight retention found there is a steep decrease in mean postpartum weight retention in the first three months [221].

BMI is calculated as weight (in kilograms) divided by height (in metres) squared. Optimal weight women (BMI: 18.5-24.9 kg/m^2) were used as the reference category throughout. BMI categories were defined according to WHO standard classification [26, 30], displayed in Table 3.12. Underweight women were excluded from the dataset after the initial descriptive background analyses because they were not relevant to the research question.

Table 3.12 WHO BMI classification scheme

Classification			Body Mass Index (kg/m^2)
Underweight			<18.5
Optimal weight			18.5 – 24.9
Overweight		Pre-Obese	25 – 29.9
	Obese	Obese Class I	30 – 34.9
		Obese Class II	35 – 39.9
		Obese Class III	≥ 40

The term "overweight" therefore applies to all women with a BMI ≥25 kg/m^2, including both the pre-obese and obese. The term "obese" applies to all women with a BMI ≥30 kg/m^2. Women who are obese class III (≥40 kg/m^2) are also sometimes known as "morbidly obese" in the literature.

3.3.3 The Validity of BMI as a Measure of Excess Adiposity

BMI is very commonly used as an indicator of overweight and obesity. It is a convenient measure which can be calculated quickly and easily, has clearly standardised cut-off boundaries for each BMI category, and does not require and expensive or specialist

equipment. This makes BMI particularly popular in large-scale surveillance projects, although it is also frequently used by clinicians on an individual level.

However, despite the very widespread use of BMI it is also acknowledged that the measure has a number of limitations. Most of these relate back to the fact that it is increased body fat, in particular abdominal fatness, which is associated with increased in morbidity and mortality amongst overweight people, rather than increased body weight per se. The proportion of body weight that is fat is not consistent across sex, ages and ethnicities, or within specific subgroups of the population who take part in high levels of physical activity.

As people age the ratio between fat and lean body mass increases even if overall body weight remains constant, particularly after the menopause [222]. Women have a higher percentage body fat for a given weight than do men. A regression analysis amongst Caucasian populations has suggested that gender explains 52% of variation in body fat for a given BMI and gender and age combined explains 88% [223].

Although the WHO BMI classifications used in this study are intended for international use there is a lot of evidence to suggest that there are ethnic differences between populations [224]. A WHO expert consultation has recommended that different cut-offs should be used in Asian populations [224]. A meta-analysis of 32 datasets by Deurenberg *et al.* (1998)[223] concluded that, compared to Caucasian populations, "American Blacks" (no further details regarding ethnic origin provided) and Polynesians tended to have a lower proportion of body fat for a given BMI, age and sex; whilst Indonesian, Thai and Ethiopian populations tended to have a relatively high proportion of body fat for their BMI. However, only 48 Ethiopian subjects were included in the review, compared to sample sizes greater than 1000 for the Caucasian, American Black, Thai and Chinese groups. Furthermore, the authors combined the results of studies using different methods to measure body fat; particularly notable most of the Thai sample was measured using skin fold thickness which is unlikely to give comparable results to the densitometry or dual energy X-ray absorptiometry (DEXA) techniques used by the majority of studies. The results are therefore of limited generalisability.

As BMI cut-offs have not been evaluated amongst African populations in the same way as Asian groups [224] this PhD will investigate the effect of BM both as a continuous variable and using the standard categorical classification described above. Alternative results will be presented throughout the thesis.

BMI is the best available measure of excess adiposity available to me. Ironically, the very fact that BMI is so widely used has itself become an advantage to its further use; because of the

benefits of comparability with other research results. Furthermore, without investment in large, high-quality studies, it is not known whether alternative candidates for a measure of body fatness would perform better [222]. BMI has been found to be an acceptable indicator for monitoring trends on the population-level, although it should be noted that the relationship between BMI and percentage body fat is only moderate on the individual level and also depends on age, gender and ethnicity [225-226].

The DHS is a secondary data source, so my choice of measure is ultimately limited by what is available. In terms of nutrition data for adult women this is limited to height and weight measurements; early DHS also collected data on arm circumference but it was found to provide inconsistent estimates of malnutrition status so discontinued [219]. Alternative weight-height indices, such as Roher's Index (kg/m^3), are less frequently used and have not been shown to be superior to BMI as a measure of fatness. Therefore, in this study BMI will be used to categorise women as overweight or obese.

3.4 Other Explanatory Variables

This section contains a brief discussion of issues surrounding the data quality and validity of two important variables common throughout the analysis: respondent's age and the DHS relative wealth quintile.

3.4.1 Respondent's Age

Heaping on age and date survey data originating from low-income countries like the DHS is not necessarily a sign of low quality data collection procedures; often it occurs because interviewees simply don't accurately know how old they are. However, it is important to discuss potential problems such as recall errors when interpreting results based on DHS data since in this study I am constructing my outcomes variables based on the respondent's report of events that have occurred to her in the preceding five years.

One measure of the quality of age and date information is the degree of heaping, for example respondents may tend to round their age to the nearest ten or five particularly in the older age groups. However, substantial heaping is not necessarily due to poor interviewing standards; heaping may also occur in cultures where little significance is place on calendar dates and women do not know their exact age.

Table 3.13 shows the degree of digit preference in the surveys included in this study. Myer's Blended Index shows the proportion of cases that would have to be shifted from one final digit (0-9) to another in order for there to be no heaping. It is similar to other indices of heaping, but Myer's Index takes into account the fact that we would expect there to be slightly more individuals at ages with digits ending in 0, 1 or 2 than 7, 8 or 9 because of mortality. It does this by determining the proportion of people at each final digit ten times, varying the starting age each time. Both Myer's Index and the percentage of excess women at final digits 0 and 5 have been calculated for women aged 20-49 years only; this is so that each final digit is "supposed" to occur the same number of times.

Small deviations from an even distribution should be ignored as some fluctuation in the number of births in certain years is to be expected. The results show that there are fairly strong geographical differences in the degree of heaping. In general, the central and southern African countries (such as Zambia, Congo, Namibia, Madagascar, Zimbabwe and Swaziland) tend to have the lowest levels of heaping; in these countries fewer than 4% of cases would need to be reclassified in order for age to be evenly distributed. In contrast, in Benin, Nigeria, Guinea and Sierra Leone more than 20% of cases are heaped on certain age values.

Table 3.13 Myer's blended index for age heaping

Country (year)	Myer's Blended Index for ages 20-49 years	% Excess at Final Digit 0 or 5 for ages 20-49 years
Benin (2006)	20.297	18.65%
Burkina Faso (2003)	7.671	6.94%
Cameroon (2004)	5.708	5.37%
Chad (2004)	19.300	16.37%
Congo-Brazzaville (2005)	2.787	1.00%
Democratic Rep. of Congo (2007)	4.110	1.65%
Ethiopia (2005)	19.675	17.03%
Ghana (2008)	10.124	7.72%
Guinea (2005)	21.282	19.16%
Kenya (2008-09)	4.103	2.64%
Lesotho (2004)	4.311	0.58%
Liberia (2007)	6.401	4.19%
Madagascar (2008-09)	3.096	3.02%
Malawi (2004)	6.366	3.35%
Mali (2006)	16.125	15.76%
Mozambique (2003)	5.856	2.23%
Namibia (2006-07)	3.014	-1.57%
Niger (2006)	19.609	19.61%
Nigeria (2008)	21.181	19.31%
Rwanda (2005)	4.039	0.84%
Senegal (2005)	8.094	7.12%
Sierra Leone (2008)	23.481	20.33%
Swaziland (2006)	3.965	-0.79%
Tanzania (2004)	6.213	4.59%
Uganda (2006)	4.188	1.40%
Zambia (2007)	2.055	-0.52%
Zimbabwe (2005-06)	3.562	0.91%

3.4.2 Relative Wealth Index

The DHS uses an asset-based wealth index to measure economic status [227]. Economic status is usually measured using an indicator based on one of (i) income (ii) consumption (iii) accumulated assets. It is not a measure of social class or status [228-229]. Income-based indices may be difficult to measure accurately because people may be unwilling to answer questions about their salary and earnings. Income measurement is particularly unreliable in developing countries because many or all members of the household are more likely to be self-employed, engage in subsistence farming or home production, or because income may be highly seasonal and fluctuate throughout the year. Similar problems underlie the use of indices

based on consumption in low-income settings. Furthermore detailed data collection on income and/or consumption is very time-consuming.

Construction of the DHS Wealth Index

The DHS Index is constructed using principal components analysis (PCA) to assign weights to possession of a range of household assets and housing characteristics, using a methodology developed with the World Bank [227, 230]. The variables usually included in the DHS Wealth Index are shown in Table 3.14; although there is variation between surveys and country-specific variables may also be included. PCA is a descriptive analysis technique that explains the variance of a set of variables by generating new components based on the underlying correlation matrix; this reduces the number of variables needed to summarise the original data [231]. The first component captures the most variance and is what is used by the DHS to represent the assumed underlying (but in tangible) construct of household wealth.

Table 3.14 Assets typically included in the DHS relative wealth index

Assets & Services Usually Asked about in the DHS	
Type of floor material	Persons sleeping per room
Water supply	Ownership of land
Sanitation facilities	Employing a domestic servant
Electricity	
Possession of a: o Radio o Television o Telephone o Refrigerator	

Taken from Rutstein (2004) [227]

Wealth quintiles are calculated using household assets rather than individual possessions. The quintiles are also generated at the household level; individuals are then assigned to the quintile of their household. This is why it is often the case that slightly more than 20% of individuals are allocated to the poorest quintile and slightly few than 20% of individuals are allocated to the richest quintile, as poorer households often have larger family sizes [227].

It has been shown that an assets-based wealth index can potentially perform as well as a consumption-based index for the purpose of measuring health inequalities in low-income countries [232]. However, other authors have suggested that the correlation is weak; a systematic review by Howe *et al.* (2009) [233] suggested that frequently there is only weak

agreement between wealth indices and consumption indices; indices including a greater number and wider range of indicators performed the best.

PCA works best when the variables included are highly correlated [231]. The best wealth indices will be produced when a large number of assets and services are included, as this makes it easier to differentiate between households and avoids problems of clumping and truncation [234]. Filmer & Pritchett (2001) found their wealth index to be internally and externally robust [230] whilst an analysis by Houweling *et al.* (2003) found that the relative wealth ranking of households varied according to the number and combination of assets used, and also that the size and direction of the change varied by country and so is difficult to predict [235].

Potential Limitations with the DHS Wealth Index

Various authors have raised a number of potential limitations with the DHS wealth index. These fall into three categories:

1. *Selection of indicator variables included in the index*

Some of the assets and utilities included in the DHS Wealth Index may have a direct effect on health outcomes. Indeed, the original index was comprised of variables that already existed in the questionnaire for purposes other than the determination of economic status. For example drinking water source and type of toilet facility will influence risk of diarrhoea which is an important cause of child mortality [235]. Some variables such as electricity are usually publically provided amenities so are a characteristic of the neighbourhood as much as the household, although conversely it is also argued that richer households will tend to live in richer neighbourhoods.

2. *Potential urban bias*

Recent publications from the DHS have described the known problem of an urban bias in the wealth index [236]. Amenities such as electricity and a piped water supply may not be available in rural areas and owning assets such as a television is dependent on having access to an electricity supply. Furthermore, households living in rural areas are more likely to store their wealth as animals or other agricultural items which were not included in the original questionnaire. There has been concern that rural dwellers are more likely to be misclassified into the poorer wealth quintiles. Future DHS will include additional questions relating to livestock ownership and other rural stores of wealth, but this information was not available for the analyses in this thesis.

Ferguson *et al.* (2003) have suggested that a similar problem might exist when using a PCA-based index for cross-country analysis [237]. Even if the same indicator variables are used then the tendency to acquire a given asset or service is likely to vary according to culture, environment and local supply and demand. Therefore, it is important to remember during the interpretation of results in this study that the relative wealth variable is only measuring wealth relative to other households within that country, it is not a measure of absolute socioeconomic status.

3. Statistical and methodological issues with PCA

PCA is best used with normally distributed data [238], so ideally variables included should be continuous or at least ordinal with multiple categories. However, nearly all of the indicators used in the creation of the DHS Wealth Index are binary.

The proportion of variance typically explained by the first (largest) component in a PCA conducted on asset data from developing countries, however this is usually only in the region of 10-30% [234]. This is relatively low and it is arguably difficult to interpret the true meaning of the DHS wealth index.

A review by Howe et al. (2008) [239] compared five alternative statistical methods to constructing a wealth index: PCA, PCA using binary variables, equal weights, inverse proportion weighting and multiple correspondence analysis (MCA). This study found that the coding of the data was more important than the statistical method used to weight the data. All the indices had a similar level of agreement with consumption expenditure [239]. MCA is a similar technique to PCA but is statistically more appropriate for use with discrete data; it has been shown to produce similar results to PCA when used with DHS data [240].

In general, it seems that the DHS wealth quintile variable, whilst it has some methodological issues, does not perform noticeably worse than the alternatives. The use of the relative wealth index as it appears in the DHS standard recode file has the advantage of enhanced comparability with other studies published using DHS data. It is not clear from the current evidence-base which, if any, method of measuring wealth given the constraints of the data available would be superior. Therefore, the relative wealth quintile value provided in the standard record file will be used to control for economic status as a covariate in all the models in this study.

3.5 Statistical Methods

The aim of this section is to give a brief overview of the statistical methods and issues encountered in this thesis that are common to all of the outcomes analysed to avoid unnecessary repetition and duplication of information throughout the remainder of the thesis. Details specific to each outcome will be described at the start of the appropriate chapter as required. All analyses in this thesis were carried out using Stata SE/11.0 [241].

3.5.1 Univariable Analysis

For each of the outcomes of interest analysed in this thesis, I initially tabulated and examined the distribution of the outcome, BMI, and all of the covariates. The extent and distribution of any missing values was also assessed.

I identified potential confounding variables from the background literature review and conceptual frameworks presented in Chapter 2. The crude association between each potential confounder and (i) the outcome; (ii) BMI was calculated (using the *-svy-* suite of commands and including the *country of survey* dummy). A correlation matrix was run to check for initial evidence of multicollinearity. Variables found to be acting as confounders were included in the multivariable model. In general variables were included as confounders in the final model if they caused a 10% or greater change in the odds ratio of the effect of being overweight on the outcome [198].

It is plausible that BMI has a linear effect on the outcome. As a first step in assessing this I graphed I graphed the observed log odds of the outcome and compared this to the model assuming a linear trend.

3.5.2 Multivariable Models

The multivariable regression model used varied according to outcome. These are displayed in Table 3.15 and Table 3.16. For binary outcomes (subfertility, delivery by caesarean section and neonatal death) a multivariable logistic regression model was used.

Time to first conception is survival data and was analysed as such. Initial descriptive analysed were carried out by constructing a life table stratified by BMI category. Subsequently, a discrete-time survival model was constructed to obtain an effect estimate for BMI category [242]. The discrete-time approach was used because each woman has one conception

opportunity per month (as a proxy for menstrual cycles). Time was analysed in one month intervals (a proxy for menstrual cycles) for the first 12 months; due to the small number of events in the later stages intervals were subsequently combined into six month (12-17 months, 28-23 months) and twelve month (24-35 months, 36-47 months and 48-59 months) intervals. The data are expanded so that each row represents one person-interval and a binary outcome taking the values 0 and 1 is constructed for each row, representing whether the failure event (in this case conception) occurred during the interval. Subsequently a logistic regression model was fitted[242].

A discrete-time model was also used in Chapter 8 to examine the timing of neonatal death amongst those women who delivered vaginally. The discrete-time model was used here to increase statistical power due to the rarity of neonatal death as an outcome. Three intervals were used (death at 0-1 days after birth, death at 2-6 days after birth, death at 7-27 days after birth) and the data expanded as previously. In this model I used a complementary log-log link (cf. logit link normally used in logistic regression). This produces a similar model, but the complementary log-log link is more appropriate if survival times are interval censored (cf. inherently discrete as in the fecundity analysis) [242]. The odds ratios presented should be interpreted as the odds of death in the exposure compared to the unexposed, given that death has not already occurred in a previous time interval.

In order to assess whether BMI had a dose-response (linear) relationship on the outcome I compared the two alternative models: (i) BMI as a categorical variable; (ii) BMI as a continuous variable. It is not possible to compare the fit of each model by comparing the log-likelihood when analysing data collected through a complex survey design because the log-likelihood assumes all observations are independent (i.e. it does not take into account clustering). Therefore, I used the F-adjusted mean residual test (executed through used of the *-svylogitgof-* command in Stata)[243-244] to compare the goodness of fit of each version of the model. This test has low power, so should only be used to assess the goodness of fit of models containing the same number of observations, or the result becomes impossible to interpret.

The final model was assessed for the presence of interaction between the primary exposure (BMI) and selected confounders, specified *a priori* on the basis of a hypothesised plausible biological interaction. These are also presented in Table 3.15and Table 3.16. It is usual for the effect of the primary exposure to vary to some extent between strata, therefore stratum-specific odds ratios were reported only in the presence of substantial interaction. As it is not appropriate to use the likelihood ratio test with clustered data the Wald test was used to test the significance of the interaction terms.

Table 3.15 Statistical methods used in the fecundity analyses

Outcome	Model	Exclusion Criteria	Confounders Included in the Final Model	Variables tested for Interaction with BMI Category (*a priori*)
Subfertility Absence of a live birth for a minimum of five years, despite exposure to conception.	Logistic regression	• Underweight women • Women currently pregnant or <3m postpartum • Never-married women, and those married less than five years preceding survey • Women who have not had sexual intercourse in the five years preceding the survey • Women who have continuously been using a contraceptive method for the five years preceding the survey • Women <20 years at the survey • Women who do not want any further births	• Age category • Urban/rural residence • Relative wealth quintile • Parity (adjusted to be correct for the start of the exposure period, 5 years preceding the survey) • Ever-use of contraception • Respondent's education • Husband's education • Respondent works outside of the home • Smoking status	• Age category
Time to First Conception Survival time from month of first marriage to month of first conception	a) Life table b) Discrete-time survival model	• Underweight women • Women currently pregnant or <3m postpartum • Women who were first married prior to the start of the period covered by the reproductive calendar. • Women with a pre-marital conception. • Women using contraception	• Age • Urban/rural residence • Relative wealth • Education level	

Table 3.16 Statistical methods used in the adverse pregnancy outcomes analyses

Outcome	Model	Exclusion Criteria	Confounders Included in the Final Model	Variables tested for Interaction with BMI Category (*a priori*)
Caesarean Delivery Delivered most recent birth by caesarean section	Logistic regression	• Underweight women • Women currently pregnant or <3m postpartum • Women <20 years at the survey • Women whose most recent birth was more than 5 years prior to survey • Women with a multiple birth at most recent delivery	• Age category • Urban/rural residence • Relative wealth quintile • Parity • Respondent's education • Time elapsed between index delivery and survey	• Age category • Parity
Neonatal Death Death of the most recent live born infant within the first 28 completed days of life.	a) Logistic regression b) Discrete-time survival model	• Underweight women • Women currently pregnant or <3m postpartum • Women <20 years at the survey • Women whose most recent birth was more than 5 years prior to survey • Women with a multiple birth at most recent delivery ********** • Women who delivered by caesarean for the index birth were also excluded from the discrete-time survival model.	• Age category • Urban/rural residence • Relative wealth quintile • Parity • Respondent's education • Mode of delivery • Time elapsed between index delivery and survey	• Age category • Parity • Mode of delivery

3.5.3 Accounting for Survey Design in the Analyses

The DHS uses a complex survey design; this usually involves the sample being stratified and subsequently the selection of primary sampling units (PSUs) takes place at random within each stratum. Observations within one PSU are very likely to be correlated, since they share a common environment. This clustering must be taken into account in the analysis stage; since the assumption of independent observations is violated. If clustering is ignored this usually means that the standard errors calculated will be too small and the confidence intervals surrounding the effect estimates will be too narrow.

Stata has a suite of commands designed specifically to deal with the analysis of complex survey data (implemented using the *-svy-* prefix); this allows design features such as sampling weights, clustering and stratification to be identified in the dataset; subsequently Stata will adjust the estimation results taking the design features into account whenever the *-svy-* prefix is used [245]. The *-subpop()-* option has been used throughout which allows the variance estimation to be correctly estimated where subgroups of the population are being analysed [245][245][231]. Estimation commands implemented using the *-svy-*commands calculate standard errors using the Taylor linearization estimator by default [245]. This produces robust standard errors, which are based on the observed variability in the data, as opposed to the variability predicted by the regression model. This approach would often be sufficient to deal with clustered data.

Whilst *-svy-* is a very valuable tool it does not allow me to take into account the fact that there is data from twenty-seven different countries included in the pooled dataset. Between countries there may be unmeasured intrinsic social and cultural differences that need to be controlled for. In order to do this a dummy variable for *country of survey* has been included in all models.

<u>Further Clustering Considerations</u>

However, in this thesis there are potentially two scenarios in which simply using robust standard errors through the *-svy-* commands may not be sufficient to adequately adjust for clustering:

(i) In certain situations the outcome of interest is heavily dependent on geographic location. For example, in very rural and remote parts of Sub-Saharan Africa women who require a caesarean section may have to travel long distances to reach a functional healthcare facility with the staff and equipment necessary to carry out the operation. If a woman is not able access emergency delivery care because the requisite facilities are simply not available

within travelling distance of her home then cluster (as an indicator of geographic location) may potentially confound the observed association between outcome and exposure. This means that cluster can influence the effect estimate itself, which is not taken into account by the use of robust standard errors.

(ii) In this thesis many of the analyses are conducted on a pooled Sub-Saharan dataset. This introduces an additional level of clustering which is not controlled for using the *-svy-* prefix (i.e. the PSU and strata are clustered within country).

The potential issues raised by each of these scenarios are quite different. The former is an issue of confounding; it can be dealt with by generating a variable for cluster prevalence of doctor-attended index births as a proxy for service availability for inclusion in both the pregnancy outcomes models (caesarean delivery and neonatal mortality) where geographic location (i.e. remoteness) might be expected to have a confounding effect.

The second point is truly related to design effect and can be dealt with by using appropriate statistical techniques in the analysis. However, the choice of method used presents a trade-off in terms of accuracy, efficiency and required computing power. An overview of the alternative options available is presented below.

1. *Robust Standard Errors*

As previously mentioned, robust standard errors are based on the sum of the residuals, i.e. the difference between the outcome observed and the outcome predicted by the regression model. Robust standard errors are calculated subsequent to the estimation of the regression coefficients (via the standard maximum likelihood estimation approach), thus the effect estimates do not take clustering into account. Use of the Stata *-svy-* commands uses this option by default.

2. *Conditional Logistic Regression*

Conditional logistic regression, commonly used to analyse case-control designs, could potentially be used to match individuals based on cluster. However, this would be an inefficient approach since a substantial proportion of my data would be discarded.

3. *Generalised Estimating Equations (GEE)*

Generalised Estimating Equations (GEE) can give differential weighting to observations within clusters for the calculation of the effect estimate, in addition to using robust standard errors to calculate the confidence intervals and p-values. The expected correlation structure in the

model must be specified in advance; the most common option is to assume exchangeable correlations within clusters, meaning that all observations within a given cluster are equally correlated but that there is no correlation between individuals living in different clusters.

GEE is more efficient than ordinary logistic regression if the assumed correlation structure is similar to the true structure. It also allows both individual-level and cluster-level covariates to be included, and thus community-level effects may be estimated. However GEE does not provide a full probability model for the data and a quasi-likelihood estimation approach is used. This makes strong assumptions about how to treat missing data which can be problematic; GEE assumes that missing data are missing completely at random (i.e. the missing observation is independent of all other observations) which is often not truly the case.

4. Random Effects Models

A random effect model (also known as hierarchical or multilevel models) assumes that cluster-level effects are drawn from a probability distribution, for logistic regression models this would generally be the normal distribution. A term for the variance of the log odds of observing the outcome is included in the regression estimation process, which differs by cluster and has mean value of zero.

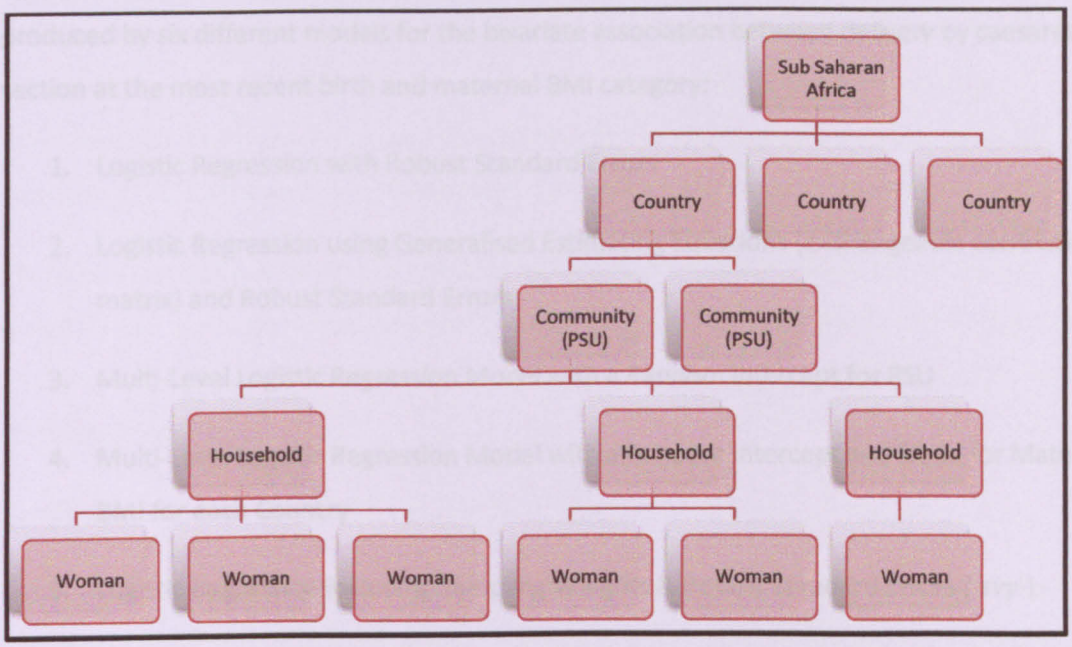
As with GEE, random-effects models allow the effect of both individual-level and cluster-level covariates to be estimated. Furthermore, the models can allow both the intercept and the slope of the effect to vary randomly, if desired.

In order to inform my decision regarding which method to use to account for clustering in this analysis I performed a sensitivity analysis investigating caesarean delivery. Caesarean delivery is arguably my outcome most dependent on geographic clustering, since women in very remote rural areas may be unable to access skilled delivery care regardless of their BMI and BMI may be associated with geographic remoteness.

Comparison of Alternative Methods Using Caesarean Delivery: a Sensitivity Analysis

In the DHS all eligible women in the household are surveyed. Households are clustered within communities/villages (PSUs) which are clustered within countries (Figure 3-E). Note that because the end unit of observation is either the individual women or her most recent birth there is no clustering of children to the same mother, which removes one of the potential levels to the model.

Figure 3-E Schematic diagram showing clustering in this study



In this PhD I am not attempting to estimate the effect of any household or community-level variables. Therefore, my primary concern with the clustered structure is to calculate appropriate standard errors so that my results may be interpreted correctly.

Ideally, in the most sophisticated model, I would be able to calculate a fully-specified multi-level model with a random intercept and random slope that allowed the effect of BMI to vary according to both geographic cluster and country of survey. However, this approach has two key using this approach has two key costs:

- It is computationally very expensive. A programme called MLwiN may be used to fit multi-level models, but it has a tendency to crash when presented with large datasets and my thesis includes many thousands of observations from twenty-seven different countries.
- The Stata command for fitting multi-level mixed effects logistic regression models - *xtmelogit*- does not allow sampling weights to be used.

Pragmatically it will not be feasible to use MLwiN to carry out the analysis, given the size of my dataset. I therefore have to choose between generating a correctly weighted model that produces the correct effect estimates for the national populations but that may under-estimate the standard errors, or using the Stata command -*xtmelogit*- to construct a multi-level model but without using sampling weights.

In order to inform this decision, a sensitivity analysis was carried out comparing the results produced by six different models for the bivariate association between delivery by caesarean section at the most recent birth and maternal BMI category:

1. Logistic Regression with Robust Standard Errors
2. Logistic Regression using Generalised Estimating Equations (exchangeable correlation matrix) and Robust Standard Errors
3. Multi-Level Logistic Regression Model with a Random Intercept for PSU
4. Multi-Level Logistic Regression Model with a Random Intercept and Slope for Maternal BMI for each Country
5. Logistic Regression including Sampling Weights & Robust Standard Errors *(-svy-)*
6. Logistic Regression including Sampling Weights & Robust Standard Errors *(-svy-)* and an Indicator Variable Included for each Country

Models 1-3 compare different approaches for analysing clustered data. Model 1 is the simplest approach; the robust standard errors take the correlation of the data into account but the effect estimate is unchanged. Model 2 is a GEE analysis; it also uses robust standard errors, but furthermore gives differential weighting to individuals depending on how many are within each cluster, so the effect estimate also takes the clustering into account. Model 3 explicitly includes the intra-cluster correlation in the estimates as a random-effect (intercept); the model assumes that cluster-effects are drawn from a normal probability distribution. Model 4 allows the effect (slope) of maternal BMI to vary by country in addition to the intercept. Unfortunately it was not possible to generate a model with more than two levels for this dataset since Stata encountered a numerical overflow (the maximum number of effective observations, 2,147,483,647, the package can handle was reached during estimation).

Estimates from Models 5-6 are not directly comparable with the previous models because they use the sample weights. The weights are important if nationally-representative results are to be derived, since certain areas or population subgroups may be over-sampled in the DHS in order to provide sufficient power to compute statistics for some vulnerable groups. Model 5 is the model produced using the default *-svy-* command. Model 6 allows for the effect of maternal BMI to be estimated within each country, relative to a baseline country, and the coefficient for BMI category is adjusted for this.

A comparison of Models 1-4 shows that the statistical approach used made very little difference to the estimated effects. Models 2 - 4 all produced slightly lower ORs than Model 1 (which did not allow for clustering in the estimation of the OR). However overall the difference was small; there was a lot of overlap in the confidence intervals and the trend, statistical significance and general interpretation of the results was unchanged.

There was more of a difference in the results of Models 5-6, which allowed for sampling weights to be used. However, even this did not substantially change the direction, magnitude or trend in the effect; and similarly there was a considerable degree of overlapping in the confidence intervals.

Conclusion

The method used to account for clustering in this sensitivity analysis did not substantially alter the interpretation of the effect estimates obtained. Given that I do not need to estimate community-level effects in my model, I have decided to prioritise weighting the data appropriately over the use of random effects models using *xtmelogit*.

Therefore the approach used to generate Model 6 will be used throughout; sampling weights and robust standard errors will be used (which will allow for clustering at the PSU-level) and a fixed indicator variable for *country of survey* will be included in all models to allow the effect of BMI to be estimated within each country relative to baseline.

Table 3.17 Sensitivity analysis for the choice of statistical model to be used in the thesis

Maternal BMI Category	OR	[95% Confidence Interval]	p-value	Standard Error
Model 1: Logistic Regression with Robust Standard Errors				
Optimal	1.00			
Pre-Obese	2.40	(2.19, 2.63)	<0.001	0.11201
Obese Class I	4.01	(3.53, 4.56)	<0.001	0.26344
Obese Class II	5.41	(4.42, 6.63)	<0.001	0.56072
Obese Class III	6.01	(4.27, 8.46)	<0.001	1.04974
Model 2: Logistic Regression using Generalised Estimating Equations (exchangeable correlation matrix) and Robust Standard Errors				
Optimal	1.00			
Pre-Obese	2.20	(2.01, 2.41)	<0.001	0.10253
Obese Class I	3.57	(3.13, 4.07)	<0.001	0.24032
Obese Class II	4.80	(3.89, 5.92)	<0.001	0.51221
Obese Class III	5.22	(3.64, 7.48)	<0.001	0.95733
Model 3: Multi-Level Logistic Regression Model with Random Intercept for PSU				
Optimal	1.00			
Pre-Obese	2.29	(2.08, 2.52)	<0.001	0.11171
Obese Class I	3.76	(3.28, 4.32)	<0.001	0.26411
Obese Class II	5.20	(4.13, 6.54)	<0.001	0.60934
Obese Class III	5.57	(3.79, 8.18)	<0.001	1.09364
Model 4: Multi-Level Logistic Regression Model with a Random Intercept and Slope for Maternal BMI for each Country				
Optimal	1.00			
Pre-Obese	2.19	(1.99, 2.41)	<0.001	0.10882
Obese Class I	3.42	(2.95, 3.96)	<0.001	0.25581
Obese Class II	4.40	(3.46, 5.60)	<0.001	0.53907
Obese Class III	5.08	(3.46, 7.46)	<0.001	0.99592
Model 5: Logistic Regression Incorporating Sampling Weights & Robust Standard Errors (-svy-)				
Optimal	1.00			
Pre-Obese	2.60	(2.34, 2.90)	<0.001	0.14201
Obese Class I	4.39	(3.78, 5.10)	<0.001	0.33456
Obese Class II	6.05	(4.77, 7.67)	<0.001	0.73329
Obese Class III	7.51	(5.16, 10.93)	<0.001	1.43793
Model 6: Logistic Regression Incorporating Sampling Weights & Robust Standard Errors (-svy-) and an Indicator Variable Included for each Country (Fixed Effect Model)				
Optimal	1.00			
Pre-Obese	2.30	(2.06, 2.57)	<0.001	0.12910
Obese Class I	3.57	(3.04, 4.19)	<0.001	0.29242
Obese Class II	4.67	(3.65, 5.98)	<0.001	0.58947
Obese Class III	6.19	(4.16, 9.22)	<0.001	1.25755

Models estimate the unadjusted odds of maternal BMI on caesarean delivery at the most recent birth.

Chapter 4

BMI Distribution among Women of Reproductive Age in Sub-Saharan Africa

This chapter presents a descriptive analysis of BMI distribution amongst women aged 15-49 years in Sub-Saharan.

The purpose of this is twofold: firstly, it will provide the most up-to-date nationally representative estimates of the prevalence of overweight and obesity in Sub-Saharan Africa currently available. Secondly, the distribution of BMI in this population is of interest to all of the main analyses as a description of the primary exposure variable and presenting these results as a discrete chapter will save repetition throughout the rest of the thesis.

Chapter 4 begins with a description of the national and regional distribution of BMI. Differentials in prevalence of overweight by age group, urban/rural residence and relative wealth quintile are then described. Finally, in Section 4.3 logistic regression was used to determine risk factors for overweight in each UN Sub-Region and the pooled dataset.

4.1 National and Regional Variations in BMI Distribution

The country-specific and regional prevalence of each BMI category calculated using the most recent survey data available are displayed in Table 1.1.

There is considerable heterogeneity in the prevalence of overweight both nationally and regionally. The highest prevalence is seen in Swaziland where half (50.5%) of all women are overweight and approaching a quarter (22.9%) are obese. This is similar to the current prevalence of overweight/obesity in England [246]. All three countries from Southern Africa exhibit high prevalence of overweight, relative to the rest of Sub-Saharan Africa, and this is reflected in the pooled regional average (36.8%). It should however be noted that this is still relatively low levels of overweight in global terms [27].

Regional averages across the remaining three regions, Eastern, Western and Middle Africa, are much more similar with approximately 15-20% of women currently overweight, but there are still some noteworthy national discrepancies between very close geographic neighbours. Two examples are neighbouring Ethiopia and Kenya, where prevalence of overweight amongst adult women is 0.6% and 23.6% respectively, and Chad and Cameroon, with 6.7% and 28.8% overweight respectively. Both these example are north-south comparisons, with the northern countries being situated in the Sahel, a region still known for food insecurity and periodic famines [247].

Under the nutrition transition the entire population BMI distribution shifts upwards, this means that more individuals enter the right-hand tail of the distribution, where they are defined as overweight or obese. Throughout this thesis I am hypothesising that increasing BMI has a dose-response relationship with each adverse health outcome, therefore the distribution of BMI is as important as the proportion falling within each category. This can be best displayed through the use of histograms.

Figure A to Figure F show the distribution of BMI in the three countries with the highest mean BMI (Swaziland, Lesotho and Cameroon) and the lowest mean BMI (Ethiopia, Madagascar and Chad). The vertical lines on each histogram represent the standard BMI category cut-offs (18.5kg/m^2, 25kg/m^2 and 30kg/m^2). As mean BMI increases, the entire curve shifts to the right and more individuals fall into the overweight and obese categories; the distribution also becomes increasingly skewed to the left as a small number of individuals become very obese.

Table 4.1 BMI distribution in all countries and regions in the study

Country	Mean BMI (kg/m^2)	BMI Category (%)			
		Underweight [<18.5kg/m^2]	Optimal [18.5-24.9kg/m^2]	Pre-Obese [25-29.9kg/m^2]	Obese [≥30kg/m^2]
Ethiopia	20.1	34.6%	61.1%	3.7%	0.6%
Kenya	22.8	17.1%	58.0%	17.9%	6.9%
Madagascar	20.3	34.4%	59.3%	5.1%	1.2%
Malawi	22.0	14.4%	72.1%	11.2%	2.4%
Mozambique	22.1	13.4%	72.5%	10.2%	3.9%
Rwanda	21.8	14.3%	74.3%	10.5%	0.9%
Tanzania	22.3	15.1%	67.3%	13.3%	4.4%
Uganda	22.2	17.9%	65.4%	12.6%	4.1%
Zambia	22.5	14.4%	66.5%	13.7%	5.4%
Zimbabwe	23.1	12.9%	62.1%	17.8%	7.2%
Eastern Africa, pooled	**22.0**	**18.4%**	**66.1%**	**11.7%**	**3.8%**
Cameroon	23.6	9.4%	61.8%	20.6%	8.2%
Chad	20.7	30.7%	62.6%	5.1%	1.7%
Congo (Brazzaville)	22.9	17.3%	57.1%	18.0%	7.6%
DRC	21.2	24.1%	65.1%	8.8%	2.0%
Middle Africa, pooled	**22.3**	**18.9%**	**61.1%**	**14.5%**	**5.5%**
Lesotho	25.0	8.2%	49.7%	25.9%	16.2%
Namibia	23.1	21.2%	51.0%	16.4%	11.5%
Swaziland	26.4	4.5%	45.1%	27.6%	22.9%
Southern Africa, pooled	**24.4**	**14.1%**	**49.1%**	**21.3%**	**15.5%**
Benin	22.6	13.9%	67.3%	13.3%	5.6%
Burkina Faso	20.9	28.4%	62.3%	7.0%	2.3%
Ghana	23.5	12.6%	57.7%	20.7%	9.0%
Guinea	21.7	18.4%	67.6%	11.1%	3.0%
Liberia	22.5	14.7%	64.7%	14.9%	5.7%
Mali	22.1	19.4%	63.0%	12.5%	5.2%
Niger	21.4	24.8%	62.2%	9.8%	3.2%
Nigeria	22.6	16.8%	61.4%	16.0%	5.8%
Senegal	22.3	23.9%	54.4%	14.5%	7.2%
Sierra Leone	23.1	15.1%	58.7%	18.8%	7.4%
Western Africa, pooled	**22.3**	**18.4%**	**62.6%**	**13.8%**	**5.3%**
Sub-Saharan Africa, pooled	**22.3**	**18.1%**	**62.6%**	**13.7%**	**5.7%**

Sampling weights used.

Figure 4-A BMI distribution in Ethiopia

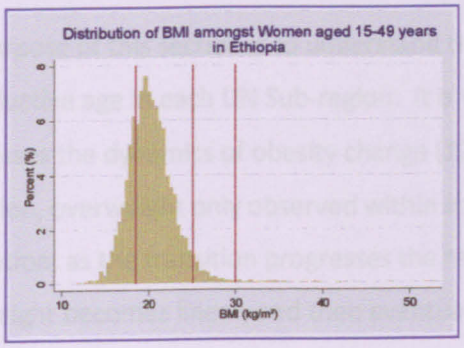


Figure 4-B BMI distribution in Chad

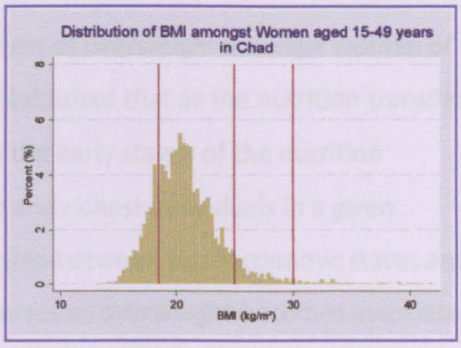


Figure 4-C BMI distribution in Madagascar

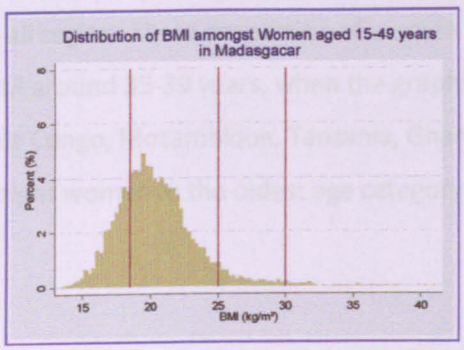


Figure 4-D BMI distribution in Cameroon

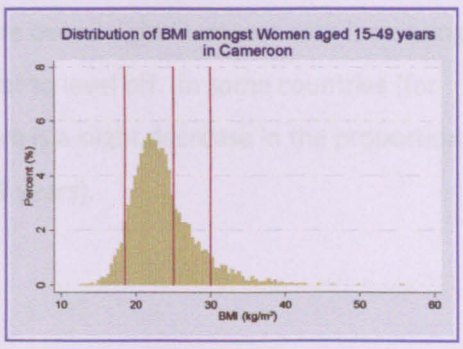


Figure 4-E BMI distribution in Lesotho

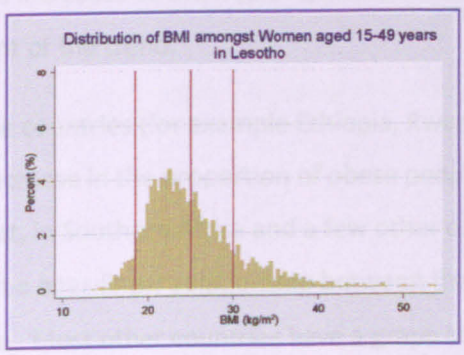
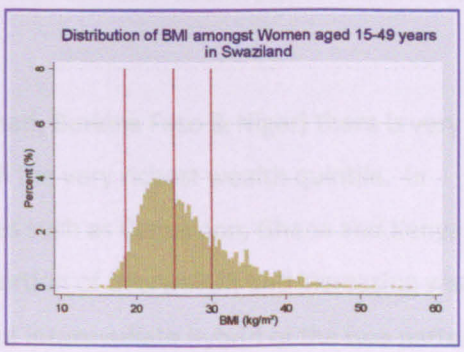


Figure 4-F BMI distribution in Swaziland



4.2 Socio-demographic Characteristics associated with Overweight in each Region

The purpose of this section is to understand the context of overweight amongst women of reproductive age in each UN Sub-region. It is well-established that as the nutrition transition progresses the dynamics of obesity change [137]. In the early stages of the nutrition transition, overweight only observed within the elite and richest individuals in a given population; as the transition progresses the relationship between socioeconomic status and overweight becomes linear, and then eventually reverses as overweight becomes associated with the poorest members of society.

4.2.1 Age

The proportion of overweight women within each age group is shown in Figure G to Figure J. Across all regions there proportion of women who are overweight increases with increasing age until around 35-39 years, when the graphs appear to level off. In some countries (for example Congo, Mozambique, Tanzania, Ghana) there is a slight decrease in the proportion of overweight women in the oldest age category (45-49 years).

4.2.2 Relative Wealth

Figure K to Figure N show the proportion of overweight women in each relative wealth quintile. If the proportion of obese women did not differ by wealth quintile the graph would be a horizontal line; however it can be seen that in all countries the proportion of overweight women increases as the wealth quintile increases. There are inter-country differences in the gradient of the trend.

In some countries (for example Ethiopia, Rwanda, Chad, Burkina Faso & Niger) there is very little increase in the proportion of obese people until the very richest wealth quintile. In contrast, in Southern Africa and a few other countries such as Cameroon, Ghana and Kenya there is a near-linear relationship between the proportion of overweight and increasing wealth quintile. Most other countries have a graph that is an intermediate hybrid of the two patterns.

Figure 4-G Proportion overweight by age, Eastern Africa

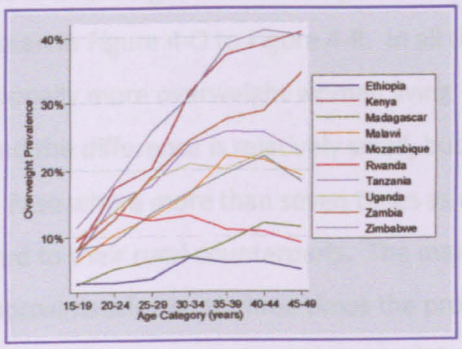


Figure 4-H Proportion overweight by age, Middle Africa

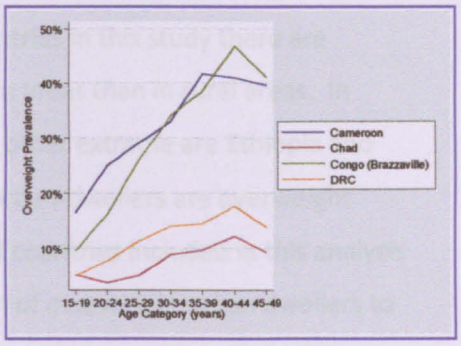


Figure 4-I Proportion overweight by age, Southern Africa

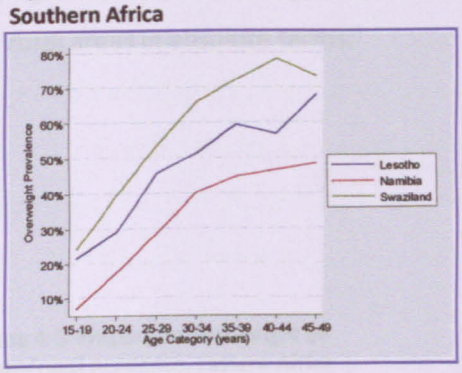


Figure 4-J Proportion overweight by age, Western Africa

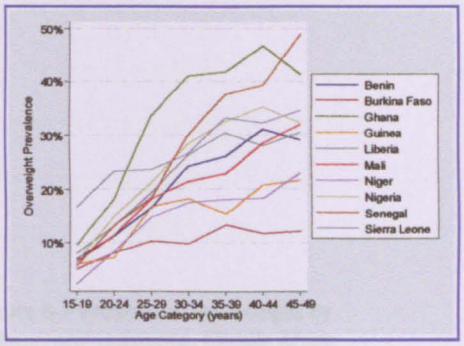


Figure 4-K Proportion overweight by wealth, Eastern Africa

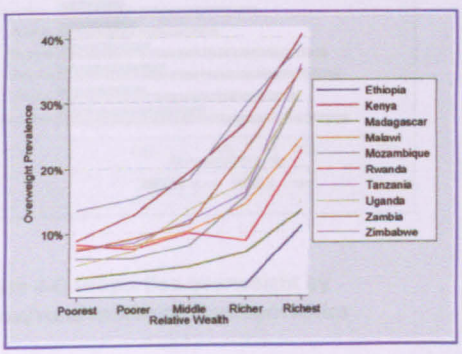


Figure 4-L Proportion overweight by wealth, Middle Africa

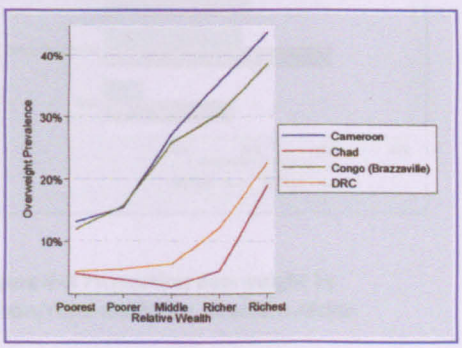


Figure 4-M Proportion overweight by wealth, Southern Africa

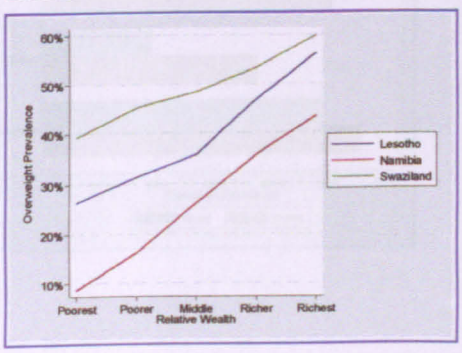
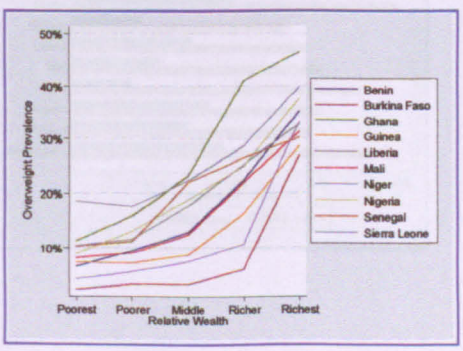


Figure 4-N Proportion overweight by wealth, Western Africa



4.2.3 Urban/Rural Residence

The ratio of overweight women living in urban areas compared to those living in rural areas can be seen in Figure 4-O to Figure 4-R. In all the countries in this study there are proportionally more overweight women living in urban areas than in rural areas. In Swaziland the difference is relatively small, but at the other extreme are Ethiopia and Burkina Faso where more than seven times as many urban-dwellers are overweight compared to their rural counterparts. The majority of countries included in this analysis have approximately two to three times the proportion of overweight urban dwellers to rural dwellers. However, it should be noted that in seven countries (Swaziland, Rwanda, Malawi, Uganda, Kenya & Madagascar) there are a greater number of overweight women living in rural areas in absolute terms.

Figure 4-O Proportion overweight by urban/rural residence, Eastern Africa

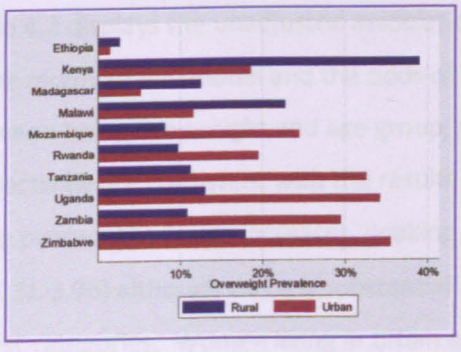


Figure 4-P Proportion overweight by urban/rural residence, Middle Africa

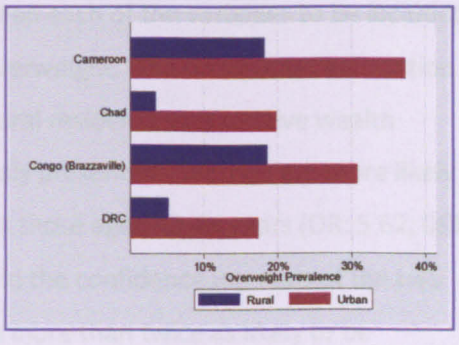


Figure 4-Q Proportion overweight by urban/rural residence, Southern Africa

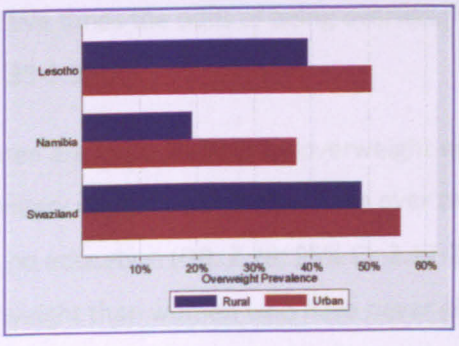
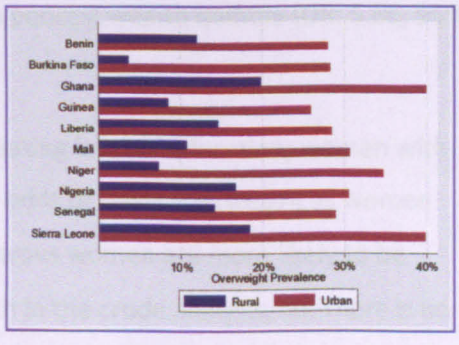


Figure 4-R Proportion overweight by urban/rural residence, Western Africa



4.3 Risk Factors for Overweight in Sub-Saharan Africa

A logistic regression model was constructed to assess the risk factors for being overweight in Sub-Saharan Africa. Underweight women (BMI<18.5kg/m2) were excluded from this and all subsequent analyses, as they are not of interest to the stated aims and objectives of this study.

4.3.1 Bivariate Analysis

Women are more likely to be overweight with increasing level of education; women with secondary education or higher have over twice the odds of being overweight as women with no education (OR: 2.28; 95% CI: 2.17-2.39). Parous women are more likely to be overweight than women who have never given birth in the crude analysis, but there is no difference in the odds of being overweight between those who have 3-5 previous births (OR: 2.49; 95% CI: 2.39-2.60) and those with six or more previous births (OR: 2.40; 95% CI: 2.29-2.51) relative to nulliparous women. Both currently married (OR: 2.25; 95% CI: 2.16-2.34) and formerly married (OR: 2.59; 95% CI: 2.45-2.74) women are more likely to be overweight than those who have never been married.

Table 4.2 displays the unadjusted association between each of the variables to be included in the multivariable model and the odds of being overweight. The unadjusted association between being overweight and age group, urban/rural residence and relative wealth respectively are consistent with the results previously presented. Women are more likely to be overweight as age increases, peaking amongst those aged 40-44 years (OR: 5.62; 95% CI: 5.31-5.96) although there is substantial overlap in the confidence intervals of the two oldest categories. Women living in urban areas are more than twice as likely to be overweight as rural dwellers (OR: 2.80; 95% CI: 2.69-2.91). Women are significantly more likely to be overweight by each increasing wealth quintile, with the richest group having over five times the odds of being overweight as the poorest wealth quintile (OR: 5.66; 95% CI: 5.35-5.99).

Women are more likely to be overweight with increasing level of education; women with secondary education or higher have over twice the odds of being overweight as women with no education (OR: 2.28; 95% CI: 2.17-2.39). Parous women are more likely to be overweight than women who have never given birth in the crude analysis, but there is no difference in the odds of being overweight between those who have 3-5 previous births

(OR: 2.49; 95% CI: 2.39-2.60) and those with six or more previous births (OR: 2.40; 95% CI: 2.29-2.51) relative to nulliparous women. Both currently married (OR: 2.25; 95% CI: 2.16-2.34) and formerly married (OR: 2.59; 95% CI: 2.45-2.74) women are more likely to be overweight than those who have never been married.

Table 4.2 Unadjusted risk factors for being overweight

Risk Factor		Unadjusted OR	[95% Confidence Interval]	p-value
Age Category	15-19 years	1.00		
	20-24 years	1.93	[1.82, 2.04]	<0.001
	25-29 years	2.97	[2.81, 3.15]	<0.001
	30-34 years	4.20	[3.97, 4.45]	<0.001
	35-39 years	5.04	[4.75, 5.34]	<0.001
	40-44 years	5.62	[5.31, 5.96]	<0.001
	45-49 years	5.45	[5.13, 5.79]	<0.001
Urban/Rural Residence	Rural	1.00		
	Urban	2.80	[2.69, 2.91]	<0.001
Relative Wealth Quintile	Poorest	1.00		
	Poorer	1.29	[1.21, 1.37]	<0.001
	Middle	1.89	[1.78, 2.00]	<0.001
	Richer	3.04	[2.86, 3.22]	<0.001
	Richest	5.66	[5.35, 5.99]	<0.001
Education Level	No education	1.00		
	Primary only	1.56	[1.49, 1.63]	<0.001
	Secondary or higher	2.28	[2.17, 2.39]	<0.001
Parity	Nulliparous	1.00		
	1-2 previous live births	1.86	[1.78, 1.94]	<0.001
	3-4 previous live births	2.49	[2.39, 2.60]	<0.001
	6 or more previous live births	2.40	[2.29, 2.51]	<0.001
Marital status	Never-married	1.00		
	Currently married	2.25	[2.16, 2.34]	<0.001
	Formerly married	2.59	[2.45, 2.74]	<0.001

Sampling weights and survey design taken into account in the analysis

4.3.2 Multivariable Model

The results of the multivariable model are displayed in Table 4.3. As in the bivariate analysis, increasing age is strongly associated with increasing odds of being overweight. A clear dose-response relationship is observed; compared to the youngest age group, women who are 20-24 years have 1.7 times the odds of being overweight (pooled OR: 1.70; 95% CI 1.60-1.81) whilst the oldest age group are more than six times as likely to be overweight (pooled OR: 6.56; 95% CI: 6.02-7.14). A similar pattern may be seen across all four regions with the magnitude of the effect appearing to be slightly larger in the oldest age groups in the Western Region (OR: 8.03; 95% 7.03-9.17).

In Eastern Middle and Western Africa women who live in urban areas are at increased odds of being overweight. However, no association was seen in Southern Region (OR: 1.00; 95% CI: 0.90-1.11). Although a slightly higher proportion of women living in urban areas are overweight compared to women in rural locations (42% compared to 33%) the association disappeared after controlling for confounding factors.

The strong association between relative wealth and odd of being overweight seen in the bivariate analysis was preserved in the multivariable model; all regions and the pooled Sub-Saharan model showed a similar effect. In the pooled dataset the odds of being overweight increased more than four times in the richest quintile relative to the poorest households (OR: 4.52; 95% CI: 4.20-4.86).

Similarly, the relationship between education and overweight was consistent across all four regions; women who had secondary education or above had 1.6 times the odds of being overweight compared to women with no education (pooled OR: 1.67; 95% CI: 1.58-1.76).

Much of the relationship between parity and the odds of being overweight disappeared after controlling for other factors; however there was a clear regional difference in the results. In Eastern, Middle and Western Africa there was no significant association and all ORs were very close to the null. However, in Southern Africa women of a higher parity were increasingly more likely to be overweight; those who had 1-2 previous births were 1.5 times more likely to be overweight compared to nulliparous women (OR: 1.52; 95% CI 1.31-1.77) whilst women in the highest parity category with six or more births were over twice as likely to be overweight (OR: 2.17; 95% CI 1.74-2.71).

Across all regions currently married women were more likely to be overweight compared to those who had never been married (pooled OR: 1.40; 95% CI 1.31-1.48). Formerly

married women were also more likely to be overweight overall (pooled OR: 1.29; 95% CI 1.20-1.39) but no significant association was observed for this category in Southern Region (OR: 1.05; 95% CI: 0.89-1.25).

Table 4.3 Multivariable model of the odds of being overweight

Risk Factor		Eastern Region			Middle Region			Southern Region			Western Region			All Sub-Saharan Africa		
		OR	[95% CI]	p-value	OR	[95% CI]	p-value	OR	[95% CI]	p-value	OR	[95% CI]	p-value	OR	[95% CI]	p-value
Age Group	15-19 years	1.00			1.00			1.00			1.00			1.00		
	20-24 years	1.63	[1.47, 1.82]	<0.001	1.40	[1.18, 1.68]	<0.001	1.59	[1.35, 1.87]	<0.001	1.88	[1.71, 2.08]	<0.001	1.70	[1.60, 1.81]	<0.001
	25-29 years	2.24	[1.98, 2.53]	<0.001	2.04	[1.66, 2.50]	<0.001	2.52	[2.06, 3.08]	<0.001	3.10	[2.79, 3.45]	<0.001	2.59	[2.42, 2.78]	<0.001
	30-34 years	3.34	[2.93, 3.79]	<0.001	2.95	[2.38, 3.65]	<0.001	3.73	[3.06, 4.54]	<0.001	4.63	[4.15, 5.17]	<0.001	3.86	[3.59, 4.15]	<0.001
	35-39 years	4.32	[3.78, 4.95]	<0.001	3.95	[3.15, 4.96]	<0.001	4.87	[3.93, 6.04]	<0.001	5.84	[5.18, 6.59]	<0.001	4.97	[4.60, 5.37]	<0.001
	40-44 years	5.20	[4.53, 5.96]	<0.001	5.13	[4.05, 6.50]	<0.001	5.24	[4.16, 6.58]	<0.001	7.15	[6.32, 8.08]	<0.001	6.02	[5.56, 6.52]	<0.001
	45-49 years	5.45	[4.72, 6.29]	<0.001	4.63	[3.60, 5.95]	<0.001	5.95	[4.73, 7.50]	<0.001	8.03	[7.03, 9.17]	<0.001	6.56	[6.02, 7.14]	<0.001
Residence	Rural	1.00						1.00			1.00			1.00		
	Urban	1.45	[1.34,1.57]	<0.001	1.36	[1.09, 1.70]	0.007	1.00	[0.90, 1.11]	0.956	1.54	[1.43, 1.67]	<0.001	1.45	[1.38, 1.52]	<0.001
Relative Wealth Quintile	Poorest	1.00			1.00			1.00			1.00			1.00		
	Poorer	1.13	[1.00, 1.27]	0.041	1.17	[0.91, 1.49]	0.224	1.59	[1.35, 1.87]	<0.001	1.30	[1.18, 1.43]	<0.001	1.26	[1.18, 1.34]	<0.001
	Middle	1.51	[1.36, 1.68]	<0.001	1.88	[1.41, 2.50]	<0.001	2.38	[2.00, 2.82]	<0.001	1.83	[1.67, 2.02]	<0.001	1.77	[1.66, 1.88]	<0.001
	Richer	2.21	[1.99, 2.45]	<0.001	2.64	[2.00, 3.48]	<0.001	3.61	[3.03, 4.29]	<0.001	2.81	[2.54, 3.11]	<0.001	2.61	[2.45, 2.79]	<0.001
	Richest	4.29	[3.81, 4.83]	<0.001	4.41	[3.26, 5.97]	<0.001	5.17	[4.26, 6.28]	<0.001	4.67	[4.18, 5.21]	<0.001	4.52	[4.20, 4.86]	<0.001
Education	No education	1.00			1.00			1.00			1.00			1.00		
	Primary	1.41	[1.29, 1.53]	<0.001	1.68	[1.42, 1.99]	<0.001	1.31	[1.10, 1.57]	0.003	1.47	[1.38, 1.57]	<0.001	1.47	[1.41, 1.54]	<0.001
	Secondary or higher	1.71	[1.53, 1.90]	<0.001	1.61	[1.32, 1.95]	<0.001	1.57	[1.30, 1.90]	<0.001	1.66	[1.54 1.78]	<0.001	1.67	[1.58, 1.76]	<0.001
Parity	Nulliparous	1.00			1.00			1.00			1.00			1.00		
	1-2 previous live births	0.93	[0.82, 1.04]	0.202	1.05	[0.88, 1.26]	0.573	1.52	[1.31, 1.77]	<0.001	1.07	[0.97, 1.17]	0.170	1.10	[1.04, 1.17]	0.002
	3-5 previous live births	0.98	[0.86, 1.12]	0.773	1.01	[0.83, 1.23]	0.901	1.81	[1.49, 2.20]	<0.001	1.00	[0.90, 1.11]	0.975	1.10	[1.03, 1.18]	0.006
	6 + previous live births	0.87	[0.75, 1.00]	0.055	0.96	[0.77, 1.20]	0.718	2.17	[1.74, 2.71]	<0.001	0.93	[0.82, 1.04]	0.199	1.01	[0.93, 1.09]	0.827
Marital status	Never-married	1.00			1.00			1.00			1.00			1.00		
	Currently married	1.31	[1.17, 1.47]	<0.001	1.61	[1.34, 1.93]	<0.001	1.33	[1.19, 1.50]	<0.001	1.54	[1.39, 1.71]	<0.001	1.40	[1.31, 1.48]	<0.001
	Formerly married	1.17	[1.02, 1.34]	0.024	1.42	[1.15, 1.75]	0.001	1.05	[0.89, 1.25]	0.55	1.63	[1.43, 1.85]	<0.001	1.29	[1.20, 1.39]	<0.001

Effect estimates adjusted for all other covariates in the model. Sampling weights and survey design taken into account in the analysis

4.3.3 Interaction between Relative Wealth and Urban/Rural Residence

Significant interaction was found between *relative wealth quintile* and *area of residence* in the pooled dataset for all of sub-Saharan Africa ($p < 0.001$) in addition to each of the four regional models (Eastern Africa $p < 0.001$; Middle Africa $p = 0.0199$; Southern Africa $p < 0.001$; Western Africa $p = 0.0471$). Stratum-specific odds ratios were therefore calculated and are presented in Table 4.4.

Effect of Wealth on the Odds of being Overweight, by Area of Residence

In all four regions in addition to the pooled sub-Saharan dataset, women in the richest quintile are more likely to be obese than women in the poorest regardless of area of residence. However, in most regions the magnitude of the effect appears to be larger amongst urban dwellers (pooled urban OR: 5.43, 95% CI 4.31-6.85; pooled rural OR: 4.43, 95% CI: 4.04-4.86) although it should be noted that there is overlap between the confidence intervals so this difference is not statistically significant.

There is heterogeneity in the magnitude of the effect size across regions. Amongst rural dwellers the smallest gradient observed was in Middle Africa (richest quintile OR: 3.27; 95% CI: 2.09-5.12) and the largest in Southern Africa (richest quintile OR: 4.83; 95% CI: 3.87-6.02). Amongst urban dwellers there was a greater differential between the richest quintile and the poorest quintile everywhere except Eastern Region. The largest effect was again observed in Southern Africa where women in the richest quintile are more than ten times as likely to be overweight as those in the poorest (OR: 10.75; 95% CI: 5.07-22.78).

Effect of Area of Residence on the Odds of being Overweight, by Wealth Quintile

Stratifying by wealth quintile revealed some interesting patterns in the data. In both Western and Middle Africa urban dwellers were significantly more likely to be overweight than rural dwellers in the higher wealth quintiles but no significant association was observed amongst the poorest women. However, in Eastern Africa women at the two extremes of the wealth spectrum, richest and poorest, were more likely to be overweight if they lived in an urban area and no relationship was observed in the middle wealth quintile.

Table 4.4 Stratum-specific odds ratios (i) by urban/rural residence; (ii) by wealth quintile

		Eastern Region			Middle Region			Southern Region			Western Region			All Sub-Saharan Africa		
		OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Rural	Poorest	1.00			1.00			1.00			1.00			1.00		
	Poorer	1.14	[1.01, 1.28]	0.032	1.18	[0.90, 1.54]	0.232	1.52	[1.29, 1.80]	<0.001	1.29	[1.17, 1.42]	<0.001	1.25	[1.17, 1.34]	<0.001
	Middle	1.55	[1.39, 1.73]	<0.001	2.10	[1.51, 2.92]	<0.001	2.35	[1.96, 2.82]	<0.001	1.80	[1.63, 1.99]	<0.001	1.78	[1.66, 1.90]	<0.001
	Richer	2.25	[2.01, 2.52]	<0.001	1.89	[1.25, 2.88]	0.003	3.76	[3.12, 4.54]	<0.001	2.61	[2.34, 2.91]	<0.001	2.52	[2.35, 2.71]	<0.001
	Richest	4.09	[3.55, 4.72]	<0.001	3.27	[2.09, 5.12]	<0.001	4.83	[3.87, 6.02]	<0.001	4.79	[4.13, 5.56]	<0.001	4.43	[4.04,4.86]	<0.001
Urban	Poorest	1.00			1.00			1.00			1.00			1.00		
	Poorer	0.92	[0.52, 1.64]	0.783	1.22	[0.66, 2.27]	0.530	4.79	[2.14, 10.71]	<0.001	1.56	[1.12, 2.18]	<0.001	1.42	[1.10, 1.84]	<0.001
	Middle	1.00	[0.63, 1.58]	0.998	1.92	[1.05, 3.52]	0.035	4.86	[2.18, 10.84]	<0.001	2.46	[1.80, 3.38]	<0.001	2.01	[1.59, 2.55]	<0.001
	Richer	1.83	[1.18, 2.83]	0.007	3.29	[1.81, 5.96]	<0.001	7.03	[3.33, 14.86]	<0.001	3.99	[2.91, 5.47]	<0.001	3.21	[2.54, 4.06]	<0.001
	Richest	3.66	[2.38, 5.65]	<0.001	5.18	[2.83, 9.47]	<0.001	10.75	[5.07, 22.78]	<0.001	6.29	[4.61, 8.58]	<0.001	5.43	[4.31, 6.85]	<0.001
Poorest	Rural	1.00			1.00			1.00			1.00			1.00		
	Urban	1.73	[1.12, 2.68]	0.013	1.16	[0.62, 2.14]	0.644	0.48	[0.23, 1.02]	0.057	1.12	[0.81, 1.53]	0.495	1.20	[0.95, 1.51]	0.133
Poorer	Rural	1.00			1.00			1.00			1.00			1.00		
	Urban	1.41	[0.98, 2.01]	0.061	1.20	[0.81, 1.77]	0.365	1.52	[1.05, 2.20]	0.025	1.35	[1.11, 1.64]	0.003	1.36	[1.17, 1.56]	<0.001
Middle	Rural	1.00			1.00			1.00			1.00			1.00		
	Urban	1.12	[0.88, 1.42]	0.370	1.06	[0.75, 1.50]	0.744	1.00	[0.82, 1.22]	0.988	1.52	[1.34, 1.73]	<0.001	1.35	[1.23, 1.49]	<0.001
Richer	Rural	1.00			1.00			1.00			1.00			1.00		
	Urban	1.41	[1.25, 1.59]	<0.001	2.01	[1.38, 2.92]	<0.001	0.91	[0.77, 1.07]	0.237	1.71	[1.52, 1.92]	<0.001	1.52	[1.41, 1.64]	<0.001
Richest	Rural	1.00			1.00			1.00			1.00			1.00		
	Urban	1.55	[1.37, 1.75]	<0.001	1.83	[1.23, 2.71]	0.003	1.08	[0.88, 1.32]	0.457	1.47	[1.28, 1.67]	<0.001	1.47	[1.35, 1.59]	<0.001

Estimates adjusted for age group, education, parity and marital status. Sampling weights and survey design taken into account in the analysis

In contrast in Southern Africa there was no association between area of residence and the odds of being overweight in the wealthier quintiles; high numbers of women in rural areas are also overweight. It should be noted that here were very few women from the poorest wealth quintile living in urban areas (63 out of a total of 2558) which may be possibly an artefact of how the wealth quintile was constructed in the DHS (see Chapter 3 for further discussion) so this result should be interpreted with some caution.

4.4 Summary

Overall prevalence of overweight is 19.4% in Sub-Saharan Africa; 5.7% of women are obese, based on the most recent available nationally-representative data for each country. This is low by global standards but still represents a substantial health concern. There is substantial regional variation. Prevalence of overweight (36.8%) and obesity (15.5%) are much higher in Southern Africa.

The distribution of overweight by age and relative wealth suggests that most countries in Sub-Saharan Africa have yet to commence the nutrition transition. However, an approximately linear relationship was observed in Southern Africa, Cameroon and the Republic of Congo, suggestive of overall rising overweight and obesity [27].

In the multivariable model, increasing age, wealth and education were risk factors for overweight. Both currently and formerly married women were more likely to be overweight than those who were never-married, after adjustment for confounding. Urban residence was a risk factor for overweight in all regions except Southern Africa. Parity was not a significant risk factor for overweight, once age and other confounding factors were taken into account in the multivariable model.

There was significant interaction between the effect of relative wealth and urban/rural residence. In most African regions being in the richest quintile was a stronger risk factor for being overweight in urban areas than in rural areas.

Chapter 5

Weight Trajectories over the Female Reproductive Life Course

Any fluctuation in body weight occurring within the five years preceding each survey may have important implications for potential exposure misclassification in this study if the change is sufficient to alter the respondent's BMI category.

This chapter will attempt to assess the extent of any potential exposure misclassification. Unfortunately, there is no single source of evidence which would allow this bias to be quantified directly. The ideal would be longitudinal anthropometric data from a low-income and high-fertility setting, however no such data are currently available. Therefore this chapter uses three different approaches to assess the problem, each with its own advantages and limitations. The findings can then be compared to increase the validity of inferences made from the results.

Table 5.1 Methods used in Chapter 5

Data Source	Objectives
Existing Epidemiological Literature	• To review the published literature on weight trajectories over the female reproductive life course.
Consecutive DHS from Ghana, Kenya and Zambia	• To describe age-specific changes in median body weight and BMI amongst women of reproductive age (15-49 years) in those countries where four successive rounds of the DHS have collected anthropometry data.
Prospective Cohort of Postpartum Women (Burkina Faso)	• To describe weight change over a four year period following delivery. • To identify risk factors for a change in BMI category (and so inform discussion of potential exposure misclassification in the main thesis results).

5.1 Statement of the Problem: Potential BMI Misclassification

Throughout my thesis I am hypothesising that any overweight-outcome association observed is a causal one. For this to truly be the case the exposure (overweight status) must exist prior to the occurrence of the outcome. Unfortunately the DHS are cross-sectional surveys, so it is not possible establish any sort of temporal effect. Each of the reproductive outcomes of interest to this study could occur at any point during the five full calendar years prior to the survey. Therefore I have to make the implicit assumption throughout my thesis that an individual's BMI category has remained constant for up to five years prior to data collection.

Data from the UK and the Philippines show that adolescent females typically gain both height and body mass rapidly during their early teens, before their rate of growth slows around age fifteen or sixteen years [248-249]. Growth patterns, nutrition and socioeconomic status prior to age twelve are all important determinants of attained adult height [249-250]. My study will be restricted to women aged 20 years or older at the time of data collection. This should mean that any height misclassification will be negligible. However, it is well-established that there are further gradual and progressive increases in body weight throughout the reproductive life course, at least until the oldest age groups are reached when BMI usually declines [248, 251-252].

As regards exposure misclassification in this thesis, my concern is not a change in body weight *per se*, only a change in body weight that is sufficient to cause an individual to move from one BMI category to another. The size of any weight fluctuation required for this to occur depends on i) how close the woman is to the category boundary initially (which can be assumed to be randomly distributed), and ii) her height. A given increase in body weight has a proportionally smaller effect on BMI the taller the individual. Standard BMI categories form quite wide groups; for example in a set of adults exactly 1.6m tall there is more than 16kg difference in weight between the heaviest and lightest individuals within the optimal BMI group.

Unfortunately, most research into weight trajectories during adulthood have been conducted in high-income countries. It seems probable that typical patterns of weight gain may be different for women in the Sub-Saharan context where average dietary intake is generally lower, high fertility and shorter birth intervals are more common, and extended breastfeeding is the norm.

The initial literature review summarises what is currently known about typical female weight trajectories across the reproductive life course. However, nearly all the literature published to

date is based in high-income settings which have already completed the demographic transition; it is not necessarily transferable to a setting such as Sub-Saharan Africa where women typically have higher fertility, so spend a greater proportion of their adult life pregnant or lactating.

In three Sub-Saharan countries (Ghana, Kenya and Zambia) there have now been four consecutive DHS collecting anthropometric data. As the DHS are nationally-representative surveys it is possible to trace changes in the median weight or BMI over this period. Nevertheless, repeat cross-sectional surveys conducted on independent samples are less informative than longitudinal data. It is difficult to distinguish between changes in weight occurring due to the ageing of each cohort, and changes observed due to temporal effects caused by the start of the nutrition transition, urbanisation or other social changes which are currently taking place across Sub-Saharan Africa. Furthermore, since it is only possible to look at trends occurring at the population-level it is not possible to determine individual risk factors for weight fluctuation, which would be required to inform a full discussion of potential exposure misclassification.

Finally, this chapter concludes with an analysis of postpartum weight change using data from a prospective cohort study of women from Burkina Faso. The key strength of this analysis is that it uses longitudinal data – and therefore risk factors for a change in BMI category during the study can be identified. Nevertheless, the findings of this study can still be enhanced by triangulation with the previously described approaches, as this cohort were followed up for a relatively short period (median 35 months) and all the women in the sample are immediately postpartum, which is a period when a woman's body weight would be expected to fluctuate.

5.2 Evidence in the Existing Epidemiological Literature

An analysis of two UK birth cohorts found that adult women gained between 0.2 to 1.2 kg/m^2 per year; however, weight trajectories differed significantly between birth cohorts [248]. The rate of BMI gain was initially low but increased as the cohort aged in the 1946 birth cohort, whilst the rate of gain was constant throughout adulthood for the 1958 birth cohort [248]. Both cohorts had a similar mean BMI (around $21kg/m^2$) during their late teens, but by age 53 years mean BMI was greater in the 1958 birth cohort ($28.70kg/m^2$ versus $27.86kg/m^2$) [248]. Results from a nationally-representative longitudinal survey amongst US adults aged 25-74 years (National Health and Nutrition Examination Survey, NHANES I), which followed

participants over a twenty year period commencing in 1971-75, found that average BMI increased by 0.6 kg/m^2 every five years [253]; although it should be noted that average BMI at baseline was approximately 3 kg/m^2 higher than in the British study. Similarly, a prospective study of the risk on atherosclerosis amongst 45-64 year olds in the USA found that White women had a 0.92 kg/m^2 mean increase in BMI over a five year period whilst amongst African-American women mean increase in BMI was 0.68 kg/m^2 [254].

The use of mean BMI conceals large differences between individuals [253]; for example, nationally-representative data from the USA has shown that 8.4% of women aged 25-34 gained ≥5 kg/m^2 over a ten year period [255. Typical weight trajectories differ across the life course according to both gender (women are at a consistently greater risk of weight gain across the adult life course than are men) and ethnicity {Clarke, 2009 #207]. Individual weight gain is associated with genetic traits [256], environmental factors such as neighbourhood deprivation, social factors such as occupation, education and socioeconomic status [256-257] , and of course with reproduction and child-bearing, as will be discussed in the remainder of this chapter. These parameters act together on the immediate determinants of weight gain: the balance of energy expenditure and dietary intake [258-259].

Reproduction is a particularly important determinant of the extent and patterns of weight change amongst adult females. A systematic review [221] including 21 studies (15 prospective, 5 retrospective, and 1 control group from a randomised controlled trial) from North America, Europe, Brazil and China found that mean body weight during the first month postpartum is 7-13% higher than mean pre-pregnancy weight. There is a steep decrease in weight retention during the first three months postpartum, followed by a slower rate of weight loss until around twelve months postpartum. One year after giving birth mean postpartum weight retention ranged between 1-5% of pre-pregnancy weight. However, the studies included were heterogeneous in terms of parity and ethnicity, which makes the findings difficult interpret. The review found that weight tended to increase subsequent to twelve months postpartum, but this is more likely to be due to lifestyle changes associated with parenting than any biological mechanism [221].

Winkvist *et. al.* have described how maternal weight changes can be divided into three categories; (i) those that occur during gestation, (ii) those that occur during lactation, and (iii) those that occur either during the period where a woman is neither pregnant nor lactating or alternatively (if she has a very short birth interval) during any period where she becomes pregnant again before the previous child is weaned [260].

1. Weight Changes during Gestation

Women with an optimal pre-pregnancy BMI are recommended to gain between 11.5-16 kg during a singleton pregnancy [261]; although in high-income countries many women exceed this threshold [262]. Components of gestational weight gain, as typically experienced during pregnancy for women without oedema are displayed in Table 5.2 [263]:

Table 5.2 Components of weight gain during pregnancy (women without oedema)

	Increase in weight (grams) up to			
	10 weeks	**20 weeks**	**30 weeks**	**40 weeks**
Foetus	5	300	1500	3400
Placenta	20	170	430	650
Amniotic fluid	30	350	750	800
Uterus	140	320	600	970
Mammary gland	45	180	360	405
Blood	100	600	1300	1250
Extracellular/extravascular fluid	0	30	80	1680
Total weight gained	**650**	**4000**	**8500**	**12500**
Weight not accounted for	310	2050	3480	3345

Taken from Scott (2007) [263]

Therefore, if a woman gains 12.5kg during pregnancy around 3.5kg of this weight will be the baby itself and just less than 6kg will be formed of the placenta and other direct products of pregnancy. This leaves around 3.3kg of excess body fat which is accumulated as an energy reserve during gestation, although many women may gain much more than this.

Reliable evidence on gestational weight gain from low-income settings is limited; but it appears that the absolute amount of weight gained is usually lower. Durnin (1987) [264-265] describes a five-country longitudinal study investigating anthropometry and nutrition during pregnancy in Scotland, the Netherlands, the Gambia, Thailand and the Philippines. The study found that women in the Gambia increased their body weight by a mean of 7.3kg during pregnancy, compared to a mean gain of 10.5kg in the Netherlands and 11.7kg in Scotland; however, weight gain as a proportion of initial body weight was fairly similar across all sites (14% in the Gambia compared to 17% and 20% in the Netherlands and Scotland, respectively [265].) This study did not control for height, which will have biased the results; average height in the low-income countries was shorter than in Scotland or the Netherland. Furthermore, the results of this study are over twenty years old and substantial changes in population health and nutrition have taken place over the intervening period.

Pre-pregnancy BMI and the magnitude of gestational weight gain are key predictors of postpartum weight retention in the medium and longer term [266-268]. The Stockholm Pregnancy and Women's Nutrition study found that women who gained more than the recommended gestational weight gain experienced a 0.72 kg/m^2 greater increase in BMI over the next fifteen years than those whose gestational weight gain was within the national health guidelines [269]. Parity has also been found to have an independent effect on both gestational weight gain and inter-pregnancy weight gain [270]. Unsurprisingly, factors such as diet and physical activity have also been found to be associated with postpartum weight retention [271-272].

2. Weight Changes during Lactation

Several studies have reported that breastfeeding is associated with reduced postpartum weight retention [273-274]; however, other research has suggested that the effects of breastfeeding are more limited [266, 275-276]. Lactation is a very energy-intensive process that requires an estimated 2.62 MJ per day [277].

Changes in body weight due to lactation are highly variable on both the individual and population level [278]. Women in industrialised countries often lose only a small amount of weight during lactation, or may even gain weight [260]. A study of Filipino women found that those with a low BMI lost more weight during lactation than those with a higher BMI [279]. Risk of weight loss during lactation was increased by longer duration and intensity of lactation, lower food intake, higher energy expenditure and older maternal age [279]. A study from Nigeria investigating the mineral composition of breast milk found a significant decrease in mean maternal weight of 1.6kg between 4 weeks postpartum and twelve weeks postpartum ($p<0.01$) but much of this weight loss would have been due to natural processes other than lactation itself [280].

A cross-sectional analysis of DHS data from Brazil found a significant interaction between parity and lactation: the effect of lactation on postpartum weight loss was reduced as parity increased [281]. However this finding should be interpreted very cautiously, as the study relied on women's recall of their weight prior to their first pregnancy, which could potentially have been up to several decades prior to the survey.

3. Weight Change during the Non-Pregnant/Non-Lactating Interval

In many areas of Sub-Saharan Africa the non-pregnancy/non-lactating interval may be very short or even non-existent. One theory proposed, the maternal depletion hypothesis [282-283], suggests that women in low-income settings progressively become malnourished due to repeated reproductive cycles, a poor diet and high energy costs. Winkvist et al. (1992)[283] described four possible patterns of weight change related to reproduction in low-income settings:

i. *Non-depleted women* who maintain an adequate energy balance through the reproductive cycle.

ii. *Repleted women* who experience weight loss during pregnancy/lactation but have sufficient birth spacing so that they are able to recover their pre-pregnancy weight prior to the next conception.

iii. *Incompletely-repleted women* who only regain part of the weight lost during pregnancy/lactation due to shorter birth intervals and lose weight over the long-term during the reproductive period.

iv. *Non-repletable women* who experience chronic under-nutrition as part of a broader pattern of malnutrition than that related to reproduction.

Nonetheless, the epidemiological evidence to support this hypothesis is quite weak. Indeed, cross-sectional studies from low and middle-income settings have suggested that increasing parity is associated with an increase in BMI [284-285], after adjustment for confounding factors; although the importance of parity as a risk factor for overweight is greater in middle income countries than amongst the least economically developed populations [286]. An analysis based on DHS data from 28 low and middle income countries found that within the least developed countries (as measured by the UN human development index) higher parity women were less likely to be overweight, but within countries in the highest tertile of national development, parity was positively associated with overweight amongst women in the richest two wealth quintiles [286].

A detailed analysis of food intake, anthropometry and breast milk composition amongst pregnant and lactating women in the Gambia has shown that the extent of nutritional stress during pregnancy and lactation was highly dependent on season, but that women showed a striking degree of adaptation to their local environment through seasonal subcutaneous fat deposits [287]. Maternal depletion has been reported in very poor nomadic populations in

Kenya; a large (n=912) cross-sectional study of dietary intake and nutritional status found that women in nomadic and remote communities had chronic energy deficiency, compared to residents in larger towns [288]. However, as countries develop economically and severe nutritional stress becomes less of an issue the maternal depletion hypothesis becomes less relevant for the majority of women.

In summary, quality longitudinal research relating to weight trajectories amongst adult women living in low-income countries is very limited. Sub-Saharan women are probably unlikely to gain weight throughout their life course to the extent typically observed in North American and European populations given the differences in nutrition, work and activity levels and fertility, but there is no evidence base upon which to generalise beyond this. Therefore, in the next section I will investigate cohort and period changes in median body weight and BMI in the three African countries where four consecutive surveys are available.

5.3 Period & Cohort Weight Change in Ghana, Kenya and Zambia

Whilst the DHS are cross-sectional in design, each is a nationally representative sample of women. It is therefore useful to examine how the anthropometric profile of the average woman has changed over time in countries where more than one survey has been conducted. There are three countries in my study where maternal anthropometric data has been collected in four successive surveys: Ghana (1993, 1998, 2003 & 2008), Kenya (1993, 1998, 2003 & 2008) and Zambia (1992, 1996, 2001 & 2007).

Anthropometric data are currently collected for all women aged 15-49 years. However, for economic and logistical reasons, DHS conducted during the 1990s only collected height and weight data for the mothers of children born since the January five years preceding fieldwork (with the exception of Ghana, 1993 where only mothers of children born in the previous three years were measured). In order to investigate period and cohort weight change, the same restriction has been applied to the more recent surveys (in this section only) to make the results comparable. It should be remembered that women in the very youngest and oldest age groups will be under-represented in the graphs presented in this section, since they are less likely to have had a recent birth. As with all analyses in this thesis, women who were currently pregnant or less than three months postpartum at the time of data collection were excluded.

5.3.1 Period Effects

Period effects are a demographic concept comparing populations in particular years, comparable to a cross-sectional design. Figure 5-A, Figure 5-B and Figure 5-Cshow the period effects of weight and BMI change for each country. Each graph may be thought of as a synthetic cohort of women, in other words the weight trajectory of a typical woman in the population if she experienced the age-specific median body mass throughout her reproductive life course, in the same way as one would do when calculating the total fertility rate from age-specific fertility rates in a given period. The graphs provide the weight trajectory that the average woman would experience if there were not underlying changes in the nutritional state of the population during her reproductive life.

This assumption appears to be reasonable enough in the cases of Kenya and Zambia, where the shapes of the graphs are close and overlapping between each successive survey. Median body weight rises slowly but steadily by about 3-4kg in total between age of 15-19 years and the 40-44 years age group, before falling slightly amongst the oldest women.

However, for Ghana a substantial increase in the median weight and BMI of the population can be seen in both the 2003 and 2008 survey. Median body weight in the 30-34 years age group was around 54kg during the 1990s; however this rose to 57.1kg in 2003 and peaked at 59.7kg in 2008. There is possibly an indication that such a pattern may occur in Kenya in the near future, as median weight does appear to have increased in the 2008 survey relative to earlier periods, but without further data it is impossible to do more than speculate on this.

Figure 5-A Period changes in body weight and BMI in Ghana, 1993-2008

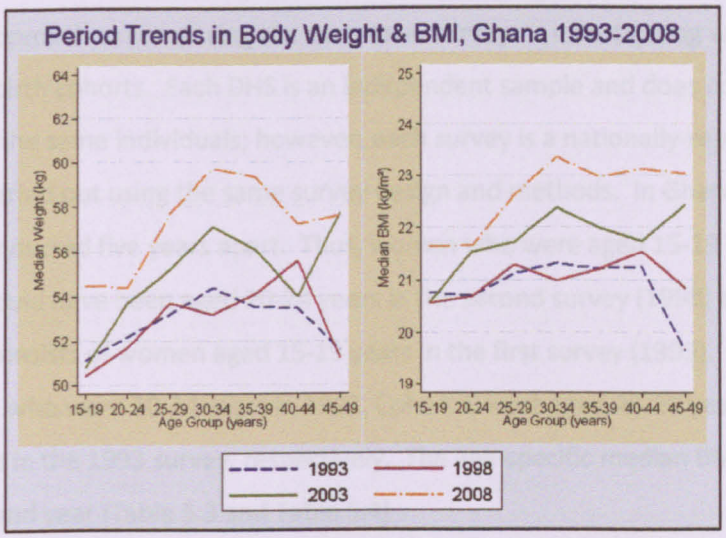


Figure 5-B Period trends in body weight and BMI in Kenya, 1993-2008

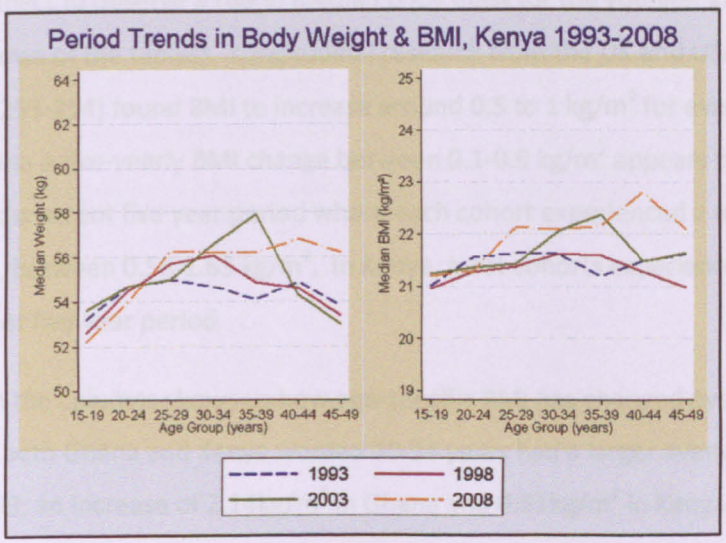
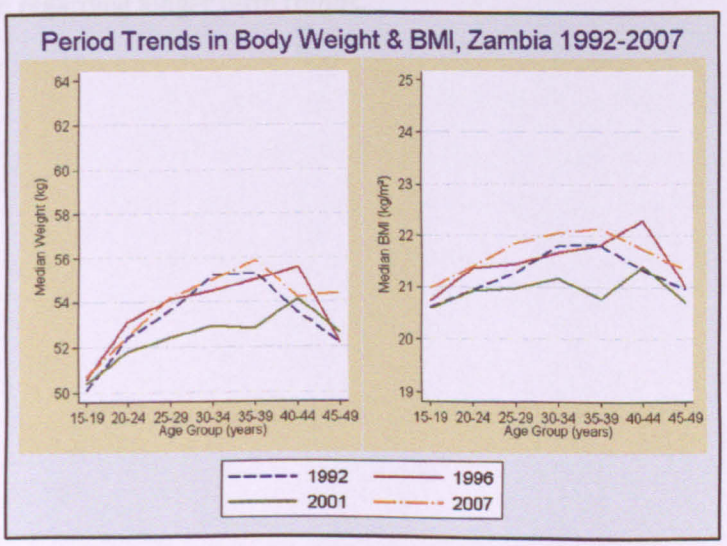


Figure 5-C Period trends in body weight and BMI in Zambia, 1992-2007



5.3.2 Birth Cohort Effects

An alternative approach to comparing the successive surveys is investigating weight change amongst actual birth cohorts. Each DHS is an independent sample and does not contain repeat observations on the same individuals; however, each survey is a nationally-representative sample and is carried out using the same survey design and methods. In Ghana and Kenya the surveys were conducted five years apart. Thus, women who were aged 15-19 years in the first survey (1993) would have been aged 20-24 years in the second survey (1998) and so forth. Here, Cohort A consists of women aged 15-19 years in the first survey (1993). Cohort B contains women who were 20-24 years in 1993, Cohort C were aged 25-29 years and Cohort D aged 30-34 years in the 1993 survey, respectively. The age-specific median BMI was calculated for each cohort and year (Table 5.3 and Table 5.4)

Each birth cohort is only followed for a fifteen year period, not the entire reproductive lifespan and we would expect to observe a rise in median body mass for the younger groups as they age (across the rows of the tables). Longitudinal research from the UK and USA discussed previously [248, 253-254] found BMI to increase around 0.5 to 1 kg/m^2 for every five years of adult life. In Ghana a five-yearly BMI change between 0.1-0.9 kg/m^2 appears typical, with the exception the most recent five year period where each cohort experienced a much larger median increase, between 0.58-1.63 kg/m^2. In Kenya, most cohorts experience less than 0.5 kg/m^2 increase per five year period

Comparing down the columns shows us how age-specific BMI has changed over the past fifteen years. In both Ghana and Kenya women 30-34 years had a larger average BMI in 2008 compared to 1993; an increase of 2.14kg/m^2 in Ghana and 0.61kg/m^2 in Kenya. Similar increases through time were observed for the 35-39 year age group and the 40-44 year age group; although this analysis is limited by the number of data points so cannot make any robust conclusion regarding longer term trends.

Table 5.3 Age-specific median BMI (kg/m^2), by birth cohort, Ghana 1993-2008

Cohort	Year of Birth	Age Group (years)						
		15-19	20-24	25-29	30-34	35-39	40-44	45-49
A	1974-78	20.69	20.77	21.72	23.35			
B	1969-73		20.77	21.30	22.38	22.96		
C	1964-68			20.99	21.12	22.00	23.12	
D	1959-63				21.21	21.32	21.74	23.03

Women with a birth in the three years preceding data collection

Table 5.4 Age-specific median BMI (kg/m^2), by birth cohort, Kenya 1993-2008

Cohort	Year of Birth	Age Group (years)						
		15-19	20-24	25-29	30-34	35-39	40-44	45-49
A	1974-78	21.02	21.28	21.42	22.09			
B	1969-73		21.37	21.56	22.05	22.16		
C	1964-68			21.63	21.64	22.37	22.80	
D	1959-63				21.48	21.59	21.62	22.08

Women with a birth in the three years preceding data collection

5.4 Weight Change amongst a Cohort of Women from Burkina Faso

The final part of this chapter is an analysis of weight change amongst a cohort of women from Burkina Faso. This analysis had three goals:

1. To establish the extent and pattern of weight change during the five years following delivery in a cohort of African women.
2. To ascertain the proportion of women who change BMI category over this period.
3. To identify socio-demographic risk factors independently associated with a change in BMI category in this cohort, and so inform a discussion of exposure misclassification for the main thesis results.

This analysis uses longitudinal data from a prospective cohort of women from Burkina Faso; the methods of which are described in detail elsewhere [8-9].

5.4.1 Methods

Women were recruited to the study after giving birth in seven public hospitals in Burkina Faso between December 2004 and March 2005. All women who presented with severe ("near-miss") obstetric complications, defined as those in which women face a high risk of death in the absence of adequate emergency care, and who lived within 30km of the hospital were approached for recruitment. In addition, two unmatched controls, each of whom had an uncomplicated delivery resulting in a live birth, were recruited from the same hospitals.

In the initial study, interviews took place at baseline (three days after each woman returned home from hospital post-delivery) and at three, six and twelve months after the index delivery. The women were interviewed again between September 2008 and November 2008. A final follow-up interview took place between October 2009 and January 2010. Data was collected on topics relating to socio-demographic characteristics and reproductive history using structured questionnaires, similar to those used in the DHS. An assets-based wealth index was constructed using principal components analysis.

Body weight was measured by the interviewer at four points during the study; six months postpartum (denoted Round A throughout the rest of this chapter) twelve months postpartum

(Round B), and each of the subsequent follow-ups (Round C and Round D, respectively.) Height was measured at the six month postpartum medical (Round A).

In order to determine plausible anthropometric values the distribution of height and weight values was assessed through tabulations and scatter plots. Height values less than 1.30m or greater than 1.80m were tabulated and examined. Three data points were deemed implausible (all of which were <1.10m). Body mass index (BMI) scores were calculated as weight (in kilograms) divided by height (in metres) squared. The plausibility of the weight measurement was done through the examination of BMI, as what may be a low but still biologically plausible weight for a short woman may be below the threshold viable for life for a taller woman. Weights at BMI values lower than 15.5 kg/m^2 or greater than 50 kg/m^2 were considered individually.

A total of thirteen weight values were deemed implausible at Round A, five values at the Round B, two values at Round C and four values at Round D. The range of BMI values in the final dataset spanned a minimum of 14.3kg/m^2 to a maximum of 62.4kg/m^2. Weight and BMI values were excluded if a woman was currently pregnant or had given birth in the three months preceding any given data collection point. This was the case for twenty women at Round A, forty women at Round B, eight-two women at Round C and sixty-six women at Round D.

To describe the weight trajectory of women during the postpartum period (Objective 1) a box plot describing BMI distribution in the sample at each time point was drawn. The paired t-test was used to consider mean change between adjacent time points. To accomplish Objective 2, the proportion of women who moved BMI category between Round A and Round D was tabulated.

The socio-demographic risk factors independently associated with a change in BMI category were identified using logistic regression (Objective 3). Variables considered were respondent's age at the index birth (5-year age groups), outcome of the index birth (severe complications with abortion or perinatal death; severe complications with live birth; no severe complications) relative wealth quintile, parity at the index birth (parity 1-2, parity 3-5, parity 6+), whether the respondent had had given birth since the index (yes, no), marital status (not married, currently married, currently cohabiting), education level (no education, educated at a Koranic school or other, primary education or secondary /higher education), whether the respondent had been able to earn an income in the year preceding the final follow-up interview (yes, no), and baseline BMI category as measured at the six months postpartum medical exam (underweight, optimal weight, overweight). Relative wealth was constructed by a score derived from PCA,

based on ownership/access to a list of assets (such as electricity supply, radio, a television, a bicycle, motorbike, car, phone and water source and toilet facilities).

5.4.2 Results

The original study recruited 1025 women. Table 5.5indicates how many women were had valid and plausible anthropometric data at each of the four survey rounds where anthropometric data was collected. Anthropometric data was first collected six months post-delivery; this has been designated Time 0.

Some women were not interviewer at one survey round but were subsequently found and interviewed at a later date. For the logistic regression analysis which investigated risk factors for moving BMI category during the study period only women with a valid BMI value at Round A and Round D were included (n=543).

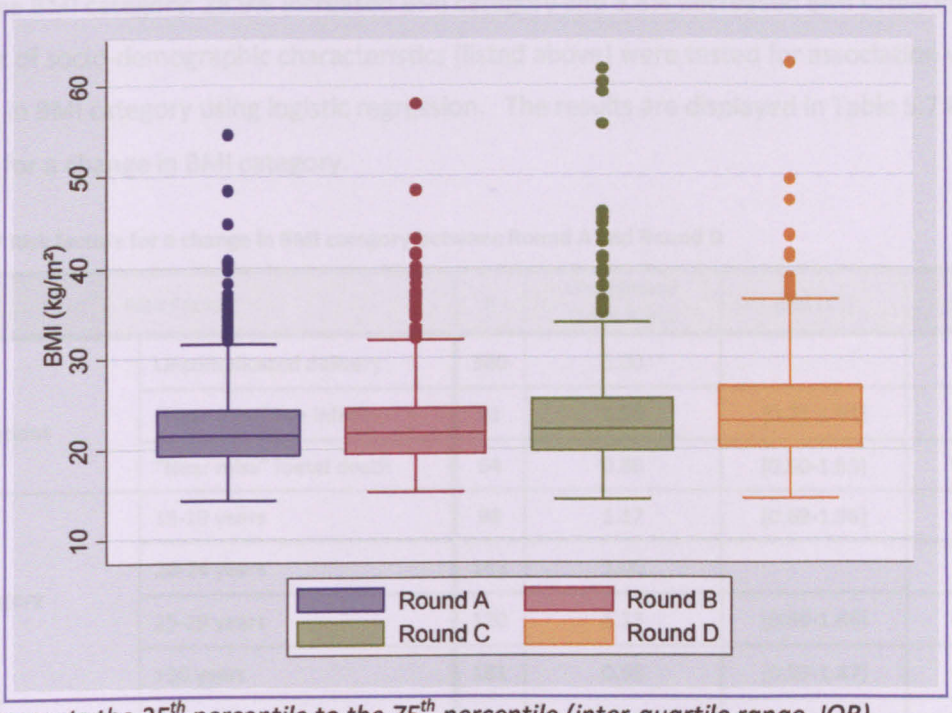
Table 5.5 Sample description

	Round A Time 0	Round B + 6m	Round C +~3.25 years	Round D + ~4.25 years
Number of women interviewed	857	804	763	708
Number of women with a valid BMI value	808	695	602	568
Mean BMI in kg/m^2 [95% CI]	22.5 [22.2-22.8]	22.8 [22.4-23.1]*	23.6 [23.1-24.1]#	24.1 [23.7-24.6]~
Proportion Overweight (%)	21.2%	22.4%	29.6%	37.2%

** Significantly different to mean BMI at Round A (p= 0.0004)*
\# Significantly different to mean BMI at Round B (p<0.0001)
~ Significantly different to mean BMI at Round C (p=0.0035)

Table 5.5 shows that there was a statistically significant rise in average BMI over the period of the study. A box plot of BMI distribution at each survey round was plotted (Figure 5-D). Although there is considerable overlap, the increase in BMI can be observed.

Figure 5-D BMI distribution at each successive survey round



*Box represents the 25th percentile to the 75th percentile (inter-quartile range, IQR). Dots represent outside values (values <= 1.5*IQR above the 75th percentile).*

The original study was designed to look at the health of women after severe obstetric complications. As two of the outcomes of my thesis (caesarean delivery and neonatal death) are also related to obstetric complications I also examined change in BMI according to "near miss" status. The results are displayed in Table 5.6. Women who had severe complications at delivery (which occurred six months prior to Round A) gained a significant of weight between Round A and Round B (p=0.0004); whilst women with an uncomplicated delivery did not (p=0.0853). Subsequent to Round B it was women with an uncomplicated delivery who gained more weight.

Table 5.6 Mean BMI at successive survey rounds, stratified by "near miss" status

	Women with an Uncomplicated Delivery	Women with Severe Obstetric Complications
Mean BMI at Round A (kg/m^2)	22.8 (22.4-23.3)	22.1 (21.5-22.8)
Mean BMI at Round B (kg/m^2)	22.9 (22.4-23.3)	22.8 (22.0-23.5)
Mean BMI at Round C (kg/m^2)	23.7 (23.2-24.3)	23.3 (22.3-24.4)
Mean BMI at Round D (kg/m^2)	24.5 (23.9-25.1)	23.3 (22.5-24.1)

Of those women with a valid BMI value at Round A and Round D (n=543) 62.3% remained in the same BMI category; 28.9% increased BMI category and 8.8% decreased BMI category. A number of socio-demographic characteristics (listed above) were tested for association with a change in BMI category using logistic regression. The results are displayed in Table 5.7 Risk factors for a change in BMI category.

Table 5.7 Risk factors for a change in BMI category between Round A and Round D

Risk Factor		*n*	Unadjusted Odds Ratio	[95% CI]	p-value
Delivery Complications	Uncomplicated delivery	380	1.00		
	"Near miss" live infant	91	1.20	[0.75-1.91]	0.439
	"Near miss" foetal death	64	0.88	[0.50-1.53]	0.646
Age Category	15-19 years	98	1.17	[0.69-1.98]	0.557
	20-24 years	143	1.00		
	25-29 years	120	1.13	[0.69-1.86]	0.626
	>30 years	181	0.93	[0.59-1.47]	0.751
Wealth Quintile	Poorest	103	1.00		
	Poorer	110	0.80	[0.45-1.41]	0.436
	Middle	109	1.20	[0.69-2.09]	0.513
	Richer	99	1.06	[0.60-1.88]	0.827
	Richest	108	1.18	[0.68-2.05]	0.567
Parity at Round A	Nulliparous	13	1.26	[0.41-3.86]	0.682
	1-2 live births	277	1.00		
	3-5 live births	172	0.83	[0.56-1.23]	0.354
	6+ live births	80	0.67	[0.39-1.14]	0.138
Marital Status	Not married	45	1.26	[0.68-2.36]	0.464
	Currently married	393	1.00		
	Currently cohabiting	96	1.18	[0.75-1.87]	0.470
Education Level	No education	217	1.00		
	Koranic or other	50	1.46	[0.77-2.75]	0.242
	Primary education	126	1.49	[0.94-2.35]	0.087
	Secondary or higher	141	1.76	[1.14-2.74]	0.011
Earned an Income (Round A)	No	174	1.00		
	Yes	358	1.09	[0.75-1.59]	0.645
Baseline BMI Category *(6m postpartum)*	Underweight *(<18.5kg/m^2)*	76	1.62	[0.98-2.67]	0.060
	Optimal *(18.5-24.9kg/m^2)*	347	1.00		
	Overweight *(≥ 25 kg/m^2)*	120	1.07	[0.70-1.66]	0.729

Education was the only variable where a significant association was observed at the 5% level. Increasing education increased the odds of a woman moving BMI category, compared to women with no education as the baseline. Whilst the association did not reach significance at the 5% level for those women with primary only education (OR: 1.49; 95% CI: 0.94-2.35), for those women with secondary education or higher the odds of moving BMI category were increased by 76% (OR: 1.76; 95% CI: 1.14-2.74).

Women who were underweight at Round A also showed a borderline association (OR: 1.62; 95% CI: 0.98-2.76). This finding is unsurprising since these women were already in the lowest BMI category available and regression to the mean may partially explain this result.

No other variables were identified as statistically significant risk factors for changing BMI category during the median 4.25 year period between Round A and Round D. Post-hoc sample size calculations showed that the sample size was too small to provide sufficient statistical power.

5.5 Implications for Exposure Misclassification in this Thesis

The findings of this section suggest that women do indeed gradually and progressively gain weight throughout the reproductive years. In this thesis I am only assuming BMI remained constant during the last five years, not over her entire reproductive lifespan; however it seems likely that some degree of exposure misclassification will have occurred.

Women in Kenya and Zambia appeared to gain less weight on average than their counterparts in industrialised countries. The same was true of Ghana during the 1990s; however more recently there seems to have been a dramatic and sudden shift in the population-level anthropometric profile. The median BMI of women aged 30-34 years in Ghana was 23.4 kg/m^2 in 2008, an increase of over 2 kg/m^2 from the median just fifteen years earlier, a very sizeable shift in population-level terms.

In the Burkina cohort, 38% of women moved BMI category in the median 4.25 years in which women were observed. The overall trend was for women to gain weight (i.e. increase in BMI category). It should be noted that this sample of women were recruited for different research purposes and approximately one third of women had undergone severe obstetric complications only six months prior to the Round A measurement. The study showed that these women had ongoing health complications far beyond the postpartum period [8-9, 12]

and a similar proportion of weight change might not be seen if it were possible to look at this in the general population. However, these findings are still concerning to the validity of the BMI variable. A sensitivity analysis will be conducted to assess how robust the thesis findings are to exposure misclassification.

The nutrition transition, whilst making the results of research such as this timely and useful, does present a problem for study validity in terms of exposure misclassification. As many Sub-Saharan African countries appear to be on the cusp of entering, or very early stages of, the nutrition transition it is difficult to predict which countries and population subgroups have experienced recent significant weight gain. Based on the national prevalence of overweight and obesity described in Chapter *4,* most countries in this study are yet to commence the transition, and probably have a similar anthropometric profile to Kenya or Zambia. Unfortunately, it is impossible to confirm this with the data available.

The following steps will be undertaken to minimise any concerns as to the study's overall validity:

- Women younger than twenty years at data collection will be excluded from the study, as women are likely to still be growing during the teenage years.
- Women who are either pregnant or less than three months postpartum at the time of data collection will be excluded.
- A sensitivity analysis will be conducted for each outcome investigating the effect of exposure misclassification using the Stata *-episens-* command [289-290] to calculate the effect estimate which would have been obtained for differing sensitivity and specificity scenarios. This is provided in Chapter 9.

Chapter 6

Systematic Review of the Effect of Female Overweight and Obesity on Waiting Time to Conception

As discussed in Chapter 2, there are many different ways of measuring reduced fecundity and infertility. As a consequence of this the epidemiological literature is somewhat fragmented and it is difficult to assess the effect of overweight/obesity on female fecundity.

I therefore decided to conduct a systematic review of the literature, focusing on the fecundity outcome with the strongest construct validity: time to pregnancy or conception. The results of this review are presented in this chapter.

6.1 Review Objective

As discussed in the background section of Chapter 2, there are many different ways of measuring reduced fecundity or infertility [56]. The ideal study design would be a prospective cohort that followed all couples who were attempting to achieve pregnancy and recorded outcome and length of the attempt. This would allow subtle variations in fecundity to be measured and allow couples across the entire spectrum of fecundity to be represented in the effect estimate, instead of relying on an arbitrary cut-off to defined infertility or relying on infertile couples to self-identify themselves as such.

However, in practice such studies are very difficult to conduct. Pregnancy attempts are often a private matter, and even close friends and family may not be aware of a couple's intention. There is thus no obvious recruitment source of study participants; a population-based survey would need to be very large (and consequently expensive) in order to capture a sufficient sample of couples about to commence a pregnancy attempt [54].

An alternative design used in infertility research is the case-control study. Cases are usually patients receiving treatment for infertility [291-292]; but these studies are methodologically weak due to the lack of an appropriate control population [293]. Often control women are recruited from a hospital maternity ward, but these patients are likely to have a very different background to the infertile cases, who are a self-identified group with the means and motivation to seek treatment for their infertility. A further problem with recruiting participants from an infertility clinic is that there will often be large variation (minimum of 12 months but no upper limit) in how long a couple had been attempting to become pregnant before deciding to seek treatment, which could bias the results.

My aim in this review was to quantify the association between overweight/obesity and fecundity, as no such review currently exists and the evidence base is mixed and difficult to interpret. I wanted to include studies from low-income countries but was aware that very little such literature existed, so decided to conduct the review with no geographic restrictions in place. I chose to review studies using the outcome of waiting time to pregnancy or conception (TTP) as I decided that this was the outcome with the strongest validity.

Review Objective: To systematically review the existing epidemiological literature in order to estimate the effect of increasing body size on waiting time to pregnancy/conception (TTP) amongst women who are overweight (BMI ≥25kg/m^2) compared to those of normal weight (BMI 18.5-24.9kg/m^2).

6.2 Methods

6.2.1 Search Strategy

The review protocol was developed following the guidelines outlined in the 'Cochrane Handbook for Systematic Reviews of Interventions' [294] and 'Systematic Reviews in Health Care: Meta-analysis in context' [295] and in consultation with a librarian at LSHTM.

A total of 14 bibliographic databases (see Box 6.1) were searched using thesaurus and free text terms to identify literature published up to the end of September 2009. A particular effort was made to retrieve literature published outside of Western Europe and North America in order to identify studies from low-income settings; this included searching the WHO regional databases and databases specialising in research from low-income settings such as Popline. The search strategy included terms related to body size such variations of "overweight", "obese", "body mass index" and terms related to fecundity such as "fertility", "infertility", "subfertility", "fecundity", "infecundity", "subfecundity", "pregnancy rate", "conception rate", "time to pregnancy", "time to conception" and "delayed conception" (see Appendix B for the full search strategy as entered into PubMed.)

Box 6.1: Electronic Databases Searched

CINHAL	EMBASE
Global Health	Popline
PubMed	Web of Science
Geographically-Specific Coverage:	
Africa-Wide NiPAD	IMEMR (WHO)
IMSEAR (WHO)	LEYES (WHO)
LILACS (WHO)	WPRIM (WHO)
ELDIS	id21

In addition, the reference lists of eligible publications were reviewed to locate previously unidentified studies. The "in press" sections of key journals (Human Reproduction, The International Journal of Obesity and Fertility & Sterility) were hand-searched for relevant articles which may not have yet been indexed in the bibliographic databases.

No date or language restrictions were applied to the search strategy. Publications were eligible for inclusion if they:

- Provided a quantitative estimate of fecundity for natural conceptions, as measured by waiting time to pregnancy.
- Included an effect estimate for women who were either overweight (≥25kg/m^2) or obese (≥30kg/m^2).
- Participants were not receiving treatment for infertility, for example hormonal ovulation induction. Patients attending an infertility clinic have already spent a variable period of time (minimum of one year) attempting to conceive before entering the study.
- Contained original data.

Case series and case reports were excluded because of the lack of an appropriate comparison group. The reference lists of eligible studies were hand-searched to identify further studies for inclusion; however no new sources were identified in this manner. Editorials and commentaries were excluded after their reference lists had been reviewed for further relevant studies. In some cases multiple sources reported on the same study, this is recorded in the summary tables; however the primary author of most relevant report to the review question has been used as the study identifier for the rest of this review.

6.2.2 Assessment of Study Quality

Whilst many tools have been developed to assist reviewers in assessing bias in non-randomised studies most are poorly developed and only a very small number have been validated. Indeed, a review by Deeks *et al.* (2003) of 213 potential tools and checklists identified only six that were suitable for use in a systematic review [296].

The Newcastle-Ottawa Scale (NOS) [297] was designed for use in systematic reviews of non-randomised studies. The tool uses a pre-defined checklist (see Appendix C) to score each study on three domains of study quality: selection of the study groups, comparability of the study groups and the measurement of the exposure or outcome of interest. NOS has been found to have satisfactory content validity and inter-user reliability, although construct validity has not yet been assessed [297]. It has previously been used by the Cochrane Collaboration Non-Randomised Studies Method Group [294]. NOS was selected as the most appropriate tool to assess study quality in this review, with the following specifications and modifications:

- The comparability section of the NOS specifies that the study must control a minimum of the most important confounder (pre-specified by the reviewer) and one other additional factor. On the basis of my background literature review I pre-specified participant's age.

- Two items were removed from the scale, and the scoring system adjusted accordingly, because they were not deemed applicable to this review:

    - Item 4 in the "selection" domain ("*Demonstration that outcome of interest was not present at start of study*") was removed because the outcome of interest (TTP) is survival data; I am interested in the time at which the outcome occurs. None of the women in a TTP study can be pregnant at entry by definition, so this score would not differentiate between the studies in terms of study quality.

    - Item 2 in the "outcome" domain ("*Was follow-up long enough for outcomes to occur?*") was removed for the same reason. Again, this item was not expected to be of any use in differentiating between the studies as it is meaningless in the survival data context.

Thus, a maximum of three stars may be allocated to the selection of the study groups, two for comparability between the groups, and two stars for the ascertainment of the outcome (see *Appendix 2* for further details).

6.2.3 Statistical Methods

Due to the increased methodological diversity likely to be present in a group of non-randomised studies (cf. a randomised controlled trial) combining the results into a single estimate of effect is far less straightforward, and some authors would argue gives misleading results [298]. Residual confounding and selection biases are likely to be a concern in non-randomised controlled trials and may be very hard to quantify [299]. A particular problem lies in studies based on routine data which may nevertheless have a large sample size and misleadingly small confidence intervals; the inclusion of such studies can obscure the results of a smaller but better quality study in the meta-analysis [294].

Decisions regarding the statistical combination of studies should be taken on the basis of the assessment of study quality and heterogeneity but without reference to the reported effect sizes [294]. In this review, the final selection of studies were too heterogeneous to combine in

one formal meta-analysis; whilst the outcome (TTP) was the same across all studies (as per the inclusion criteria), there was notable inconsistency in the effect measure reported. Some studies analysed TTP using a discrete-time model, others treated time as a continuous variable and two studies reported a dichotomous variable based on TTP with a cut-off of 12 months. As the outcome of interest is survival data, rather than a binary outcome, it is not straightforward to re-calculate the effect estimate.

The results of this review have been grouped by reported effect measure for ease of evidence synthesis.

6.3 Results

The initial search strategy identified 11 047 articles, of which 4104 were duplicates. A total of 6848 articles were excluded on the basis of their title and/or abstract and 95 were put to a full-text review (Figure 6-A).

Unfortunately, it proved impossible to retrieve the full-text of five sources identified as potentially relevant, all of which were missing an abstract. In four cases [300-303] there were no UK holdings of the source despite extensive attempts to trace the papers, including through the British Library. In the other remaining case [304] the citation from the bibliographic databases identified in the search was incorrect and I was unable to work out the correct citation either by using internet search engines and attempting to trace the author. In total, nine independent studies were identified after exclusion of further duplicates and of studies with insufficient data.

6.3.1 Characteristics of Included Studies

A total of nine studies are included in this review [305-313]. A summary of the characteristics of each study is displayed in Table 6.1. All of the studies identified were investigating overweight or obesity as a main exposure on the effect of TTP.

Figure 6-A Flow diagram of review search strategy

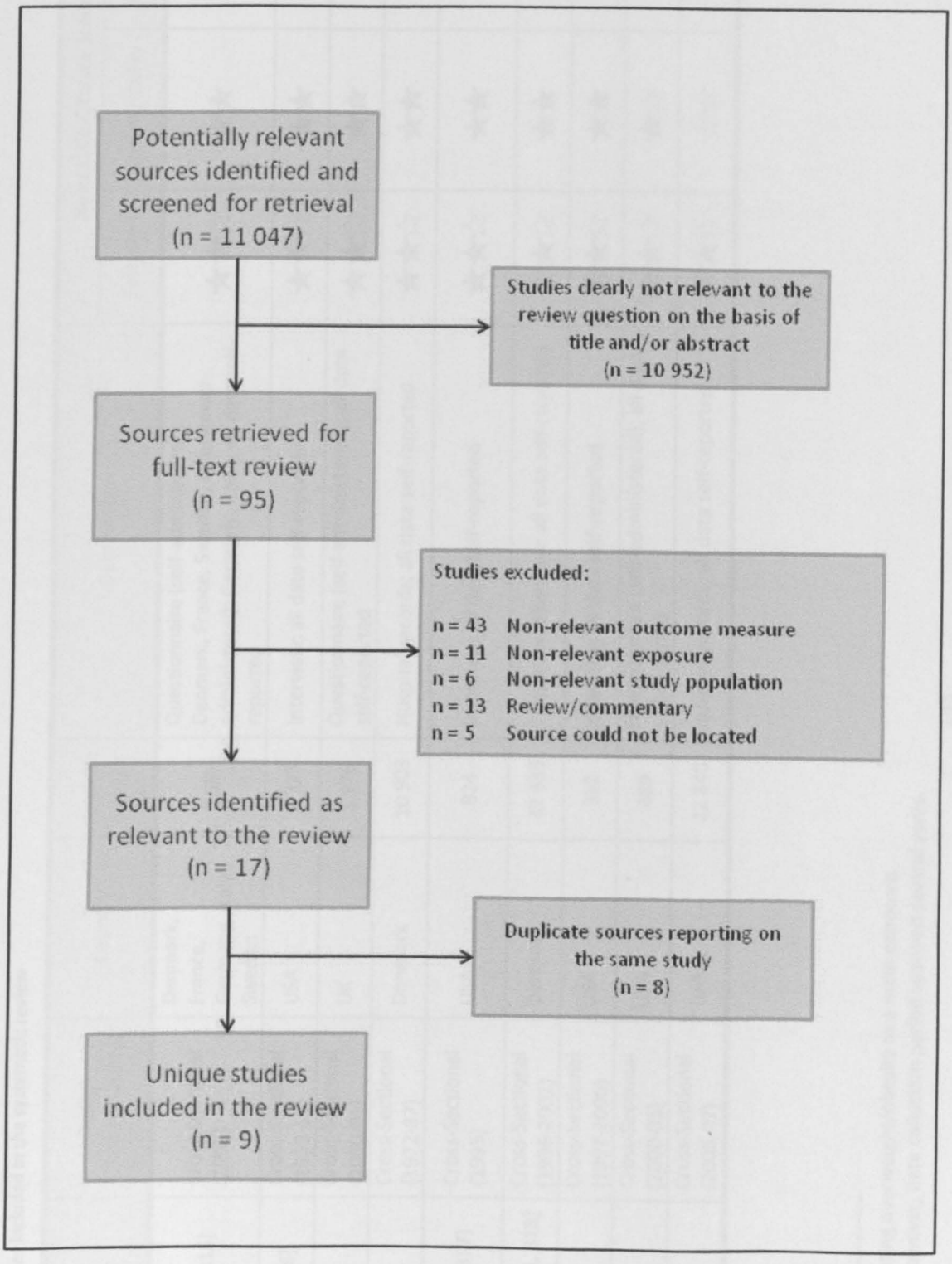


Table 6.1 Description of studies included in the systematic review

Primary Author (Publication Year)	Design (Dates of Study)	Country	Analytic Sample	Data Source	Newcastle-Ottawa Score		
					Selection	Comparability	Outcome
Bolumar (2000)[307, 314-315]	Cross-Sectional (1992)	Denmark, France, Germany, Italy, Sweden	2 587	Questionnaire (self-administered: Denmark, France, Sweden; interviewer-administered: Germany, Italy); all data self-reported	★★☆	★★	★☆
Gesink Law (2007)[305, 316]	Cross-Sectional (1959-65)	USA	7 327	Interview; all data self-reported	★★☆	★★	☆☆
Hassan (2004)[309]	Cross-Sectional (2000-01)	UK	1 976	Questionnaire (self-administered); all data self-reported	★★☆	★★	☆☆
Jensen (1999)[306]	Cross-Sectional (1972-87)	Denmark	10 903	Hospital records; all data self-reported	★★☆	★★	★☆
Kelly-Weeder (2006)[310, 317]	Cross-Sectional (1995)	USA	824	Interview; all data self-reported	★★☆	★★	☆☆
Ramlau-Hansen (2007)[311, 318]	Cross-Sectional (1996-2002)	Denmark	47 835	Telephone interview; all data self-reported	★★☆	★★	☆☆
Richman (2008)[308]	Cross-Sectional (1997-2000)	USA	362	Interview; all data self-reported	★★☆	★★	☆☆
Wellons (2008)[312]	Cross-Sectional (2000-01)	USA	489	Questionnaire (self-administered); all data self-reported	★★☆	★☆	☆☆
Yilmaz (2009)[313]	Cross-Sectional (2006-07)	Turkey	22 840	Hospital records; all data self-reported	★★☆	☆☆	★☆

‡ All studies were investigating overweight/obesity as a main exposure.

Cross-sectional design; however, data collection period spanned several years.

In spite of the effort to retrieve developing-country research in the original search strategy, all relevant studies identified were based in Europe (Denmark, France, Germany, Italy, Sweden, Turkey and the UK) or in the USA. There were no restrictions placed on dates in the initial search strategy.

All nine studies identified used a cross-sectional design, and asked collected retrospective data on TTP for the current or previous pregnancy. In most cases participants were recruited during gestation and asked questions relating to the conception of their current pregnancy; however in two cases [310, 312] participants were interviewed as part of a population-based survey, although only parous women were included in the reported analysis. As the studies were retrospective in design, the effect estimate reported is conditioned on pregnancy, i.e. none of the participants were totally infertile. The implications of this are discussed below.

The findings of this review have been organised according to reported effect measure: (i) studies that provide an estimate of fecundability, i.e. a monthly probability of conception [305-308] (ii) studies that presented a dichotomous variable using a cut-off of 12 months waiting time to conception [309-312] (iii) one remaining study that provide descriptive results only [313].

6.3.2 Evidence Synthesis

i. Fecundability (monthly probability of conception)

Fecundability is defined as the average probability of a couple achieving a clinically recognisable pregnancy in a menstrual cycle [77]; if retrospective data are used (as in all studies included in this review) then the effect estimate produced is conditional on pregnancy, i.e. underlying fecundity [54].

The results in this section are presented in Table 6.2. It is possible to model survival data treating time as either a continuous variable or discrete intervals [319-320]. The discrete-time model is theoretically more appropriate in the case of TTP, since biologically women have one window of opportunity per menstrual cycle in which conception can occur: thus TTP should ideally be measured by menstrual cycles elapsed. However the continuous-time approach has been used by some authors, since it arguably gives a more intuitively understandable measure of effect (a hazard ratio) [54].

The two studies using a discrete-time model both show a significant association between a longer TTP and the female partner being overweight [305-306]. Gesink Law (2007) provides an effect estimate for both pre-obese and obese women suggestive of a pattern of declining fecundability as body mass increases, although the result for the pre-obese women is of borderline statistical significance [305]. A fecundability odds ratio of 0.82, as reported by Gesink Law (2007), should be interpreted as showing that the odds of conception in any given menstrual cycle (given that conception has not already occurred) are 18% lower amongst obese women compared to those of optimal weight.

The results for the continuous models are less conclusive: neither study produced statistically significant results, with the exception of the obese smokers in the Bolumar (2000) study which showed a drop in fecundability [307-308]. Bolumar (2000) controlled for a total of fourteen different confounders in addition to the primary exposure (BMI) and also stratifying on smoking status; the reported estimates may well be over-adjusted as some of these confounders (for example cystic ovaries and endometriosis) are likely to lie on the causal pathway between overweight and subfecundity.

It should be noted that Richman(2008) [308] has used a different reference category to the other studies in this review of underweight women (<18.5kg/m^2), as opposed to those of normal weight (18.5-24.9kg/m^2).

ii. Dichotomous Outcome

The studies in this section are detailed in Table 6.3 and Table 6.4. Four studies reported a dichotomous variable with a cut-off value of 12 months. One of the studies presented a relative risk, Hassan(2004) [309], and three of the studies presented an odds ratio [310-312]. Although the label applied to this variable differed across the studies, in all cases it was defined as where a woman had reported it taking 12 months or longer to conceive, and for the rest of this report I shall refer to this as subfecundity.

Hassan(2004) [309] found that women with a BMI between 25-39kg/m^2 had more than twice the risk of subfecundity compared to women of normal weight (RR: 2.2; 95%CI: 1.6,3.2), and women who were morbidly obese (a BMI >39kg/m^2) were nearly seven times more likely to be subfecund (RR: 6.9; 95%CI: 2.9,16.8).

Ramlau-Hansen(2007) [311] also found that women who were pre-obese were significantly more likely to be subfecund than women of normal weight (OR: 1.27; 95%CI: 1.18,1.36) and that the effect was stronger amongst obese women (OR: 1.78; 95%CI: 1.63,1.95).

The remaining two studies in this category both made the comparison between women who were obese and women who were not obese, using a BMI of 30 kg/m^2 as the cut-off. This is likely to account for the weakened effect estimate observed, Kelly-Weeder (2006) [310] found that obese women still had a significantly increased odds of subfecundity (OR: 1.69; 95%CI: 1.07,2.67) whilst Wellons (2008) [312] found obese women to have increased odds of subfecundity but for this effect to be statistically insignificant at the 95% level (OR: 1.13; 95%CI: 0.75,1.71).

A further important difference with the Kelly-Weeder (2006) and Wellons (2008) studies is that data was obtained from a probability sample of women from the general population, who were asked if they had ever had unprotected intercourse for 12 months without becoming pregnant, in contrast to all the other studies in this review where the participants were pregnant women responding to questions regarding their current pregnancy. The Kelly-Weeder (2006) sample was also restricted to married and cohabiting women only, missing any single women who were attempting pregnancy.

iii. Descriptive Results

One further study was identified that fulfilled the review criteria but did not calculate and effect estimate (Table 6.5). Yilmaz (2009) [313] calculated the mean TTP for each BMI category and found a significant trend ($p < 0.001$) for women to take longer to conceive with increasing BMI. The mean TTP in women of normal weight was 12.5 months (± 4.6), amongst overweight women it was 17.4 months (± 5.7) and amongst obese women it was 21.3 months (± 6.1). However, this study did not adjust the results for any confounding factors.

Table 6.2 Studies presenting a fecundability estimate

Primary Author	Description of Analytic Sample	Statistical Method	Reference Group	Fecundability Estimate (95% CI)		Variables Adjusted for in Analysis
				Pre-Obese	Obese	
Gesink Law (2007)	Pregnant women (median 16wks gestation) who reported to have planned their pregnancy.	Cox proportional hazards model modified for discrete-time data.	Optimal weight (18.5-24.9 kg/m^2)	0.92 (0.84, 1.01)	0.82 (0.72, 0.95)	Age, smoking, race, education, occupation, study centre
Jensen (1999)	Pregnant women (approx 20wks gestation) who had planned their pregnancy. Women were excluded if they had existing cardiovascular or kidney problems, tuberculosis, rheumatic fever or diabetes prior to pregnancy, if they did not live in the municipality of Odense.	Cox proportional hazards model modified for discrete-time data.	Optimal weight (18.5-24.9 kg/m^2)	0.77 (0.70, 0.84)		Age, parity, previous abortion, marital status, occupation, smoking, use of oral contraceptive as most recent method, data recorder, cycle number, cycle regularity, duration of menstrual cycles
Bolumar (2000)	Pregnant women recruited post-20 wks gestation or at delivery, who reported to have planned their pregnancy.	Cox proportional hazards model	Optimal weight (18.5-24.9 kg/m^2)	Non-smokers 1.11 (0.92, 1.34) Smokers 1.14 (0.85, 1.53)	Non-smokers 1.07 (0.73, 1.58) Smokers 0.52 (0.33, 0.83)	Age, daily cigarettes (in smoking stratum), alcohol consumption, caffeine intake, menstrual cycle length, cycle regularity, ever-use of oral contraceptives, frequency of intercourse, previous miscarriages, paid employment, cystic ovary, endometriosis, appendectomy, country
Richman (2008)	Pregnant women (prior to 24wks gestation) with a previous pregnancy.	Cox proportional hazards model	Underweight (<18.5 kg/m^2)	0.63 (p-value: 0.60)	0.39 (p-value: 0.43)	Age, smoking, exercise frequency

Table 6.3 Studies presenting a relative risk

Primary Author	Description of Analytic Sample	Statistical Method	Reference Group	Relative Risk (95% CI)	Variables Adjusted for in Analysis
Hassan (2004)	Pregnant women attending antenatal appointments.	Relative risk of a time to pregnancy > 12 months	Optimal weight (19-24.9 kg/m^2)	BMI 25-39 kg/m^2: 2.2 (1.6, 3.2) BMI >39kg/m^2: 6.9 (2.9, 16.8)	Women's age, smoking, alcohol consumption, tea/coffee intake, drug abuse, parity, contraceptive use, menstrual regularity, men's age, smoking alcohol consumption, drug abuse, coital frequency and living standard

Table 6.4 Studies presenting an odds ratio

Primary Author	Description of Analytic Sample	Statistical Method	Reference Group	Odds Ratio (95% CI)		Variables Adjusted for in Analysis
				Pre-Obese	Obese	
Kelly-Weeder (2006)	National probability sample of women aged 15-45 years	Odds ratio for subfecundity (12 months unprotected intercourse with no pregnancy)	Non-obese women (<30 kg/m2)		1.69 (1.07 - 2.67)	Age, education, race, smoking status, number of ectopic pregnancies, condom use, history of chronic illness, PAP smear in last 12 months, family income, self-reported health status
Ramlau-Hansen (2007)	Pregnant women (approx 16 wks gestation) who had planned or partly planned their pregnancy	Odds ratio for subfecundity (time to pregnancy > 12 months)	Optimal weight (18.5-24.9 kg/m^2)	1.27 (1.18, 1.36)	1.78 (1.63, 1.95)	Women's age, men's age, previous pregnancies, socioeconomic group, women's smoking, men's smoking
Wellons (2008)	Women aged 34-44yrs who were participants in the CARDIA study (a prospective cohort study of risk factors for heart disease).	Odds ratio for subfecundity (unprotected intercourse for >12 months without conception)	Non-obese women (<30 kg/m2)		1.13 (0.75, 1.71)	Women's age, race, use of hormonal contraception

Table 6.5 Studies presenting descriptive results only

Primary Author	Description of Analytic Sample	Statistical Method	Mean Time to Pregnancy in months (Standard Deviation)		
			Optimal	Pre-Obese	Obese
Yilmaz (2009)	Women who delivered live infants during the study timeframe. Women with multiple births, prior endocrine or gynaecological disorders were excluded.	Differences between BMI groups were analysed using the one-way posthoc ANOVA Tukey test	12.5m (± 4.6)	17.4m (± 5.7)*	21.3m (± 6.1)* #

** Significantly different to normal weight women ($p < 0.001$)*
 # Significantly different to pre-obese women ($p < 0.001$)

6.4 Discussion & Conclusions

All the studies included in this review found either a negative association between fecundity and overweight, or did not find a statistically significant result. Unfortunately, due to the inconsistency in the measures of effect reported in the various studies, it was not possible to conduct a formal meta-analysis to calculate a single effect estimate or to test its significance.

All of the analytical studies adjusted for the woman's age and a minimum of two other potential confounders, all except one, Wellons (2008) [312], adjusted for smoking behaviour which is known associated with reproductive problems .

The most important limitation of the studies retrieved in this review is the use of retrospective TTP data; the unit of analysis was pregnancy, rather than an attempt at pregnancy. Women who are either sterile a result of severe obesity or those couples who take a long time to conceive are either completely excluded or under-represented from the study populations; this may have had the consequence of weakening the reported effect measures [54]. One advantage of carrying out an analysis using DHS data are that the sample is representative of all women of reproductive age (15-49 years) regardless of underlying fecundity or reproductive history. Furthermore, the review identified no studies with a focus on low-income settings, which is an important gap in the literature. A fecundity analysis using DHS data forms the next part of my thesis, reported in Chapter 7.

All studies included in this review used self-reported height and weight to calculate BMI, as well as using self-reported TTP. The outcome, TTP, was also based on recall. However, recall

has found to be very accurate in retrospective TTP studies conducted in high-income countries [321]. It has been shown that women tend to understate their body weight and overstate their height [322]; this would have the effect of under-estimating BMI. In the studies included in this review, women are being asked to recall their weight from prior to pregnancy which, depending on the study, may have been anything from between few months previously to several years ago [305, 312]. Therefore it is likely that misclassification of the primary exposure variable caused some degree of bias to the studies in this review. A further advantage of using the DHS is that the height and weight of women are measured during the interview.

Publication bias is a significant problem in systematic reviews. Unfortunately, in this particular review the reported effect measures were inconsistent and the number of included studies small; this makes it difficult to assess publication bias using funnel plots, as is standard procedure [295].

6.5 Summary

- Women who are overweight appear likely to have lower fecundity that those of normal weight, however studies of sufficient homogeneity and quality were not identified in this review to allow this association to be quantified and statistically tested.
- Where sufficiently detailed data was reported, a dose-response relationship was suggested.
- All studies retrieved in this review used a retrospective TTP design, which produces results conditioned on pregnancy. This is a substantial limitation because completely infertile couples cannot be recruited into the sample.
- No studies from low-income countries were identified.
- An analysis of reduced fecundity on a nationally-representative sample, including women across the entire spectrum of fecundity, and using data from a low-income setting will fill an important gap in the current evidence base.

Chapter 7

BMI and Reduced Fecundity in Sub-Saharan Africa

The systematic review presented in Chapter 6 revealed two important gaps in the current literature on obesity and reduced fecundity. First of all, no research on the association between high BMI and reduced fecundity has previously been conducted in low-income settings. Secondly, all of the studies retrieved presented effect estimates that were conditioned on pregnancy, excluding women who are completely infertile.

In this chapter, I use data from the DHS to examine the effect of increased BMI on reduced fecundity. Two complementary outcomes were used. In the first part of the chapter I examine the effect of overweight and obesity on the odds of subfertility, a dichotomous outcome intended to proxy clinical infertility. Following this, I use data from the reproductive calendar module included in the most recent DHS to examine the time from date of first marriage to date of first conception, analogous to the TTP studies reviewed in the previous chapter but with the advantage of including potentially infertile women in the sample.

7.1 Subfertility in Sub-Saharan Africa

This analysis contributes to investigation on the association between increased BMI and reduced fecundity. Specifically, this analysis quantifies the effect of BMI on the odds of subfertility, defined as women who have not have a live birth for a minimum of 60 months, despite being at risk of conception during this period. The sample excluded:

- Never-married women, and those married less than five years preceding survey
- Women who have not had sexual intercourse in the five years preceding the survey
- Women who have continuously been using a contraceptive method for the five years preceding the survey
- Women who do not want any further births
- In addition to underweight women, women who were currently pregnant or less than three months pregnant and women younger than 20 years at the time of data collection, common to all analyses presented in this thesis.

A full description of the study exclusion criteria, variable definitions and statistical methods used is provided in Chapter 3.

7.1.1 Sample Description

A total of 53,853 women were included in this analysis. National contributions to the pooled dataset ranged from just 320 women in Swaziland (2006-07) to 9,445 women in Nigeria (2008) (see Table 7.1). Countries were grouped according to UN Sub-Region; the available sample in Eastern and Western Africa was substantially larger than for either Middle Africa or Southern Africa. The proportion of women deemed subfertile varied nationally between 17-62%. Approximately 4% were subfertile and nulliparous, suggesting primary infertility; the remainder of the sample had at least one live birth prior to the start of the exposure period.

National BMI distribution is described fully in Chapter 4. The prevalence of each BMI category within the sample used in this analysis is displayed in Table 7.1. As noted previously, there is considerable disparity in the proportion of overweight women by country; lowest level of overweight was observed in Ethiopia (5.5%), but in sixteen countries more than 20% of the sample were overweight and very high levels were observed in Lesotho (53%) and Swaziland (70%). The overall proportion of overweight in the pooled dataset for this analysis was 23.8%, with 6.6% being classified as obese.

Table 7.1 Distribution of subfertility and BMI in the subfertility analytic sample

Country		*n*	Proportion Subfertile (%)	Optimal	Pre-Obese	Obese
Eastern Africa	Ethiopia	1,109	23.2%	94.6%	4.6%	0.9%
	Kenya	1,175	37.4%	64.1%	26.8%	9.0%
	Madagascar	1,338	38.7%	89.3%	8.9%	1.8%
	Malawi	2,355	23.3%	83.7%	13.7%	2.6%
	Mozambique	3,669	38.6%	85.4%	11.0%	3.6%
	Rwanda	891	20.6%	87.6%	11.2%	1.3%
	Tanzania	2,719	32.7%	78.1%	16.5%	5.4%
	Uganda	550	26.0%	80.1%	14.3%	5.6%
	Zambia	1,532	23.6%	77.8%	17.2%	5.0%
	Zimbabwe	1,354	27.4%	71.4%	21.3%	7.3%
	Pooled	**16,692**	**30.8%**	**81.6%**	**14.2%**	**4.2%**
Middle Africa	Cameroon	1,553	36.0%	67.7%	22.3%	10.1%
	Congo	1,824	35.9%	61.7%	26.4%	11.9%
	DRC	1,292	30.0%	85.6%	11.9%	2.6%
	Pooled	**4,669**	**34.3%**	**70.2%**	**21.0%**	**8.7%**
Southern Africa	Lesotho	453	53.3%	47.1%	33.7%	19.2%
	Namibia	690	40.5%	56.9%	26.6%	16.6%
	Swaziland	320	62.4%	29.8%	35.1%	35.1%
	Pooled	**1,463**	**49.4%**	**47.8%**	**30.7%**	**21.4%**
Western Africa	Benin	4,953	24.4%	77.9%	15.6%	6.5%
	Burkina Faso	3,202	21.5%	87.6%	9.1%	3.3%
	Ghana	1,156	39.2%	61.8%	27.3%	10.9%
	Guinea	1,391	35.3%	79.9%	15.4%	4.7%
	Liberia	1,907	36.8%	72.3%	19.7%	8.1%
	Mali	5,043	27.5%	75.8%	16.9%	7.4%
	Niger	1,691	17.6%	81.8%	13.9%	4.3%
	Nigeria	9,445	26.0%	72.3%	20.0%	7.7%
	Senegal	1,256	33.5%	67.9%	22.6%	9.6%
	Sierra Leone	985	37.7%	70.5%	21.8%	7.6%
	Pooled	**31,029**	**27.3%**	**75.6%**	**17.5%**	**6.9%**
Pooled, all Sub-Saharan Africa		**53,853**	**29.6%**	**76.3%**	**17.2%**	**6.6%**

Sampling weights used

7.1.2 Univariable Analysis

The unadjusted results of the effect of BMI as both a continuous and categorical variable are displayed in Figure 7-A. Assuming a linear effect, the crude odds of subfertility increased by 8% for each unit increase in BMI (OR: 1.08; 95% CI: 1.07-1.09). The observed log odds of subfertility were calculated for each BMI unit (kg/m^2) and graphed against the linear predicted model with BMI entered as a continuous variable. In Figure 7-A BMI values greater than

40kg/m^2 have been combined in the final data point due to the very small number of morbidly obese women in the sample.

Figure 7-A Observed versus linear predicted unadjusted log odds of subfertility

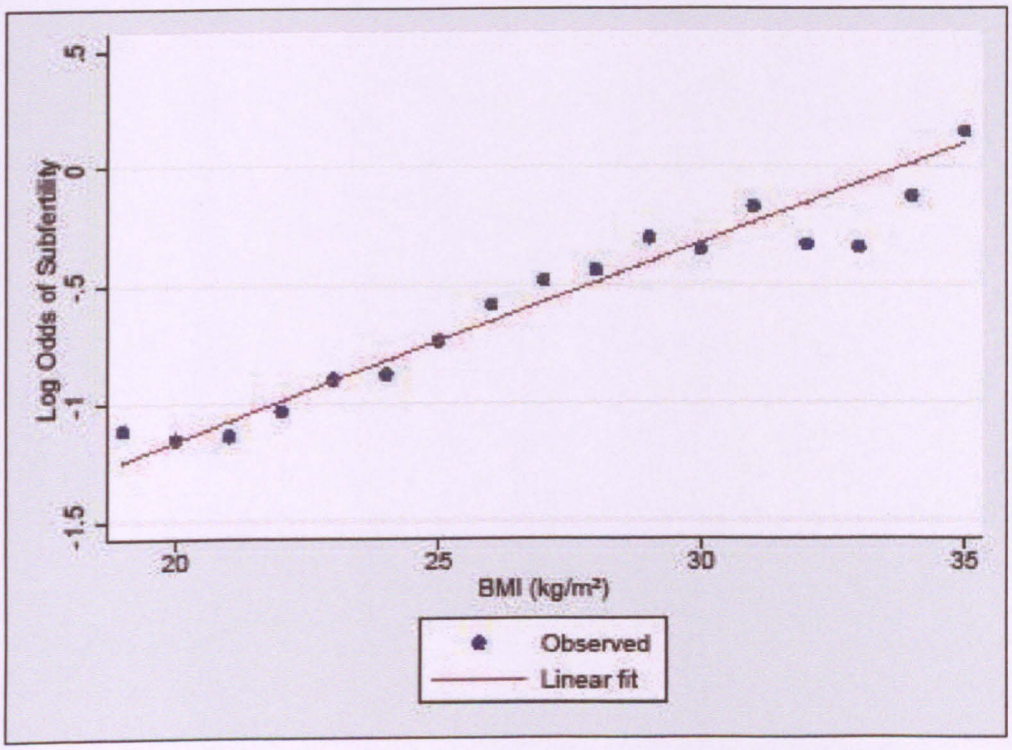


Table 7.2 provides the unadjusted association between subfertility and of each of the confounders identified in my conceptual framework. The odds of subfertility increase with age; the magnitude of the association is particularly large in the oldest age group where women aged 45-49 years have 38 times greater odds of subfertility than women aged 20-24 years (OR: 38.78; 95% CI: 32.60-46.13).

Women are more likely to be subfertile if they live in an urban area (OR: 1.55; 95% CI: 1.47-1.65). The odds of subfertility increase with increasing relative wealth. Women in the richest wealth quintile have nearly twice the odds of subfertility compared to the poorest group (OR: 1.96; 95% CI: 1.81-2.12).

The parity variable represents each respondent's parity at the start of the exposure period (i.e. 60 months prior to data collection) to prevent confounding by births which occurred whilst subfertility status was being determined. Compared to women who are nulliparous, women with 1-2 previous live births are less likely to be subfertile (OR: 0.83; 95% CI: 0.77-0.89); there is no significant difference between those women who have 3-5 previous births and the

nullipara (OR: 1.05; 95% CI: 0.98-1.12); however, women with 6+ previous births have two times the odds of subfertility (OR: 2.23; 95% CI: 2.05-2.43). This is probably reflective of the fact that women who are parous have demonstrated their fertility previously; however those women of a very high parity are at increased risk of subfertility due to confounding by age, they are also increasingly likely to have suffered severe delivery complications, which may have contributed to subfertility, on a previous occasion.

Ever-users of contraception were substantially less likely to be subfertile (OR: 0.56; 95% CI: 0.53-0.60). This finding partly represents confounding by the increased wealth and education level of many contraceptive users in Sub-Saharan Africa, but may also be partially accounted for because women who believe they are infertile are unlikely to use contraception.

Women with primary education were not similar to women with no education (OR: 0.94; 95% CI: 0.88-1.00); however women with secondary education were more likely to be subfertile (OR: 1.34; 95% CI: 1.25-1.43). Women were also more likely to be subfertile if their husband was educated beyond secondary school level compared to a baseline of no education (OR: 1.54; 95% CI: 1.39-1.70) but slightly less likely to be subfertile if he had primary education only (OR; 0.87; 95% CI: 0.82-0.93).

Women who worked outside of the home were slightly more likely to be subfertile (OR: 1.11; 95% CI: 1.05-1.16). Smokers had over two times increased odds of subfertility (OR: 2.32; 95% CI: 2.08-2.58).

Table 7.2: Unadjusted logistic regression model of the risk factors for subfertility

Risk Factor		Proportion in Category	OR	[95% CI]	p-value
BMI Category	Optimal	76.3%	1.00		
	Pre-Obese	17.2%	1.66	[1.55, 1.78]	<0.001
	Obese	6.6%	2.47	[2.23, 2.73]	<0.001
BMI per unit increase (kg/m^2)			1.08	[1.07, 1.09]	<0.001
Age Group	20-24 years	14.8%	1.00		
	25-29 years	28.3%	1.56	[1.38, 1.76]	<0.001
	30-34 years	23.1%	2.82	[2.50, 3.19]	<0.001
	35-39 years	16.3%	5.35	[4.68, 6.11]	<0.001
	40-44 years	10.0%	13.82	[12.23, 15.63]	<0.001
	45-49 years	7.5%	38.78	[32.60, 46.13]	<0.001
Area of Residence	Rural	70.1%	1.00		
	Urban	29.9%	1.55	[1.47, 1.65]	<0.001
Relative Wealth Quintile	Poorest	20.7%	1.00		
	Poorer	20.2%	1.17	[1.09, 1.26]	<0.001
	Middle	20.1%	1.23	[1.14, 1.33]	<0.001
	Richer	19.6%	1.43	[1.32, 1.55]	<0.001
	Richest	19.4%	1.96	[1.81, 2.12]	<0.001
Parity prior to Exposure Period	Para 0	14.7%	1.00		
	Para 1-2	41.1%	0.83	[0.77, 0.89]	<0.001
	Para 3-5	31.5%	1.05	[0.98, 1.12]	0.186
	Para 6+	12.7%	2.23	[2.05, 2.43]	<0.001
Ever-Use of Contraception	Never Used	56.6%			
	Has Used	43.4%	0.56	[0.53, 0.60]	<0.001
Respondent's Education	No education	51.5%	1.00		
	Primary only	30.4%	0.94	[0.88, 1.00]	0.036
	Secondary or more	18.2%	1.34	[1.25, 1.43]	<0.001
Husband's Education Level	No Education	40.9%	1.00		
	Primary	28.3%	0.87	[0.82, 0.93]	<0.001
	Secondary or more	22.2%	1.01	[0.94, 1.08]	0.765
	Above secondary	5.6%	1.54	[1.39, 1.70]	<0.001
	Don't know	3.0%	1.20	[1.03, 1.39]	0.019
Respondent Works Outside Home	No	48.7%	1.00		
	Yes	51.3%	1.11	[1.05, 1.16]	<0.001
Smoking Behaviour	Non-smoker	96.3%	1.00		
	Smoker	3.7%	2.32	[2.08, 2.58]	<0.001

Sampling weights and survey design taken into account in the analysis

7.1.3 Multivariable Model

The effect of BMI on subfertility was calculated for each UN Sub-Region (Table 7.3). BMI category had a significant effect on the odds of subfertility in Eastern Africa (Obese OR: 1.46; 95% CI: 1.13-1.87) and Western Africa (Obese OR: 1.55; 95% CI: 1.34-1.79), but not in Middle Africa (Obese OR: 1.17; 95% CI: 0.86-1.58) or Southern Africa (Obese OR: 1.16; 95% CI: 0.79-1.69). There are three potential reasons for this (i) BMI truly has no effect on subfertility in Middle and Southern Africa; (ii) the study was underpowered in these two regions; (iii) the subfertility outcome performed poorly in these regions due to higher contraceptive prevalence and lower overall fertility rates. This is discussed further in Chapter 9. A sensitivity analysis was also carried out excluding ever-users of contraception from the dataset.

The magnitude of the effect of age category was increased in the multivariable model. There was a very substantial increase in odds in the oldest age group aged 45-49 years (Pooled OR: 99.80; 95% CI: 82.47-120.77). The effect of urban/rural residence and relative wealth quintile was slightly reduced in the adjusted analyses but remained significant.

Once adjusted for age and the other confounding factors in the model, increased parity had a protective effect on the odds of subfertility. Women with six or more children were much less likely to be subfertile than nulliparous women (Pooled OR: 0.24; 95% CI: 0.21-0.27). This is partially because women of a higher parity are demonstrably fecund, whilst the nullipara group will contain women with primary infertility. However, it is interesting that the effect is stronger amongst high para woman (6+) compared to those with 1-2 previous births. This possibly indicates some residual confounding with women intentionally limiting their fertility by means not captured by the model parameters.

Educated women remained slightly more likely to be subfertile than those with no education (Pooled OR: 1.21; 95% CI: 1.09-1.35). However the effect of husband's education lost statistical significance in the multivariable model. Women who worked outside of the home had a small but statistically significant increase in their odds of subfertility (Pooled OR: 1.11; 95% CI: 1.05-1.18) and women who were smokers were also most likely to be subfertile (Pooled OR: 1.63; 95% CI: 1.44-1.85).

In order to investigate whether the linear dose-response relationship previously observed in the crude analysis remained in the multivariable model the model was re-run, once using BMI as a categorical exposure with obesity subdivided into detailed categories and once using BMI as a continuous variable, assuming a linear effect (Table 7.4). An F-adjusted mean residual test was used to compare the fit of the two models. The null hypothesis for this test is that

"there is no lack of fit", therefore a large p-value suggests that the observed data fit the model well.

The F-adjusted mean residual test did not distinguish between the continuous vs. categorical BMI models in terms of goodness of fit; the two alternative models performed equally. However, the pattern of the ORs was more suggestive of a threshold effect, around the 30 kg/m^2 (obesity) cut-off.

7.1.4 Effect Modification

An a priori decision was made to test for an interaction between BMI category and age group, given the known importance of age on underlying fecundity. However, the adjusted Wald test showed no significant evidence of interaction (F=0.79; p=0.6426).

Table 7.3 Multivariable logistic regression model of the odds of subfertility

Risk Factor		Eastern Africa			Middle Africa			Southern Africa			Western Africa			Pooled Sub-Saharan Africa		
		OR	[95% CI]	p	OR	[95% CI]	p	OR	[95% CI]	p	OR	95% CI	p	OR	[95% CI]	p
BMI Category	Optimal	1.00			1.00			1.00			1.00			1.00		
	Pre-Obese	1.45	[1.27, 1.66]	<0.001	0.86	[0.69,1.06]	0.160	0.91	[0.66, 1.25]	0.553	1.39	[1.23, 1.57]	<0.001	1.35	[1.24, 1.47]	<0.001
	Obese	1.46	[1.13, 1.87]	0.003	1.17	[0.86,1.58]	0.314	1.16	[0.79,1.69]	0.452	1.55	[1.34, 1.79]	<0.001	1.51	[1.35, 1.69]	<0.001
Age Group	20-24 years	1.00			1.00			1.00			1.00			1.00		
	25-29 years	1.89	[1.58, 2.27]	<0.001	2.11	[1.52, 2.94]	<0.001	1.34	[0.75, 2.41]	0.318	1.78	[1.44, 2.21]	<0.001	1.85	[1.62, 2.12]	<0.001
	30-34 years	4.49	[3.70,5.44]	<0.001	3.82	[2.63, 5.53]	<0.001	1.90	[1.08, 3.36]	0.027	3.85	[3.10, 4.78]	<0.001	4.08	[3.57, 4.67]	<0.001
	35-39 years	10.82	[8.75, 13.39]	<0.001	10.72	[7.30, 15.73]	<0.001	5.59	[3.03, 10.34]	<0.001	8.34	[6.62, 10.50]	<0.001	9.27	[8.02, 10.72]	<0.001
	40-44 years	32.83	[25.72, 41.91]	<0.001	23.04	[14.56, 36.46]	<0.001	15.34	[7.85, 30.00]	<0.001	27.34	[22.35, 33.43]	<0.001	28.49	[24.81, 32.72]	<0.001
	45-49 years	127.03	[91.47, 176.42]	<0.001	115.93	[63.56, 211.47]	<0.001	38.30	[15.23, 96.32]	<0.001	88.01	[66.74, 116.07]	<0.001	99.80	[82.47, 120.77]	<0.001
Area of Residence	Rural	1.00			1.00			1.00			1.00			1.00		
	Urban	1.35	[1.17, 1.57]	<0.001	1.41	[1.09, 1.82]	0.009	1.71	[1.18, 2.48]	0.005	1.20	[1.07, 1.34]	0.002	1.26	[1.16, 1.37]	<0.001
Relative Wealth Quintile	Poorest	1.00			1.00			1.00			1.00			1.00		
	Poorer	1.13	[0.96, 1.32]	0.138	1.45	[1.01, 2.06]	0.041	1.20	[0.76, 1.91]	0.432	1.26	[1.12, 1.41]	0.000	1.22	[1.12, 1.34]	<0.001
	Middle	1.31	[1.12, 1.53]	0.001	1.48	[1.02,2.13]	0.038	2.08	[1.28, 3.39]	0.003	1.22	[1.09, 1.37]	0.001	1.30	[1.19, 1.42]	<0.001
	Richer	1.70	[1.44,2.01]	<0.001	1.43	[0.97, 2.12]	0.070	1.90	[1.15, 3.13]	0.012	1.35	[1.19, 1.53]	0.000	1.50	[1.36, 1.65]	<0.001
	Richest	2.38	[1.92, 2.96]	<0.001	1.80	[1.18, 2.73]	0.006	1.72	[0.92, 3.23]	0.092	1.59	[1.37, 1.85]	0.000	1.86	[1.65, 2.09]	<0.001
Parity	Para 0	1.00			1.00			1.00			1.00			1.00		
	Para 1-2	0.76	[0.66,0.88]	<0.001	0.61	[0.48, 0.77]	<0.001	1.37	[0.96,1.95]	0.087	0.57	[0.50, 0.65]	0.000	0.65	[0.60, 0.71]	<0.001
	Para 3-5	0.38	[0.32, 0.46]	<0.001	0.27	[0.20,0.36]	<0.001	1.04	[0.67, 1.62]	0.854	0.37	[0.32, 0.42]	0.000	0.37	[0.34,0.41]	<0.001
	Para 6+	0.23	[0.18, 0.29]	<0.001	0.16	[0.10, 0.23]	<0.001	0.48	[0.23, 0.99]	0.048	0.25	[0.21, 0.29]	0.000	0.24	[0.21, 0.27]	<0.001
Ever-Use of Contraception	Never Used	1.00			1.00			1.00			1.00			1.00		
	Has Used	0.41	[0.36, 0.45]	<0.001	0.59	[0.45, 0.78]	<0.001	0.59	[0.41, 0.86]	0.006	0.56	[0.51, 0.60]	0.000	0.50	[0.47, 0.54]	<0.001
Respondent's Education	None	1.00			1.00			1.00			1.00			1.00		
	Primary only	1.20	[1.06,1.35]	0.003	1.03	[0.75, 1.41]	0.846	1.24	[0.77, 2.00]	0.377	1.11	[0.99, 1.25]	0.070	1.15	[1.06, 1.24]	0.001
	Secondary or more	1.22	[0.99, 1.51]	0.062	1.13	[0.78, 1.63]	0.533	1.00	[0.60, 1.65]	0.991	1.24	[1.08, 1.42]	0.002	1.21	[1.09, 1.35]	<0.001
Husband's Education Level	None	1.00			1.00			1.00			1.00			1.00		
	Primary	1.03	[0.89, 1.19]	0.708	0.87	[0.61, 1.25]	0.455	1.03	[0.69, 1.53]	0.890	1.01	[0.90, 1.13]	0.842	1.01	[0.93,1.09]	0.873
	Secondary or more	1.03	[0.85, 1.25]	0.757	0.96	[0.68, 1.37]	0.831	0.88	[0.54, 1.46]	0.628	1.17	[1.05, 1.32]	0.006	1.10	[1.00,1.20]	0.049
	Above secondary	1.02	[0.76, 1.38]	0.899	1.01	[0.65, 1.56]	0.977	0.66	[0.33, 1.31]	0.235	1.13	[0.95, 1.35]	0.163	1.06	[0.92, 1.23]	0.397
	Don't know	1.32	[0.97,1.80]	0.082	1.33	[0.83, 2.12]	0.242	1.59	[0.61, 4.17]	0.345	1.15	[0.89, 1.50]	0.288	1.23	[1.03, 1.48]	0.026
Works outside Home	No	1.00			1.00			1.00			1.00			1.00		
	Yes	1.08	[0.98, 1.19]	0.128	1.07	[0.89,1.28]	0.463	1.45	[1.07, 1.97]	0.017	1.13	[1.04, 1.22]	0.005	1.11	[1.05, 1.18]	0.001
Smoking Behaviour	Non-smoker	1.00			-			1.00			1.00			1.00		
	Smoker	1.94	[1.58, 2.38]	<0.001	-	-	-	1.22	[0.82, 1.83]	0.332	1.41	[1.17, 1.69]	0.000	1.63	[1.44, 1.85]	<0.001

Effect estimates adjusted for all other covariates in the model. Sampling weights and survey design taken into account in the analysis

Table 7.4: Comparison of BMI as a categorical versus continuous variable

Risk Factor		Pooled Sub-Saharan Africa		
		OR	[95% CI]	p-value
BMI Category	Optimal (18.5-24.9 kg/m^2)	1.00		
	Pre-Obese (25-29.9 kg/m^2)	1.35	[1.24, 1.47]	<0.001
	Obese Class I (30-34.9 kg/m^2)	1.50	[1.32, 1.69]	<0.001
	Obese Class II (35-39.9 kg/m^2)	1.55	[1.18, 2.04]	0.002
	Obese Class III (≥40 kg/m^2)	1.53	[1.04, 2.26]	0.033
F = 0.421; p= 0.925				
Risk Factor		**Pooled Sub-Saharan Africa**		
		OR	**[95% CI]**	**p-value**
per increase unit BMI (kg/m^2)		1.04	[1.03, 1.05]	<0.001
F = 0.534; p=0.851				

Estimates adjusted for age group, urban/rural residence, wealth quintile, parity, ever-use of contraception, respondent's education, husband's education, whether the woman works outside of the home, smoking behaviour. Sampling weights and survey design taken into account in the analysis

7.1.5 Sensitivity Analyses

Two different sensitivity analyses were carried out to test the robustness of the model to the assumptions made during the construction of the outcome variable. These were:

1. **Excluding ever-users of contraception**

In the DHS information is available on ever-use of contraception and current use of contraception. However, many countries have yet to introduce the full reproductive calendar module and, in particular, there are inadequate data on contraceptive behaviour of women who report having used a contraceptive method previously but are not doing so at the time of the survey. Ever-use of contraception was controlled for in the multivariable model, and women who had continuously been using a contraceptive method throughout the exposure period were excluded, but it is likely that some residual confounding still occurs.

In order to assess this potential limitation, the model was re-run excluding all women who had ever-used a contraceptive method (Table 7.5). This will provide estimates of the effect of BMI where a woman is not using an effective means of birth control; the possibility still remains that some women are controlling their fertility through coital frequency or other means.

Table 7.5: Sensitivity analysis; multivariable model excluding ever-users of contraception

Risk Factor		OR	[95% CI]	p-value
BMI Category	Optimal	1.00		
	Pre-Obese	1.39	[1.26, 1.54]	<0.001
	Obese	1.93	[1.55, 2.39]	<0.001
Age Group	20-24 years	1.00		
	25-29 years	2.10	[1.73, 2.55]	<0.001
	30-34 years	4.99	[4.05, 6.15]	<0.001
	35-39 years	11.83	[9.57, 14.61]	<0.001
	40-44 years	36.73	[29.74, 45.37]	<0.001
	45-49 years	132.07	[105.30, 165.64]	<0.001
Area of Residence	Rural	1.00		
	Urban	1.25	[1.12, 1.39]	<0.001
Relative Wealth Quintile	Poorest	1.00		
	Poorer	1.24	[1.12, 1.38]	<0.001
	Middle	1.27	[1.15, 1.42]	<0.001
	Richer	1.53	[1.37, 1.72]	<0.001
	Richest	1.98	[1.69, 2.31]	<0.001
Parity	Para 0	1.00		
	Para 1-2	0.47	[0.42, 0.53]	<0.001
	Para 3-5	0.21	[0.18, 0.24]	<0.001
	Para 6+	0.13	[0.12, 0.16]	<0.001
Respondent's Education	No education	1.00		
	Primary only	1.10	[0.99, 1.21]	0.072
	Secondary or more	1.17	[0.99, 1.37]	0.061
Husband's Education Level	No Education	1.00		
	Primary	0.99	[0.89, 1.09]	0.771
	Secondary or more	1.11	[0.98, 1.26]	0.109
	Above secondary	0.97	[0.79, 1.19]	0.766
	Don't know	1.21	[0.94, 1.55]	0.135
Respondent Works Outside Home	No	1.00		
	Yes	1.10	[1.02, 1.18]	0.012
Smoking Behaviour	Non-smoker	1.00		
	Smoker	1.57	[1.35, 1.82]	<0.001

Estimates adjusted for age group, urban/rural residence, wealth quintile, parity, ever-use of contraception, respondent's education, husband's education, whether the woman works outside of the home, smoking behaviour. Sampling weights and survey design taken into account in the analysis

The magnitude of the effect of pre-obese and obesity increased in the model excluding ever-users of contraception from the dataset. It was not considered appropriate to exclude all ever-users of contraception from the main results because non-contraceptive users are selected for lower fecundity; an individual who believes that they are infertile has little reason to use contraception for birth control purposes. Therefore the "true" effect estimate is likely to lie somewhere between the effect reported in the main results section and this sensitivity analysis; my results represent a conservative estimate of the effect of overweight/obesity on subfertility.

2. Length of the exposure period

I also re-ran the model varying the length of the exposure period required to determine subfertility to assess the robustness of the model to this assumption. The results are shown in Table 7.6 and Table 7.7. Note that in each model the sample size is slightly different, reflecting differences in the number of women who were excluded because they had either not been ever-partnered throughout the exposure period, had used contraception continuously throughout the exposure period or had not had sexual intercourse since the start of the exposure period.

The effect of BMI category was very similar to the original model, suggesting that the length of the exposure period did not have an important effect, despite the concerns with data heaping at the five year cut-off described in the methods section (Chapter 3).

Table 7.6 Sensitivity analysis; multivariable model restricting exposure period to 48 months

Risk Factor		OR	[95% CI]	p-value
BMI Category	Optimal	1.00		
	Pre-Obese	1.38	[1.26, 1.51]	<0.001
	Obese	1.53	[1.35, 1.72]	<0.001
Age Group	20-24 years	1.00		
	25-29 years	2.19	[1.91, 2.52]	<0.001
	30-34 years	5.35	[4.67, 6.14]	<0.001
	35-39 years	13.22	[11.39, 15.34]	<0.001
	40-44 years	43.06	[37.36, 49.62]	<0.001
	45-49 years	161.08	[132.05, 196.48]	<0.001
Area of Residence	Rural	1.00		
	Urban	1.26	[1.15, 1.37]	<0.001
Relative Wealth Quintile	Poorest	1.00		
	Poorer	1.22	[1.12, 1.33]	<0.001
	Middle	1.29	[1.18, 1.41]	<0.001
	Richer	1.47	[1.34, 1.62]	<0.001
	Richest	1.74	[1.54, 1.96]	<0.001
Parity	Para 0	1.00		
	Para 1-2	0.33	[0.30, 0.36]	<0.001
	Para 3-5	0.15	[0.14, 0.17]	<0.001
	Para 6+	0.08	[0.07, 0.09]	<0.001
Ever-Use of Contraception	Never Used	1.00		
	Has Used	0.52	[0.48, 0.55]	<0.001
Respondent's Education	No education	1.00		
	Primary only	1.13	[1.04, 1.22]	0.003
	Secondary or more	1.12	[1.01, 1.25]	0.038
Husband's Education Level	No Education	1.00		
	Primary	1.00	[0.92, 1.09]	0.986
	Secondary or more	1.07	[0.97, 1.18]	0.194
	Above secondary	0.98	[0.84, 1.14]	0.807
	Don't know	1.15	[0.94, 1.41]	0.166
Respondent Works Outside Home	No	1.00		
	Yes	1.11	[1.05, 1.19]	0.001
Smoking Behaviour	Non-smoker	1.00		
	Smoker	1.62	[1.43, 1.85]	<0.001

Estimates adjusted for age group, urban/rural residence, wealth quintile, parity, ever-use of contraception, respondent's education, husband's education, whether the woman works outside of the home, smoking behaviour. Sampling weights and survey design taken into account in the analysis

Table 7.7 Sensitivity analysis; multivariable model restricting exposure period to 72 months

Risk Factor		OR	95% Confidence Interval	p-value
BMI Category	Optimal	1.00		
	Pre-Obese	1.37	[1.26, 1.50]	<0.001
	Obese	1.53	[1.36, 1.71]	<0.001
Age Group	20-24 years	1.00		
	25-29 years	1.59	[1.36, 1.85]	<0.001
	30-34 years	3.46	[2.97, 4.04]	<0.001
	35-39 years	7.75	[6.57, 9.15]	<0.001
	40-44 years	23.57	[20.19, 27.52]	<0.001
	45-49 years	81.64	[66.29, 100.56]	<0.001
Area of Residence	Rural	1.00		
	Urban	1.27	[1.16, 1.39]	<0.001
Relative Wealth Quintile	Poorest	1.00		
	Poorer	1.22	[1.11, 1.33]	<0.001
	Middle	1.30	[1.19, 1.42]	<0.001
	Richer	1.51	[1.37, 1.66]	<0.001
	Richest	1.86	[1.65, 2.10]	<0.001
Parity	Para 0	1.00		
	Para 1-2	0.65	[0.59, 0.71]	<0.001
	Para 3-5	0.37	[0.33, 0.41]	<0.001
	Para 6+	0.27	[0.23, 0.30]	<0.001
Ever-Use of Contraception	Never Used	1.00		
	Has Used	0.51	[0.48, 0.54]	<0.001
Respondent's Education	No education	1.00		
	Primary only	1.14	[1.05, 1.23]	0.001
	Secondary or more	1.25	[1.12, 1.39]	<0.001
Husband's Education Level	No Education	1.00		
	Primary	1.01	[0.93, 1.10]	0.761
	Secondary or more	1.12	[1.02, 1.23]	0.019
	Above secondary	1.09	[0.94, 1.27]	0.229
	Don't know	1.22	[1.01, 1.47]	0.037
Respondent Works Outside Home	No	1.00		
	Yes	1.12	[1.05, 1.19]	0.001
Smoking Behaviour	Non-smoker	1.00		
	Smoker	1.64	[1.44, 1.87]	<0.001

Estimates adjusted for age group, urban/rural residence, wealth quintile, parity, ever-use of contraception, respondent's education, husband's education, whether the woman works outside of the home, smoking behaviour. Sampling weights and survey design taken into account in the analysis

7.1.6 Summary

This analysis focused on women who were subfertile, a dichotomous variable intended to proxy infertility status. Obesity was observed to increase the odds of subfertility in Eastern Africa, Western Africa and in the pooled Sub-Saharan dataset, although not in Middle Africa or Southern Africa.

It seems plausible that BMI may also influence underlying fecundity in a dose-response manner which cannot be observed using a dichotomous variable. Furthermore, this analysis is limited by the need to make substantial assumptions regarding each woman's exposure to conception and desire to conceive.

The next section of this chapter attempts to address these concerns by conducting a survival analysis using reproductive calendar data, analogous to the TTP studies in my systematic review.

7.2 Time to First Conception in Sub-Saharan Africa

The reproductive calendar provides detailed monthly data on pregnancies, births, terminations and contraceptive use. Therefore, for those countries in which such data has been collected it could potentially be used to address the main limitation of the TTP studies identified in my systematic review as it provides monthly reproductive data for all women in the population. In addition, conception can be used as an endpoint, regardless of whether the pregnancy ends in a miscarriage, still birth, abortion or live birth.

This section presents a discrete-time survival analysis of the time from date of first marriage (meaning the date in which a couple began cohabitation) to date of first conception for women who married in the period covered by the reproductive calendar using pooled data from thirteen countries in Sub-Saharan Africa (Ethiopia, Ghana, Kenya, Madagascar, Malawi, Namibia, Nigeria, Sierra Leone, Swaziland, Tanzania, Uganda, Zambia and Zimbabwe) which included the reproductive calendar module in the most recent DHS. Full methodological details were provided in Chapter 3.

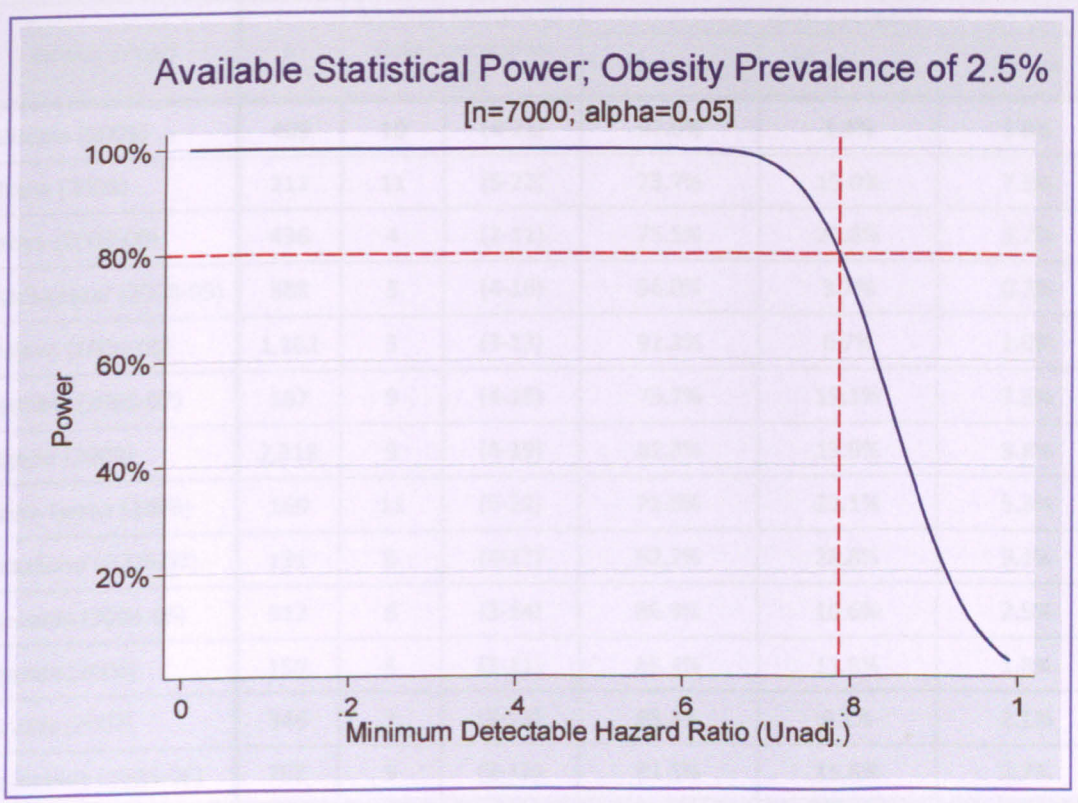
This analysis is somewhat exploratory in nature. The reproductive calendar has not previously been analysed in this manner and due to the low contraceptive prevalence in most of Sub-Saharan Africa the reproductive calendar data was only available for half my countries. I

decided to restrict the analysis to recently married women. This enhanced validity (as it is highly likely that women in this group are attempting conception given the social and cultural importance of child-bearing in the region) and complemented the previous subfertility analysis by addressing one of the major limitations (no data on attempted conceptions).

Pooling the data from the thirteen countries where calendar data are available created a dataset of just over 7000 women; however prevalence of obesity was particularly low (just 2.9%) in this relatively young cohort of recently married women.

A retrospective power calculation showed that a scenario similar to this would allow a minimum unadjusted hazard ratio of 0.78 to be detected with 95% confidence and 80% power (Figure 7-B). However, this falls within the range of estimates observed in the systematic review; furthermore these studies were also generated through the use of a retrospective TTP design conditioned on pregnancy, which would have weakened the magnitude of any observed effect estimate.

Figure 7-B Survival analysis power graph



7.2.1 Sample Description

A total of 7,761 nulliparous women who had married for the first time during the period covered by the contraceptive calendar, had not been pregnant at the time of marriage and did not use any method of contraception between their marriage and their first conception were included in this study (Table 7.8). Of these women, 85.2% had an optimal BMI value and 14.8% were overweight (11.9% were pre-obese and 2.9% were obese). Data from thirteen different countries was pooled for this study; national contributions to the dataset ranged between 159 women (Sierra Leone) to 2,318 women (Nigeria).

There is a considerable range in the national median time to first conception (Table 7.8); in general women in Eastern Africa appear to have typically shorter waiting times than those living in Western Africa or Ethiopia. There are also substantial national differences in the prevalence of overweight, with Western and Southern African countries having a relatively higher proportion of obese women.

Table 7.8 Median time to first conception and BMI distribution

Survey (Year)	*n*	Median Months to First Conception (IQR)		BMI Category		
				Optimal	Pre-Obese	Obese
Ethiopia (2005)	409	10	(4-21)	97.0%	1.4%	1.6%
Ghana (2008)	212	11	(5-22)	73.7%	19.0%	7.3%
Kenya (2008-09)	436	4	(2-11)	75.5%	20.8%	3.7%
Madagascar (2008-09)	588	8	(4-16)	96.0%	3.7%	0.3%
Malawi (2004-05)	1,162	5	(3-13)	92.3%	6.7%	1.0%
Namibia (2006-07)	167	9	(4-18)	73.7%	19.1%	7.3%
Nigeria (2008)	2,318	9	(4-19)	82.3%	13.9%	3.8%
Sierra Leone (2008)	169	11	(5-22)	71.6%	23.1%	5.3%
Swaziland (2006-07)	131	8	(4-17)	62.2%	28.8%	9.1%
Tanzania (2004-05)	912	6	(3-14)	86.9%	10.6%	2.5%
Uganda (2006)	159	6	(3-11)	86.4%	11.8%	1.8%
Zambia (2007)	346	7	(3-14)	88.8%	9.1%	2.1%
Zimbabwe (2005-06)	752	5	(2-12)	81.5%	15.8%	2.7%
Pooled Dataset	**7,761**	**7**	**(3-16)**	**85.2%**	**11.9%**	**2.9%**

Sample weights used

Descriptive characteristics of this analytic sample are displayed in Table 7.9. As the study was restricted to women who had first married within the five years preceding the survey the sample is a relatively young cohort and very few women are obese. An analysis of variance indicated that, although mean time to conception increased with increasing BMI category; from 11.8 months amongst optimal weight women to 12.2 months amongst pre-obese women and 12.6 months amongst obese women, this difference was not statistically significant (F-0.82; p=0.4413).

Table 7.9 Descriptive characteristics of sample

Characteristic		All Women (n=7,761)	
		% (95% CI) or Median (IQR)	
BMI Category	Optimal	85.5%	(84.2%-86.2%)
	Pre-Obese	11.9%	(11.0%-12.8%)
	Obese	2.9%	(2.4%-3.3%)
Median Age at First Marriage (years)		18	(16-20)
Relative Wealth Quintile	Poorest	18.5%	(17.4%-19.7%)
	Poorer	21.1%	(19.9%-22.3%)
	Middle	18.9%	(17.7%-20.0%)
	Richer	20.0%	(18.8%-21.1%)
	Richest	21.5%	(20.2%-22.8%)
Area of Residence	Rural	71.9%	(70.6%-73.2%)
	Urban	28.1%	(26.8%-29.4%)
Education Level	No education	26.6%	(25.2%-28.0%)
	Primary school only	41.0%	(39.6%-42.5%)
	Secondary or higher	32.3%	(31.0%-33.7%)

Sample weights used

A life table was constructed to investigate monthly conception rates after first marriage in each BMI category (Table 7.10). The cumulative conception rate appeared to be lower amongst both the pre-obese and obese women compared to optimal weight women at most time points. Five years after the date of first marriage 9.3% of optimal weight women had yet to conceive, compared to 12.5% of pre-obese women and 17% of obese women. However, the log-rank test for equality of survivor functions did not detect a statistically significant difference ($\chi^2 = 1.24$; p=0.5378). I combined the pre-obese and obese women into one overweight group to see if the additional statistical power made a difference; but the study remained under-powered ($\chi^2 = 1.04$; p=0.3078).

Table 7.10 Life table showing the cumulative monthly conception rate, stratified by BMI category

Interval months	Optimal Weight					Pre-Obese					Obese				
	Total	Conceptions	Censored	Cumulative Conception Rate [95% CI]		Total	Conceptions	Censored	Cumulative Conception Rate [95% CI]		Total	Conceptions	Censored	Cumulative Conception Rate [95% CI]	
0	6644	0	43			912	0	3			205	0	1		
1	6601	599	93	0.091	[0.084, 0.098]	909	72	18	0.079	[0.063, 0.099]	204	19	1	0.093	[0.060, 0.142]
2	5909	547	81	0.175	[0.166, 0.184]	819	84	7	0.174	[0.150, 0.200]	184	16	1	0.172	[0.127, 0.231]
3	5281	470	78	0.248	[0.238, 0.259]	728	63	9	0.245	[0.218, 0.275]	167	12	2	0.232	[0.179, 0.296]
4	4733	391	82	0.310	[0.299, 0.322]	656	62	15	0.317	[0.287, 0.348]	153	14	2	0.302	[0.244, 0.370]
5	4260	316	66	0.362	[0.350, 0.374]	579	51	6	0.377	[0.346, 0.410]	137	9	1	0.348	[0.286, 0.418]
6	3878	263	62	0.405	[0.393, 0.417]	522	29	4	0.411	[0.380, 0.445]	127	7	1	0.384	[0.320, 0.455]
7	3553	236	50	0.444	[0.432, 0.457]	489	31	10	0.449	[0.416, 0.483]	119	8	2	0.425	[0.360, 0.497]
8	3267	217	59	0.481	[0.469, 0.494]	448	34	6	0.491	[0.458, 0.525]	109	8	1	0.467	[0.401, 0.539]
9	2991	193	41	0.515	[0.502, 0.527]	408	25	4	0.522	[0.489, 0.556]	100	6	2	0.499	[0.432, 0.571]
10	2757	160	39	0.543	[0.531, 0.556]	379	17	3	0.543	[0.510, 0.577]	92	6	1	0.532	[0.464, 0.603]
11	2558	151	41	0.570	[0.558, 0.582]	359	20	1	0.569	[0.535, 0.602]	85	6	2	0.565	[0.496, 0.636]
12-17	2366	711	206	0.699	[0.687, 0.711]	338	94	25	0.689	[0.657, 0.720]	77	26	6	0.712	[0.646, 0.775]
18-23	1449	363	139	0.775	[0.763, 0.786]	219	57	29	0.770	[0.739, 0.799]	45	8	5	0.763	[0.698, 0.823]
24-35	947	329	202	0.853	[0.843, 0.863]	133	36	32	0.832	[0.803, 0.859]	32	9	8	0.830	[0.768, 0.883]
36-47	416	115	124	0.894	[0.884, 0.903]	65	15	18	0.871	[0.842, 0.897]	15	0	6	0.830	[0.768, 0.883]
48-59	177	22	90	0.907	[0.897, 0.916]	32	1	14	0.875	[0.846, 0.901]	9	0	7	0.830	[0.768, 0.883]

7.2.3 Discrete-time survival model

Table 7.11 shows the results of the discrete-time survival model. The monthly odds of conception did not differ for the first four months of marriage; subsequent to this the odds of conceiving decreased as time elapsed. After one year of marriage the length of the discrete-time interval was increased to six or twelve months due to the small monthly numbers of conceptions.

As previously, BMI category did not have a statistically significant effect on the odds of conception (Pre-Obese OR: 0.93; 95% CI: 0.84-1.04; Obese OR: 0.91; 95% CI: 0.73-1.12). Women aged 15-19 (OR: 0.70; 95% CI: 0.64-0.75) and those older than thirty years (OR: 0.60; 95% CI: 0.51-0.71) were less likely to conceive in the five years following first marriage relative to the 20-24 year old age group, after adjusting for confounding. Women with some form of education were more likely to conceive than those with no education. Neither relative wealth nor urban/rural residence had a significant effect on conception rate.

7.2.4 Summary

Analysis of the DHS reproductive calendar data in this manner has potential, as demonstrated by the discrete-time model results which showed a significant reduction in fecundability with increasing age. However, this study is under-powered to detect differences in conception rates according to BMI category. It would be interesting to repeat the analysis in the future once more data becomes available.

Table 7.11 Multivariable logistic discrete-time survival model for the first conception after first marriage

Risk Factor		OR	[95% CI]	p-value
Time Elapsed since Date of First Marriage	Month 1	1.00		
	Month 2	1.04	[0.91, 1.19]	0.535
	Month 3	1.00	[0.87, 1.14]	0.944
	Month 4	0.96	[0.83, 1.10]	0.535
	Month 5	0.84	[0.72, 0.98]	0.028
	Month 6	0.73	[0.62, 0.86]	<0.001
	Month 7	0.73	[0.62, 0.87]	<0.001
	Month 8	0.80	[0.67, 0.95]	0.011
	Month 9	0.69	[0.58, 0.82]	<0.001
	Month 10	0.62	[0.51, 0.76]	<0.001
	Month 11	0.67	[0.55, 0.82]	<0.001
	Months 12-17	4.79	[4.21, 5.45]	<0.001
	Months 18-23	3.62	[3.09, 4.24]	<0.001
	Months 24-35	6.74	[5.66, 8.03]	<0.001
	Months 36-47	5.26	[4.10, 6.77]	<0.001
	Months 48-59	2.20	[1.33, 3.64]	0.002
BMI Category	Optimal	1.00		
	Pre-Obese	0.93	[0.84, 1.04]	0.216
	Obese	0.91	[0.73, 1.12]	0.371
Age	15-19 years	0.70	[0.64, 0.75]	<0.001
	20-24 years	1.00		
	25-29 years	0.93	[0.85, 1.02]	0.139
	≥30 years	0.60	[0.51, 0.71]	<0.001
Relative Wealth Quintile	Poorest	1.00		
	Poorer	1.10	[0.99, 1.21]	0.070
	Middle	1.12	[1.01, 1.24]	0.038
	Richer	1.09	[0.97, 1.22]	0.149
	Richest	1.06	[0.92, 1.22]	0.452
Area of Residence	Rural	1.00		
	Urban	0.95	[0.86, 1.05]	0.309
Education Level	No education	1.00		
	Primary school only	1.49	[1.37, 1.61]	<0.001
	Secondary education or higher	1.56	[1.41, 1.73]	<0.001

Effect estimates adjusted for all other covariates in the model. Sampling weights and survey design taken into account in the analysis.

Chapter 8

BMI and Adverse Pregnancy Outcomes in Sub-Saharan Africa

The background literature reviewed in Chapter 2 suggested that maternal obesity is a risk factor for a large number of adverse pregnancy outcomes, particularly those that occur around the intra-partum period.

Chapter 8 investigates the effect of overweight/obesity on adverse pregnancy outcomes, specifically (i) caesarean delivery; (ii) neonatal deaths. After the initial multivariable regression models I conducted a further investigation into the timing of death within the neonatal period, which is also presented here. This analysis is the most detailed investigation into the effect of maternal obesity on the timing of neonatal death published to-date.

8.1 Maternal Overweight/Obesity and Caesarean Delivery

8.1.1 Sample Description

A total of 73,545 women were included in the analysis, of which 3.8% had delivered by caesarean section at their most recent delivery (Table 8.1). The number of women included in each national survey ranged from 964 (Uganda, 2006) to 10,324 (Nigeria, 2008). The size of the datasets from Western Region (n=35,166) and Eastern Region (n=26,248) were substantially larger than those from the Middle (n=6,908) and Southern Regions (n=5,223).

Table 8.1 Sample description

Country (year)		*n*	Caesarean Deliveries (%)	Maternal BMI Category				
				Optimal	Pre-Obese	Obese Class I	Obese Class II	Obese Class III
Eastern Africa	Ethiopia	1,574	1.7%	94.9%	4.1%	0.8%	0.2%	0.0%
	Kenya	2,501	7.7%	72.2%	20.5%	6.3%	0.8%	0.1%
	Madagascar	2,031	2.0%	91.9%	7.0%	1.0%	0.1%	0.0%
	Malawi	4,366	3.6%	85.7%	12.0%	2.1%	0.1%	0.1%
	Mozambique	4,141	2.5%	85.5%	10.9%	2.8%	0.6%	0.2%
	Rwanda	1,863	2.8%	87.5%	11.3%	1.1%	0.1%	0.0%
	Tanzania	3,475	4.4%	81.4%	14.2%	3.7%	0.6%	0.1%
	Uganda	964	4.6%	81.0%	14.1%	4.4%	0.4%	0.2%
	Zambia	2,510	4.1%	79.8%	15.4%	4.0%	0.6%	0.3%
	Zimbabwe	2,823	5.8%	73.4%	20.1%	5.4%	1.0%	0.1%
	Pooled	**26,248**	**3.9%**	**82.9%**	**13.3%**	**3.2%**	**0.5%**	**0.1%**
Middle Africa	Cameroon	1,691	2.0%	68.9%	22.8%	6.7%	1.4%	0.2%
	Chad	1,578	0.6%	90.2%	7.5%	1.9%	0.5%	0.0%
	Congo	2,136	3.7%	67.5%	22.9%	7.9%	1.7%	0.0%
	DRC	1,503	4.2%	85.3%	11.9%	2.4%	0.2%	0.3%
	Pooled	**6,908**	**2.7%**	**77.0%**	**16.9%**	**5.0%**	**1.0%**	**0.1%**
Southern Africa	Lesotho	1,048	6.4%	54.6%	27.8%	14.4%	2.3%	1.0%
	Namibia	2,585	15.7%	62.4%	22.8%	10.9%	3.2%	0.7%
	Swaziland	1,590	8.4%	42.1%	32.3%	19.2%	4.2%	2.3%
	Pooled	**5,223**	**11.6%**	**54.6%**	**26.7%**	**14.2%**	**3.3%**	**1.2%**
Western Africa	Benin	6,373	4.3%	79.8%	14.7%	4.3%	0.9%	0.4%
	Burkina Faso	3,911	0.9%	89.4%	8.2%	2.0%	0.4%	0.2%
	Ghana	1,439	7.3%	66.0%	24.8%	7.4%	1.5%	0.3%
	Guinea	1,325	2.2%	84.2%	12.2%	3.3%	0.3%	0.0%
	Liberia	2,501	3.9%	78.4%	15.8%	4.7%	0.8%	0.3%
	Mali	5,155	2.2%	80.0%	14.9%	4.4%	0.5%	0.1%
	Niger	1,619	1.5%	82.1%	14.0%	3.3%	0.5%	0.2%
	Nigeria	10,324	2.4%	72.8%	20.0%	5.7%	1.0%	0.5%
	Senegal	1,304	4.5%	72.1%	19.0%	8.0%	0.8%	0.2%
	Sierra Leone	1,215	2.2%	71.6%	21.8%	4.9%	1.2%	0.6%
	Pooled	**35,166**	**2.9%**	**77.9%**	**16.3%**	**4.7%**	**0.8%**	**0.3%**
Pooled, Sub-Saharan Africa		**73,545**	**3.8%**	**78.0%**	**16.0%**	**4.9%**	**0.9%**	**0.3%**

Sample weights used

There was considerable variation in the caesarean rate between countries, as shown in Table 8.1. Only 0.6% of women in Chad and 0.9% of women in Burkina Faso had a caesarean section at their most recent delivery, compared to 15.7% of women in Namibia. Women in Southern Africa have a substantially higher caesarean rate (11.6%) than across the rest of the continent; 3.9% in Eastern Africa, 2.7% in Middle Africa and 2.9% in Western Africa.

8.1.2 Univariable Analysis

Assuming a linear effect, the odds of caesarean delivery increased by 11% for every unit increase in BMI (OR: 1.11; 95% CI: 1.10-1.12). In order to assess the validity of the linearity assumption the observed log odds by per unit BMI were graphed against the predicted linear mode (Figure 8-A).

Figure 8-A Observed versus linear predicted odds of caesarean delivery

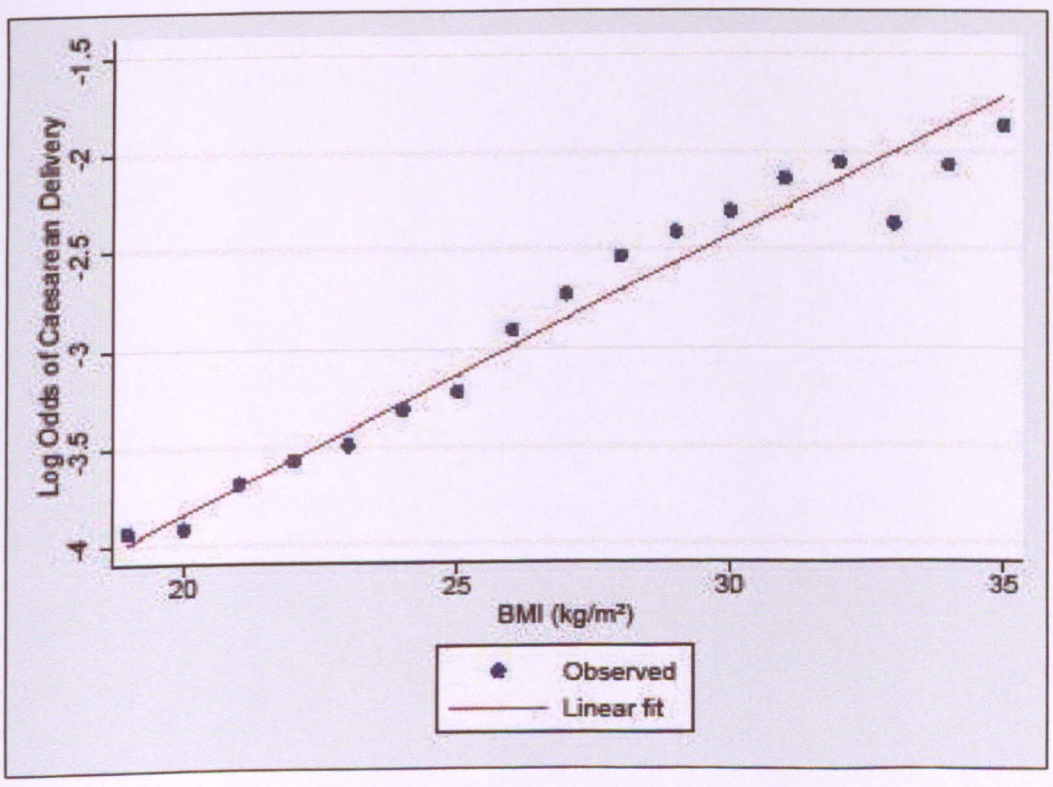


Table 8.2 Unadjusted odds of caesarean delivery by risk factor

Risk Factor		Proportion (%) or Mean	OR	[95% CI]	p-value
BMI Category	Optimal	78.0%	1.00		
	Pre-Obese	16.0%	2.29	[2.04, 2.56]	<0.001
	Obese Class I	4.9%	3.59	[3.07, 4.19]	<0.001
	Obese Class II	0.9%	5.12	[3.88, 6.75]	<0.001
	Obese Class III	0.3%	6.00	[3.75, 9.58]	<0.001
Per unit increase in BMI (kg/m^2)		23.18	1.11	[1.10, 1.12]	<0.001
Age Group	20-24 years	24.5%	1.00		
	25-29 years	27.0%	1.29	[0.97, 1.71]	0.080
	30-34 years	20.8%	1.52	[1.15, 2.00]	0.003
	35-39 years	15.4%	1.61	[1.22, 2.13]	0.001
	40-44 years	8.6%	1.47	[1.10, 1.95]	0.008
	45-49 years	3.6%	1.41	[1.04, 1.90]	0.026
Area of Residence	Rural	69.9%	1.00		
	Urban	30.1%	2.97	[2.69, 3.28]	<0.001
Relative Wealth Quintile	Poorest	19.4%	1.00		
	Poorer	19.7%	1.53	[1.25, 1.88]	<0.001
	Middle	20.0%	1.81	[1.47, 2.22]	<0.001
	Richer	20.6%	3.45	[2.86, 4.17]	<0.001
	Richest	20.3%	7.05	[5.88, 8.45]	<0.001
Parity	First birth	14.9%	1.49	[1.33, 1.66]	<0.001
	2-3 previous births	34.8%	1.00		
	4-5 previous births	24.2%	0.60	[0.53, 0.69]	<0.001
	6+ previous births	26.1%	0.44	[0.38, 0.51]	<0.001
Respondent's Education	No education	42.9%	1.00		
	Primary only	33.9%	2.36	[2.02, 2.76]	<0.001
	Secondary or more	23.2%	5.66	[4.86, 6.60]	<0.001
Time elapsed (months)		22.76	1.01	[1.01, 1.01]	<0.001

Sampling weights and survey design taken into account in the analysis

The socio-demographic characteristics of the pooled sub-Saharan sample are shown in Table 8.2. The unadjusted odds of a caesarean delivery (versus vaginal delivery) rise with increasing BMI category: women who are pre-obese have more than twice the odds of delivering by caesarean compared to those who are optimal weight (OR 2.29; 95% CI 2.04-2.56) whilst those women who are morbidly obese in the highest BMI category have six times the odds of delivering by caesarean (OR 6.00; 95% CI 3.75-9.58).

From a baseline of 20-24 years, the odds of caesarean delivery increase with age. The difference is not statistically significant in the 25-29 years age group, but all older age groups have significantly higher odds of delivery by caesarean section.

Urban women have nearly three times the odds of delivery by caesarean, compared to rural inhabitants (OR: 2.97; 95% CI: 2.69-3.28). There is a strong association between odds of caesarean delivery and relative wealth. Odds of caesarean delivery increase with every increase in wealth quintile; in the richest category women have seven times the odds of caesarean delivery compared to the poorest wealth quintile (OR: 7.05; 95% CI: 5.88-8.45).

Odds of caesarean delivery decreased as parity increased. Using 2-3 previous births as the baseline, women were nearly 50% more likely to have a caesarean for their first delivery (OR: 1.49; 95% CI 1.33-1.66), however they were significantly less likely to have a caesarean delivery in higher order births.

Caesarean deliveries increased with higher education; women with secondary education or higher had over five times the odds of delivering by caesarean compared to those with no education (OR: 5.66; 95% CI: 4.86-6.60).

The 'time elapsed' variable was included to control for difference in the time between the index birth event and the survey. Time elapsed had a very small, albeit statistically significant effect of a 1% increase in odds for each month elapsed (OR: 1.01; 95% CI: 1.01-1.01).

8.1.3 Multivariable Model

Table 8.3 provides the results of the multivariable model. The effect of maternal BMI category was strongly statistically significant in all five of the pooled regional results. In the pooled sub-Saharan African dataset women who are pre-obese had 1.6 times the odds of having a caesarean during their most recent delivery (Pooled OR: 1.63; 95% CI: 1.45-1.83) after adjusting for age category, urban/rural residence, relative wealth quintile, birth order, respondent's education and the time elapsed for the index birth and the survey. Morbidly obese women in the highest BMI category had 3.5 times the odds of caesarean delivery compared to women in the optimal weight category (Pooled OR: 3.55; 95% CI: 2.25-5.61).

The relationship between BMI category and caesarean delivery was similar across all geographic regions. The magnitude of the effect did appear slightly smaller across all BMI categories in Southern Africa, but this effect could be due to chance since there was some overlap in the confidence intervals.

The effect of age increased in the multivariable model. Women living in urban areas were still more likely to deliver by caesarean section after accounting for confounding, but the

magnitude of the association was substantially reduced compared to in the unadjusted analysis (Pooled OR: 1.17; 95% CI: 1.03-1.33).

The size of effect of wealth was also reduced in the multivariable model. Although it still represented a substantial risk factor and women in the richest wealth quintile had 2.8 times the odds of delivering via caesarean section, compared to the poorest group (Pooled OR: 2.82; 95% CI: 2.27-3.49).

In the multivariable model, parity had a similar effect to the unadjusted results. Women for whom the index birth was the first birth had 1.8 times the odds of caesarean delivery, a slight increase in magnitude from previously but the confidence intervals still overlapped (Pooled OR: 1.80; 95% CI: 1.58-2.05). Higher parity women remained less likely to deliver by caesarean section.

The effect of education was attenuated in the multivariable model, although it remained statistically significant. Women with secondary education or more had 1.9 times the odds of caesarean delivery compared to women with no education (1.93; 95% CI: 1.62-2.29).

In order to investigate whether the dose-response effect of BMI existed in the multivariable model the model was re-run, once using BMI as a categorical exposure and once using BMI as a continuous variable, assuming a linear fit. An F-adjusted mean residual test was used to compare the fit of the two models; a large p-value suggests that the observed data fit the model well. The model fit is compared in Table 8.4. The F-adjusted mean residual test was unable to distinguish between the fit of the two models; both fit the data equally well. However, the trend in the magnitude of the odds ratios observed was indicative of a dose-response effect, as the size of the effect increased with increasing BMI and there was no overlap in the confidence intervals of the effect amongst pre-obese women and women in the most severely obese (obese class III) category.

8.1.4 Effect Modification

An *a priori* decision was made to test for interaction between (i) BMI and age, and (ii) BMI parity using the Wald test. There was no significant evidence of effect modification according to parity (F=0.42; p=0.9566) however, the test for age category showed borderline evidence for interaction (F=1.56; p=0.0579). As the Wald test for interaction has low power I decided to investigate stratum-specific odds ratios for age category; these are presented in Table 8.5. There was no substantial effect modification of the effect of BMI by age category and the odds ratios were similar across each stratum.

Table 8.3 Multivariable model of the odds of caesarean delivery

Risk Factor		Eastern Africa			Middle Africa			Southern Africa			Western Africa			Pooled Sub-Saharan Africa		
		OR	[95% CI]	p	OR	[95% CI]	p	OR	[95% CI]	p	OR	[95% CI]	p	OR	[95% CI]	p
BMI Category	Optimal	1.00			1.00			1.00			1.00			1.00		
	Pre-Obese	1.62	[1.33, 1.97]	<0.001	2.51	[1.66, 3.78]	<0.001	1.17	[0.89, 1.54]	0.263	1.76	[1.48, 2.10]	<0.001	1.63	[1.45, 1.83]	<0.001
	Obese Class I	2.13	[1.57, 2.90]	<0.001	2.39	[1.29, 4.42]	0.006	1.82	[1.31, 2.51]	<0.001	2.44	[1.89, 3.15]	<0.001	2.20	[1.88, 2.59]	<0.001
	Obese Class II	4.18	[2.39, 7.28]	<0.001	5.77	[2.22, 14.99]	<0.001	2.11	[1.26, 3.52]	0.004	3.01	[1.93, 4.70]	<0.001	3.09	[2.34, 4.09]	<0.001
	Obese Class III	4.88	[1.73, 13.79]	0.003	5.40	[0.70, 41.68]	0.105	2.48	[1.20, 5.11]	0.014	3.55	[1.78, 7.08]	<0.001	3.55	[2.25, 5.61]	<0.001
Age Group	20-24 years	1.00			1.00			1.00			1.00			1.00		
	25-29 years	1.67	[1.34, 2.08]	<0.001	1.05	[0.66, 1.69]	0.825	1.16	[0.84, 1.61]	0.364	1.53	[1.20, 1.95]	0.001	1.46	[1.27, 1.68]	<0.001
	30-34 years	2.42	[1.86,3.13]	<0.001	1.05	[0.59, 1.88]	0.871	1.84	[1.29, 2.64]	0.001	1.95	[1.48, 2.57]	<0.001	1.99	[1.69, 2.34]	<0.001
	35-39 years	2.59	[1.88, 3.57]	<0.001	0.99	[0.48, 2.05]	0.975	2.16	[1.42, 3.29]	<0.001	2.70	[1.96, 3.71]	<0.001	2.39	[1.97, 2.90]	<0.001
	40-44 years	4.23	[2.92, 6.12]	<0.001	1.93	[0.74, 5.03]	0.178	1.96	[1.11, 3.45]	0.020	3.04	[2.05, 4.49]	<0.001	3.04	[2.40, 3.85]	<0.001
	45-49 years	3.54	[1.93, 6.50]	<0.001	0.72	[0.19, 2.71]	0.626	4.72	[2.33, 9.57]	<0.001	2.59	[1.45, 4.63]	0.001	2.94	[2.09, 4.14]	<0.001
Area of Residence	Rural	1.00			1.00			1.00			1.00			1.00		
	Urban	1.12	[0.89, 1.41]	0.323	1.29	[0.79, 2.12]	0.305	1.35	[1.04, 1.76]	0.027	1.07	[0.88,1.30]	0.485	1.17	[1.03, 1.33]	0.016
Relative Wealth Quintile	Poorest	1.00			1.00			1.00			1.00			1.00		
	Poorer	1.26	[0.90, 1.77]	0.181	1.19	[0.55, 2.60]	0.661	1.28	[0.88, 1.88]	0.200	1.74	[1.21, 2.50]	0.003	1.36	[1.11, 1.67]	0.003
	Middle	1.27	[0.91, 1.77]	0.152	1.13	[0.52, 2.43]	0.761	1.27	[0.83, 1.94]	0.276	1.86	[1.29, 2.69]	0.001	1.39	[1.13, 1.70]	0.002
	Richer	1.86	[1.37, 2.54]	<0.001	1.52	[0.66, 3.53]	0.329	1.81	[1.20, 2.71]	0.004	3.11	[2.18, 4.45]	<0.001	2.10	[1.72, 2.56]	<0.001
	Richest	2.72	[1.93, 3.83]	<0.001	1.68	[0.68, 4.10]	0.258	2.34	[1.53, 3.59]	<0.001	4.04	[2.76, 5.92]	<0.001	2.82	[2.27, 3.49]	<0.001
Parity	First birth	1.80	[1.46, 2.21]	<0.001	1.28	[0.76, 2.14]	0.354	1.65	[1.25, 2.18]	<0.001	2.02	[1.61, 2.53]	<0.001	1.80	[1.58, 2.05]	<0.001
	2-3 previous births	1.00			1.00			1.00			1.00			1.00		
	4-5 previous births	0.46	[0.36, 0.58]	<0.001	0.47	[0.28, 0.78]	0.004	0.48	[0.32, 0.71]	<0.001	0.61	[0.49, 0.75]	<0.001	0.52	[0.45, 0.60]	<0.001
	6+ previous births	0.28	[0.21, 0.38]	<0.001	0.49	[0.23, 1.03]	0.058	0.56	[0.32, 0.96]	0.036	0.40	[0.30, 0.53]	<0.001	0.37	[0.31, 0.44]	<0.001
Education	No education	1.00			1.00			1.00			1.00			1.00		
	Primary only	1.39	[1.05, 1.84]	<0.001	1.31	[0.57, 2.99]	0.522	1.57	[0.85, 2.90]	0.149	1.69	[1.37 2.08]	<0.001	1.56	[1.33, 1.82]	<0.001
	Secondary or more	1.95	[1.41, 2.70]	<0.001	1.35	[0.55, 3.35]	0.513	2.09	[1.13, 3.87]	0.019	1.82	[1.44, 2.30]	<0.001	1.93	[1.62, 2.29]	<0.001
Time elapsed (months)		1.00	[0.99, 1.00]	0.263	1.01	[1.00, 1.02]	0.230	1.00	[0.99, 1.01]	0.651	1.00	[1.00. 1.01]	0.750	1.00	[1.00, 1.00]	0.752

Estimates adjusted for all other covariates in the model. Sampling weights and survey design taken into account in the analysis

Table 8.4 Comparison of BMI as a categorical versus continuous risk factor

Risk Factor		Pooled Sub-Saharan Africa			
		OR	[95% CI]		p-value
BMI Category	Optimal (18.5-24.9 kg/m^2)	1.00			
	Pre-Obese (25-29.9 kg/m^2)	1.63	1.45	1.83	<0.001
	Obese Class I (30-34.9 kg/m^2)	2.20	1.88	2.59	<0.001
	Obese Class II (35-39.9 kg/m^2)	3.09	2.34	4.09	<0.001
	Obese Class III (≥40 kg/m^2)	3.55	2.25	5.61	<0.001
F =1.15; p= 0.325					
Risk Factor		**Pooled Sub-Saharan Africa**			
		OR	**[95% CI]**		**p-value**
per increase unit BMI (kg/m^2)		1.07	1.06	1.08	<0.001
F = 1.11; p= 0.354					

Estimates adjusted for age group, urban/rural residence, wealth quintile, parity, education and time elapsed. Sampling weights and survey design taken into account in the analysis

Table 8.5 Stratum-specific odds ratios for the effect of BMI in each age group in the Pooled Dataset

Stratum		OR	[95% CI]		p-value
Increase in odds of caesarean delivery per unit increase BMI (kg/m^2)	20-24 years	1.08	1.06	1.11	<0.001
	25-29 years	1.08	1.06	1.10	<0.001
	30-34 years	1.05	1.03	1.07	<0.001
	35-39 years	1.08	1.06	1.10	<0.001
	40-44 years	1.09	1.06	1.12	<0.001
	45-49 years	1.10	1.05	1.14	<0.001

Estimates adjusted for urban/rural residence, wealth quintile, parity, education and time elapsed. Sampling weights and survey design taken into account in the analysis

8.1.5 Summary

The odds of caesarean section rise with increasing maternal BMI category; a clear dose-response effect is observable. Women who are morbidly obese have over three times the odds of delivering by caesarean section compared to women of optimal body weight (Obese Class III OR: 3.55; 95% CI: 2.25-5.6). For each unit increase in BMI (kg/m^2) the odds of caesarean deliver increase by 7% (OR: 1.07; 95% CI: 1.06-1.08).

A similar effect exists across all geographic regions in Sub-Saharan Africa and no effect modification was observed by either maternal age or parity.

8.2 Maternal Overweight/Obesity and Neonatal Death

8.2.1 Sample Description

A total of 73,545 women were included in analysis (Table 8.6). The smallest contribution was from Uganda with 964 births and the largest sample size was Nigeria with 10,324 women. The proportion of births resulting in a neonatal death ranged between 0.8% (Zimbabwe) and 2.5% (Guinea); overall 1.63% of women experienced a neonatal death after the index birth.

Table 8.6 Sample description

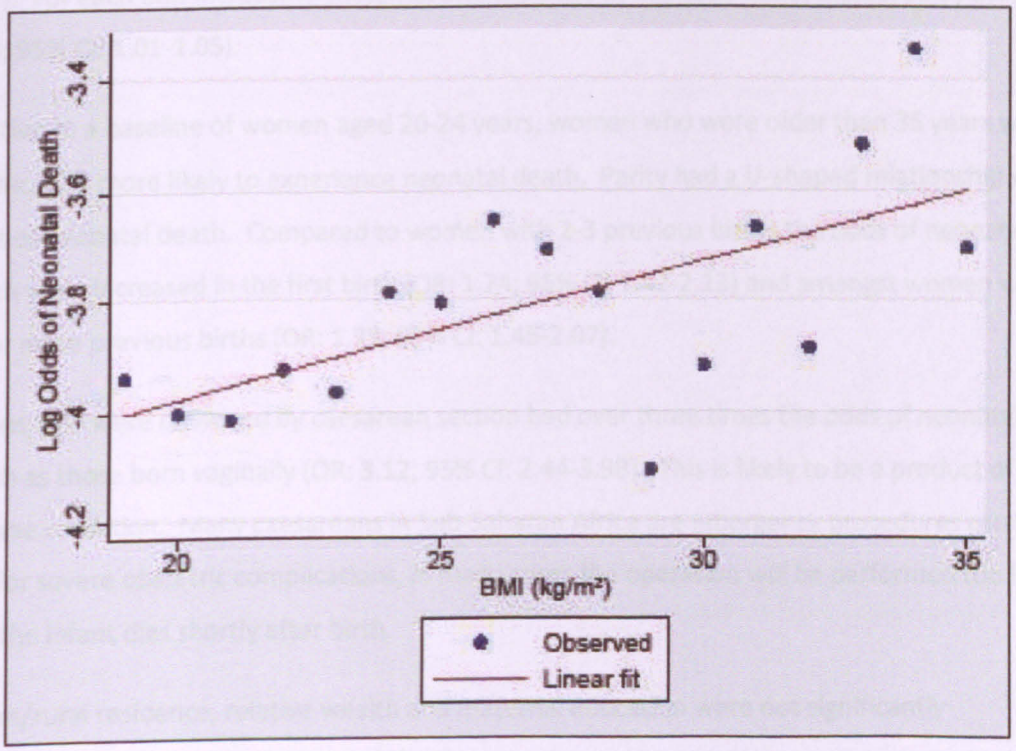
Country (year)		*n*	Neonatal Deaths (%)	Maternal BMI Category		
				Optimal	Pre-Obese	Obese
Eastern Africa	Ethiopia	1,574	1.7%	94.9%	4.1%	1.0%
	Kenya	2,501	1.7%	72.2%	20.5%	7.2%
	Madagascar	2,031	1.4%	91.9%	7.0%	1.2%
	Malawi	4,366	1.2%	85.7%	12.0%	2.3%
	Mozambique	4,141	2.0%	85.5%	10.9%	3.6%
	Rwanda	1,863	1.5%	87.5%	11.3%	1.2%
	Tanzania	3,475	1.3%	81.4%	14.2%	4.4%
	Uganda	964	0.8%	81.0%	14.1%	5.0%
	Zambia	2,510	2.2%	79.8%	15.4%	4.9%
	Zimbabwe	2,823	0.8%	73.4%	20.1%	6.5%
	Pooled	**26,248**	**1.5%**	**82.9%**	**13.3%**	**3.8%**
Middle Africa	Cameroon	1,691	1.7%	68.9%	22.8%	8.3%
	Chad	1,578	1.8%	90.2%	7.5%	2.4%
	Congo	2,136	1.3%	67.5%	22.9%	9.6%
	DRC	1,503	1.8%	85.3%	11.9%	2.9%
	Pooled	**6,908**	**1.6%**	**77.0%**	**16.9%**	**6.1%**
Southern Africa	Lesotho	1,048	2.2%	54.6%	27.8%	17.7%
	Namibia	2,585	1.4%	62.4%	22.8%	14.8%
	Swaziland	1,590	1.4%	42.1%	32.3%	25.7%
	Pooled	**5,223**	**1.5%**	**54.6%**	**26.7%**	**18.7%**
Western Africa	Benin	6,373	1.3%	79.8%	14.7%	5.5%
	Burkina Faso	3,911	1.8%	89.4%	8.2%	2.5%
	Ghana	1,439	1.5%	66.0%	24.8%	9.2%
	Guinea	1,325	2.5%	84.2%	12.2%	3.6%
	Liberia	2,501	1.5%	78.4%	15.8%	5.8%
	Mali	5,155	1.7%	80.0%	14.9%	5.1%
	Niger	1,619	1.2%	82.1%	14.0%	3.9%
	Nigeria	10,324	2.1%	72.8%	20.0%	7.2%
	Senegal	1,304	1.9%	72.1%	19.0%	8.9%
	Sierra Leone	1,215	2.0%	71.6%	21.8%	6.7%
	Pooled	**35,166**	**1.8%**	**77.9%**	**16.3%**	**5.8%**
Pooled, all Sub-Saharan Africa		**73,545**	**1.6%**	**78.0%**	**16.0%**	**6.0%**

Sampling weights used

8.2.2 Univariable Analysis

Figure 8-B presents the observed odds versus the predicted linear odds of neonatal death in the unadjusted analysis. Neonatal death is a rare event and the observed events showed some degree of noise around the linear regression line, but an increasing trend is still discernible.

Figure 8-B Observed versus linear predicted odds of neonatal death



Infants born to pre-obese mother had 22% increased odds of death during the neonatal period (OR: 1.22; 95% CI: 1.03-1.46) whilst babies born to obese mothers had 52% increased odds (OR: 1.52; 95% CI: 1.18-1.97). For each unit increase in maternal BMI the odds of neonatal death increased by 3% (OR: 1.03; 95% CI: 1.01-1.05).

Relative to a baseline of women aged 20-24 years, women who were older than 35 years were significantly more likely to experience neonatal death. Parity had a U-shaped relationship with odds of neonatal death. Compared to women with 2-3 previous births the odds of neonatal death were increased in the first birth (OR: 1.74; 95% CI: 1.42-2.13) and amongst women with six or more previous births (OR: 1.73; 95% CI: 1.45-2.07). Babies who were delivered by caesarean section had over three times the odds of neonatal death as those born vaginally

(OR: 3.12; 95% CI: 2.44-3.98). This is likely to be a product of reverse causation. Many caesareans in Sub-Saharan Africa are emergency procedures carried out for severe obstetric complications, in many cases the operation will be performed too late and the infant dies shortly after birth.

Urban/rural residence, relative wealth and maternal education were not significantly associated with the odds of neonatal death. Table 8.7 presents the unadjusted relationship between each of the confounders in the model and neonatal death. Infants born to pre-obese mother had 22% increased odds of death during the neonatal period (OR: 1.22; 95% CI: 1.03-1.46) whilst babies born to obese mothers had 52% increased odds (OR: 1.52; 95% CI: 1.18-1.97). For each unit increase in maternal BMI the odds of neonatal death increased by 3% (OR: 1.03; 95% CI: 1.01-1.05).

Relative to a baseline of women aged 20-24 years, women who were older than 35 years were significantly more likely to experience neonatal death. Parity had a U-shaped relationship with odds of neonatal death. Compared to women with 2-3 previous births the odds of neonatal death were increased in the first birth (OR: 1.74; 95% CI: 1.42-2.13) and amongst women with six or more previous births (OR: 1.73; 95% CI: 1.45-2.07).

Babies who were delivered by caesarean section had over three times the odds of neonatal death as those born vaginally (OR: 3.12; 95% CI: 2.44-3.98). This is likely to be a product of reverse causation. Many caesareans in Sub-Saharan Africa are emergency procedures carried out for severe obstetric complications, in many cases the operation will be performed too late and the infant dies shortly after birth.

Urban/rural residence, relative wealth and maternal education were not significantly associated with the odds of neonatal death.

Table 8.7 Unadjusted risk factors for neonatal death

Risk Factor		Proportion (%) or Mean	OR	[95% CI]	p-value
BMI Category	Optimal	78.0%	1.00		
	Pre-Obese	16.0%	1.22	[1.03, 1.46]	0.024
	Obese	6.0%	1.52	[1.18, 1.97]	0.001
BMI		23.18	1.03	[1.01, 1.05]	<0.001
Age Group	20-24 years	24.5%	1.00		
	25-29 years	27.0%	0.92	[0.76, 1.12]	0.404
	30-34 years	20.8%	0.98	[0.78, 1.21]	0.827
	35-39 years	15.4%	1.36	[1.10, 1.69]	0.005
	40-44 years	8.6%	1.55	[1.21, 1.98]	<0.001
	45-49 years	3.6%	2.37	[1.76, 3.19]	<0.001
Area of Residence	Rural	69.9%	1.00		
	Urban	30.1%	1.06	[0.92, 1.23]	0.424
Relative Wealth Quintile	Poorest	19.4%	1.00		
	Poorer	19.7%	0.95	[0.77, 1.18]	0.660
	Middle	20.0%	1.11	[0.90, 1.38]	0.320
	Richer	20.6%	1.26	[1.02, 1.55]	0.032
	Richest	20.3%	1.05	[0.84, 1.31]	0.665
Parity	First birth	14.9%	1.74	[1.42, 2.13]	<0.001
	Para 2-3	34.8%	1.00		
	Para 2-5	24.2%	1.12	[0.92, 1.37]	0.247
	Para 6+	26.1%	1.73	[1.45, 2.07]	<0.001
Respondent's Education	No education	42.9%	1.00		
	Primary only	33.9%	1.10	[0.92, 1.32]	0.286
	Secondary or more	23.2%	1.11	[0.91, 1.35]	0.291
Mode of Delivery at Index Birth	Vaginal	96.2%	1.00		
	Caesarean	3.8%	3.12	[2.44, 3.98]	<0.001
Time elapsed (months)		22.76	1.00	[1.00, 1.01]	0.823

Sampling weights and survey design taken into account in the analysis

8.2.3 Multivariable Model

The multivariable model was only constructed for the pooled dataset for the neonatal outcome, due to a lack of statistical power to perform regional analyses. Table 8.8 shows the risk factors for neonatal death, adjusted for all other confounders in the model.

Babies born to obese mothers remained at significantly increased odds of death during the neonatal period, compared to those whose mothers were of optimal weight (OR: 1.34; 95% CI: 1.02-1.75). However, the relationship amongst pre-obese mothers lost statistical significance at the 5% level (OR: 1.13; 95% CI: 0.95-1.36).

The magnitude of the association between maternal age and neonatal death increased slightly in the multivariable model compared to the unadjusted association, but it remained statistically significant only for those mothers older than 35 years.

Compared to women with 2-3 previous births the odds of neonatal death were still increased at the first birth (OR: 1.83; 95% CI: 1.48-2.28); however having six or more previous births lost significance as a risk factor for neonatal death after adjustment for the other variables in the model.

The relationship between mode of delivery and neonatal death was very similar in both the unadjusted and multivariable models. After adjustment, babies born by caesarean were had around three times the odds of death during the neonatal period (OR: 2.96; 95% CI: 2.27-3.87).

Urban/rural residence, relative wealth and maternal education were not significantly associated with the odds of neonatal death in the multivariable model.

Table 8.8 Multivariable model of the odds of neonatal death

Risk Factor		OR	[95% CI]	p-value
BMI Category	Optimal	1.00		
	Pre-Obese	1.13	[0.95, 1.36]	0.170
	Obese	1.34	[1.02, 1.75]	0.035
Age Group	20-24 years	1.00		
	25-29 years	1.12	[0.90, 1.39]	0.309
	30-34 years	1.22	[0.93, 1.58]	0.147
	35-39 years	1.69	[1.26, 2.27]	<0.001
	40-44 years	1.93	[1.39, 2.68]	<0.001
	45-49 years	2.97	[2.03, 4.35]	<0.001
Area of Residence	Rural	1.00		
	Urban	1.00	[0.82, 1.20]	0.963
Relative Wealth Quintile	Poorest	1.00		
	Poorer	0.94	[0.76, 1.17]	0.586
	Middle	1.08	[0.87, 1.34]	0.498
	Richer	1.15	[0.92, 1.44]	0.222
	Richest	0.88	[0.65, 1.17]	0.378
Parity	First birth	1.83	[1.48, 2.28]	<0.001
	Para 2-3	1.00		
	Para 2-5	0.98	[0.79, 1.21]	0.829
	Para 6+	1.17	[0.91, 1.49]	0.214
Respondent's Education	No education	1.00		
	Primary only	1.12	[0.93, 1.35]	0.226
	Secondary or more	1.03	[0.81, 1.32]	0.802
Mode of Delivery at Index Birth	Vaginal	1.00		
	Caesarean	2.96	[2.27, 3.87]	<0.001
Time elapsed (months)		0.99	[0.99, 1.00]	0.022

Estimates adjusted for all other factors in model. Sampling weights and survey design taken into account

8.2.4 Effect Modification

An *a priori* decision was made to test for interaction between BMI category and age category; BMI category; and parity and BMI category and mode of delivery. There was no significant evidence of effect modification according to age category (F=0.93; p=0.5058) or parity (F=1.17; p=0.3194). However, the test for mode of delivery showed some evidence of effect modification (F=3.16; p=0.0424) and so stratum-specific odds ratios were calculated. These are presented in Table 8.9.

Table 8.9 Stratum-specific odds ratios by mode of delivery

Stratum		Adjusted OR	[95% CI]	p-value
Women who had a vaginal birth:				
BMI Category	Optimal	1.00		
	Pre-Obese	1.18	[0.98, 1.42]	0.086
	Obese	1.54	[1.16, 2.05]	0.003
Women who delivered by caesarean:				
BMI Category	Optimal	1.00		
	Pre-Obese	0.82	[0.48, 1.40]	0.456
	Obese	0.68	[0.38, 1.24]	0.210

Estimates adjusted for age group, urban/rural residence, wealth quintile, parity, education and time elapsed. Sampling weights and survey design taken into account in the analysis

The magnitude of the effect of maternal obesity was slightly increased amongst the vaginal deliveries. Amongst women who delivered by caesarean, the results were statistically insignificant, but there was the appearance of a protective effect. This could be an artefact; due to the very small numbers in this group (only 23 women were obese, delivered by caesarean and experienced a neonatal death). However, it could also be an effect of residual confounding. In some areas of Sub-Saharan Africa the elite socio-economic groups will have a pre-booked caesarean section; this would be expected to carry a low risk of neonatal death so the suggested protective effect could be real.

Infants born by caesarean section are all at an increased risk of neonatal death (OR: 2.96; 95% CI: 2.27-3.87). Therefore the results presented in Table 8.9 were re-calculated so that the lowest risk group (optimal weight women who had a vaginal birth) formed the baseline. These are presented in Table 8.10.

Table 8.10 Stratum-specific odds ratios by mode of delivery

Stratum		Adjusted OR	[95% CI]	p-value
Women who had a vaginal birth:				
BMI Category	Optimal	1.00		
	Pre-Obese	1.18	[0.98, 1.42]	0.086
	Obese	1.54	[1.16, 2.05]	0.003
Women who delivered by caesarean:				
BMI Category	Optimal	3.78	[2.71, 5.25]	<0.001
	Pre-Obese	3.07	[1.93, 4.88]	<0.001
	Obese	2.58	[1.50, 4.43]	0.001

Estimates adjusted for age group, urban/rural residence, wealth quintile, parity, education and time elapsed. Sampling weights and survey design taken into account in the analysis

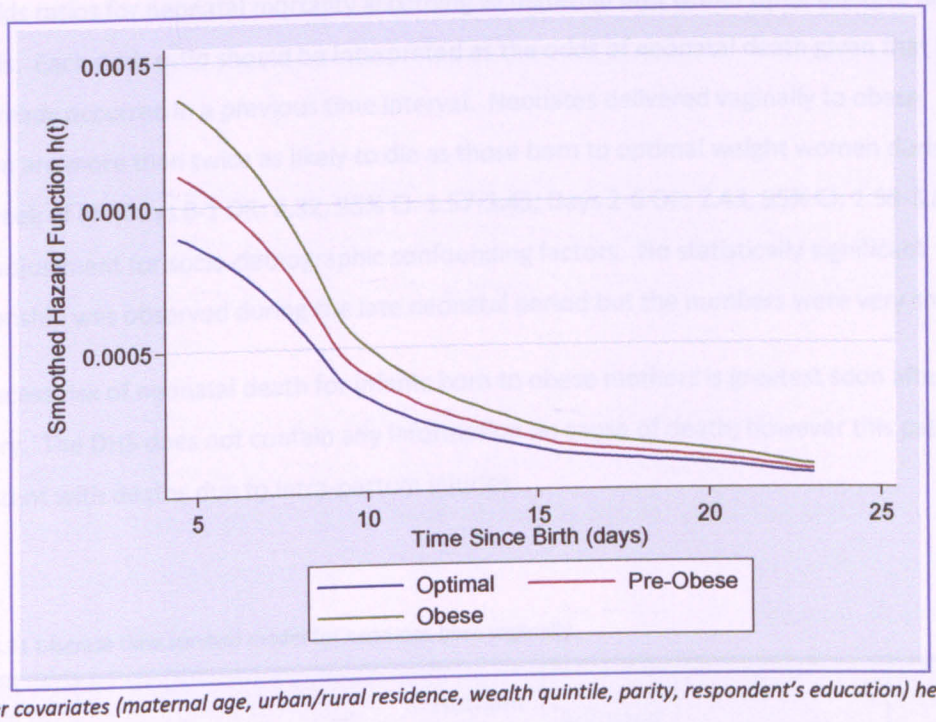
8.2.5 Timing of Neonatal Death

I subsequently estimated the effect of maternal BMI category on the timing of neonatal death. For this analysis the caesarean deliveries were excluded.

Figure 8-C shows the daily hazard of death for infants during the neonatal period stratified by maternal BMI with all other covariates held at the mean value, and Figure 8-D shows daily survivorship.

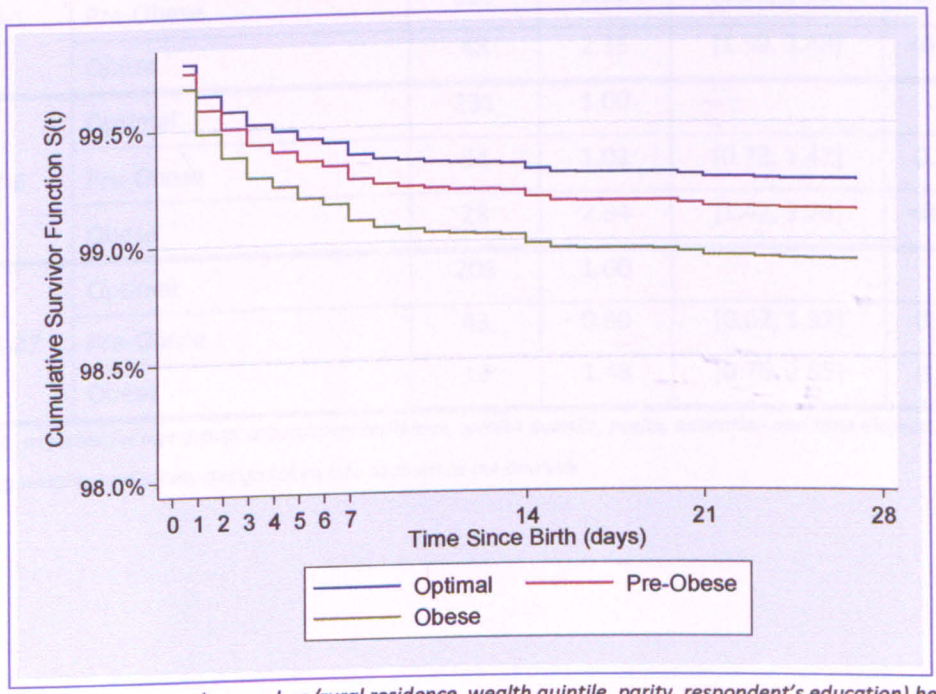
As to be expected, the risk of death is greatest early in the neonatal period for all infants, regardless of maternal BMI. However infants born to obese mothers have a greater excess hazard compared to those born to women of optimal weight. This differential is reduced after the first week of life, and from around the eighth day of life onwards the hazard curves appear to be parallel, although the hazard is still slightly elevated amongst infants born to obese mothers.

Figure 8-C Smoothed hazard function for infant survival in the first month of life



All other covariates (maternal age, urban/rural residence, wealth quintile, parity, respondent's education) held at mean values

Figure 8-D Daily survivorship for infants in the first month of life



All other covariates (maternal age, urban/rural residence, wealth quintile, parity, respondent's education) held at mean values

In order to quantify this, I constructed a discrete-time survival analysis. Table 8.11 provides the odds ratios for neonatal mortality according to maternal BMI within three discrete time periods. Each odds ratio should be interpreted as the odds of neonatal death given that it has not already occurred in a previous time interval. Neonates delivered vaginally to obese women are more than twice as likely to die as those born to optimal weight women during the first week of life(Days 0-1 OR: 2.32, 95% CI: 1.57-3.43; Days 2-6 OR: 2.43, 95% CI: 1.53-3.88), after adjustment for socio-demographic confounding factors. No statistically significant relationship was observed during the late neonatal period but the numbers were very small.

The excess risk of neonatal death for infants born to obese mothers is greatest soon after delivery. The DHS does not contain any information on cause of death; however this pattern is consistent with deaths due to intra-partum injuries.

Table 8.11 Discrete time survival model for neonates born vaginally

Timing of Neonatal Death	Maternal BMI Category	Number of Deaths	Adjusted OR	[95% CI]	p-value
Days 0-1	Optimal	370	1.00		
	Pre-Obese	105	1.22	[0.95, 1.55]	0.119
	Obese	48	2.35	[1.59, 3.48]	<0.001
Days 2-6	Optimal	231	1.00		
	Pre-Obese	54	1.02	[0.73, 1.41]	0.923
	Obese	28	2.34	[1.47, 3.74]	<0.001
Days 7-27	Optimal	205	1.00		
	Pre-Obese	43	0.90	[0.62, 1.32]	0.576
	Obese	13	1.48	[0.76, 2.85]	0.246

Estimates adjusted for age group, urban/rural residence, wealth quintile, parity, education and time elapsed. Sampling weights and survey design taken into account in the analysis

8.2.6 Summary

Maternal obesity significantly increased the odds of neonatal death (OR: 1.34; 95% CI: 1.02-1.75). However, the effect of maternal BMI was modified by mode of delivery (caesarean or vaginal).

Stratum-specific odds ratios were calculated. The magnitude of the association was slightly increased amongst vaginal deliveries (OR: 1.54; 95% CI: 1.16-2.05) but amongst caesarean deliveries there was the appearance of a protective effect, although this observation was statistically insignificant.

Timing of neonatal death was investigated amongst the vaginal deliveries. As expected, the risk of death is greatest early in the neonatal period for all infants, regardless of maternal BMI. However infants born to obese mothers have a greater excess hazard compared to those born to women of optimal weight. In the first week of life infants born to obese mothers have more than two times the odds of death compared to those born to mothers of optimal weight (Day 0-1 OR: 2.35; 95% CI: 1.59-3.48; Day 2-6 OR: 2.34; 95% CI: 1.47-3.74).

Chapter 9
DISCUSSION

The overall aim of this thesis was to investigate the effect of obesity on reproductive health in Sub-Saharan Africa. My analysis focused on three outcomes (reduced fecundity, caesarean delivery and neonatal death) available within the DHS. Therefore the research questions for this thesis were:

1. Is high BMI a risk factor for reduced female fecundity in the low-income, high-fertility setting of Sub-Saharan Africa?
2. Is high BMI a risk factor for adverse pregnancy outcomes in Sub-Saharan Africa?
    a. What is the effect of increased maternal BMI on the odds of delivery by caesarean section in Sub-Saharan Africa?
    b. What is the effect of increased maternal BMI on the odds of neonatal death in Sub-Saharan Africa?

In this section I will summarise the findings of this thesis, reviewing the extent to which I was able to answer the above research questions and explaining how my findings integrate with previous work. I shall then go on to consider the strengths and limitations of my thesis. The chapter concludes with a discussion of the public health implications of the research and suggestions for future research.

9.1 Summary of the Main Findings

9.1.1 Sub-Saharan Africa and the Nutrition Transition

Chapter 4 showed that there is substantial variation in the prevalence of overweight/obesity in Sub-Saharan Africa. The proportion of adult women who are overweight ranges from less than 5% of the population in Ethiopia to just over 50% in Swaziland. Prevalence of overweight is generally highest in Middle and Southern Africa.

The relationship between overweight and relative wealth quintile in most countries in Sub-Saharan Africa suggests that the nutrition transition is still in the initial stages. The relationship between proportion overweight and socio-economic status is a good guide to the current stage of a country within the nutrition transition [137-138]; in the early stages obesity is rare in a population, and nearly only occurs amongst the richest elite. As the transition progresses the relationship between wealth and overweight becomes linear, then eventually reverses as obesity becomes a problem of the poorest social groups and the elite adopt healthier lifestyle behaviours [154]. Work presented in Chapter 4 showed that most countries in Sub-Saharan obesity is a characteristic of the elite population groups, in line with earlier DHS analysis [163]. However, there are exceptions: an approximately linear relationship between obesity and wealth quintile was observed in Cameroon, Congo, Kenya, Lesotho, Namibia and Swaziland indicating a rise in BMI throughout the population.

The effect of relative wealth on the odds of being overweight varied according to whether an individual lived in an urban or rural area. Whilst the richest women were the most likely to be overweight in all regions, the magnitude of this effect was strongest amongst urban dwellers. In Southern Africa there was no association between urban/rural residence in the top three wealth quintiles as, in contrast to the rest of Sub-Saharan Africa, there were similarly high proportions of overweight women living in both rural and urban areas.

Other evidence in support of the hypothesis that some countries in Sub-Saharan Africa may have entered transition may be obtained from examining trends in the age-specific median BMI in those countries where several nationally-representative cross-sectional surveys now exist, as presented in Chapter 5. The age-specific median BMI profile of women in Zambia has remained relatively consistent over recent successive surveys conducted between 1992 and 2007. However, in Ghana and to a lesser extent Kenya, a shift in the age-specific median BMI of women is observable during the most recent surveys (2003 and 2008) compared to data collected during the 1990s. Women aged 30-34 years in Ghana in 2008 had a median BMI 2.23 kg/m^2 greater than their counterparts in 1998, a very sizeable shift to occur in a population-averaged measure during just one decade.

In global terms prevalence of overweight/obesity in Sub-Saharan Africa is currently relatively low. However, there is evidence to suggest that in several countries average BMI is increasing rapidly, and it is likely that this trend will be shortly observed in other countries as urbanisation and economic development progress. Obesity is therefore set to be an important public health issue in Africa in the twenty-first century.

9.1.2 Obesity and Reduced Fecundity

My thesis investigated whether high BMI is a risk factor for reduced female fecundity in the low-income, high-fertility setting of Sub-Saharan Africa.

The most valid and appropriate way of measuring underlying fecundity is through time to conception. The results of the systematic review (Chapter 6) showed that increased BMI is associated with increased waiting time to conception in most published studies, although it was not possible to generate a single pooled effect estimate to quantify this effect due to heterogeneity in the design and analysis of the retrieved studies. All of the studies were limited by the use of a retrospective design, which caused the effect estimate to be conditioned on pregnancy and excluded completely infertile women. Furthermore, no studies were identified from low-income settings. The systematic review this identified two important gaps in the literature.

My quantitative analysis for the research question on reduced fecundity investigated two complementary outcomes (i) subfertility, a dichotomous outcome designed to proxy clinical infertility; and (ii) time from marriage to first conception, analogous to the TTP studies identified in my systematic review but with the theoretical advantage of sampling all women regardless of underlying fecundity.

In the pooled Sub-Saharan dataset, women who were pre-obese had 35% increased odds of subfertility (OR: 1.35; 95% CI 1.24-1.47) and women who were obese had 51% increased odds of subfertility (OR: 1.51; 95% CI 1.35-1.69) after adjusting for socio-demographic confounders. The F-adjusted mean residual test did not distinguish between the model with a linear dose-response effect of BMI and the categorical model; however the magnitude of the effect estimates suggested a possible threshold effect (occurring around a cut-off of around 30kg/m^2) although this observation could not be tested or explored further due to the small numbers of women who were morbidly obese.

A significant relationship between BMI category and odds of subfertility was observed in Eastern Africa and Western Africa, but not in Middle Africa or Southern Africa. Three potential

reasons for this observation are: (i) BMI truly has no effect on subfertility in Middle and Southern Africa; (ii) the study was underpowered in these two regions; (iii) the subfertility indicator performed poorly in these regions due to higher contraceptive prevalence and lower overall fertility rates [86]. The results of the sensitivity analysis, excluding ever-users of contraception suggest that both (ii) and (iii) may play a role, although the possibility of obesity having no effect in Middle or Southern Africa cannot be excluded. Once ever-users of contraception were excluded from the analysis, obese women were significantly more likely to be subfertile in Middle Africa (OR: 2.50; 95% CI: 1.13-5.55). No significant effect was observed amongst pre-obese women in Middle Africa (OR: 0.95; 95% CI: 0.58-1.57). However, in Southern Africa, no significant relationship was found between BMI category and odds of subfertility even after ever-users of contraception were excluded from the dataset (Pre-Obese OR: 0.55; 95% CI: 0.23-1.31; Obese OR: 0.82; 95% CI: 0.26-1.57) but, particularly for obese women, the confidence intervals were very wide. Both Middle and Southern Africa have relatively high contraceptive usage and it has been noted in previous work that using birth history data to construct measures of infertility becomes substantially less reliable once fertility control becomes prevalent in a population [18, 62].

The second fecundity-related analysis, investigated survival time between first marriage and first conception; by doing this I aimed to complement the subfertility analysis by providing a more valid measure of underlying fecundity. The most important limitation of my subfertility analysis was my inability to adequately control for contraceptive usage and without data on current fertility intentions (i.e. if a woman was actively attempting pregnancy at any given point in time) I could not determine if a woman was limiting her fertility through other means, such as frequency of intercourse [211-212]. Therefore the time to conception analysis was restricted to women married within the preceding five years, as it is reasonable to assume that nulliparous, recently married women will wish to become pregnant.

Obesity was not significantly associated with reduced odds of conception in Sub-Saharan Africa (OR: 0.91; 95% CI: 0.73-1.12). However, the direction and magnitude of the effect estimate observed was relatively consistent with that observed from larger studies in high-income settings [305-306] and the sample in this thesis may have had insufficient power to detect a difference, particularly given the relatively young age of the sample and consequent very low prevalence of obesity.

These findings represent the first investigation of overweight/obesity as a harmful exposure for reduced fecundity in Sub-Saharan Africa.

An important distinction between the results from the two Sub-Saharan analyses is that the endpoint used to define the outcome differs; the subfertility analysis necessarily uses live birth as the endpoint due to a lack of reliable data on abortions and miscarriages; whilst the survival analysis investigates time to first conception regardless of whether the pregnancy ended in a termination or a live birth. Excess adiposity is detrimental to both conception chances and successful gestation [38, 323]. However, since the underlying biological mechanisms may differ, it is conceptually preferable that conception should be used as the endpoint for a fecundity outcome analysis wherever the data allows, and additional separate analyses conducted for the risk of pregnancy termination if required. This may have contributed to the stronger exposure effect observed in the subfertility analysis: both women experiencing difficulties in conception and gestation would have been classified as subfertile, whereas a woman who was able to conceive but subsequently found it difficult to carry her pregnancy to term would be classified as fertile in the TTP survival analysis.

Whilst there is ample biological evidence to suggest an association between increased adiposity and reduced fecundity is plausible [67], it is possible that the reduced fecundity observed amongst overweight women could also be at least partly explained by a complicated relationship of biological, psychological and social factors. There is some evidence from high-income countries to suggest that overweight women engage in sexual intercourse less frequently [324-325] which would reduce the number of occasions she is exposed to the risk of conception. Whilst the analyses in this thesis were restricted to ever-partnered women, obese women may also be less likely to have a sexual partner [302, 326] and in high-income settings where obesity is stigmatised may find it more difficult to find a partner [327]. Obese women may also have negative self-perceptions which may influence sexual behaviour [328]. However, this argument is less likely to hold in the Sub-Saharan setting. Qualitative interviews on body image from Sub-Saharan Africa suggest that overweight is seen as a positive attribute and is associated with wealth, beauty and success [160-161, 329]; although this perception may differ according to culture, urban/rural residence and socio-economic status [330]. It seems less likely that self-esteem or stigmatisation (self-perceived or otherwise) has an important effect on the obesity-fecundity relationship in this context.

The results of the thesis constitute the first investigation of the effect of overweight/obesity into Sub-Saharan Africa. The findings reveal that increased adiposity, as measured by high BMI, does lower fecundity amongst women in this setting, after adjustment for socio-demographic factors. Nevertheless, the magnitude of the effect of obesity remains relatively small, particularly in comparison to the effect of other non-environmental exposures such as age or parity. The observed effect in the subfertility analysis (OR: 1.55; 95% CI: 1.34-1.79) was

however similar to the size of the effect of smoking (OR: 1.61; 95% CI: 1.40-1.85) in the multivariable model which has been also been shown to reduce female fecundity in high-income countries [194-195].

9.1.3 Obesity and Adverse Pregnancy Outcomes

This thesis investigated two adverse reproductive health outcomes, caesarean delivery and neonatal death, as determined by the data available in the DHS.

The odds of delivery by caesarean section increased by around 7% for each unit increase in BMI (OR: 1.07; 95% CI: 1.06-1.08). Morbidly obese women (BMI ≥40kg/m^2) were over three times more likely to have a caesarean than women of optimal weight after adjusting for confounding factors (OR: 3.55; 95% CI: 2.25-5.61).

These results represent the first quantitative estimates of the effect of overweight/obesity on the odds of caesarean delivery from the Sub-Saharan setting. Comparison to the results of two previous systematic reviews, looking at the obesity-caesarean association in studies conducted in high-income settings, it can be seen that maternal BMI has a strikingly similar effect in Sub-Saharan Africa (Table 9.1).

Table 9.1 Comparison of my findings with previous systematic reviews

Maternal BMI Category	Chu *et al.* (2007) [41] Meta-Analysis*	Poobalan *et al.* (2009) [42] Meta-Analysis *#		Pooled Sub-Saharan Results
		All Studies	Emergency Caesareans Only	
Optimal	1.00	1.00	1.00	1.00
Pre-Obese	1.46 (1.34, 1.60)	1.53 (1.48, 1.58)	1.64 (1.55, 1.73)	1.63 (1.45, 1.83)
Obese Class I	2.05 (1.86, 2.27)	2.26 (2.04, 2.51)	2.23 (2.07, 2.42)	2.20 (1.88, 2.59)
Obese Class II	2.89 (2.28, 3.79)	3.38 (2.49, 4.57)		3.09 (2.34, 4.09)
Obese Class III				3.55 (2.25, 5.61)

** Both Chu et al. (2007) and Poobalan et al. (2009) presented crude ORs in the meta-analysis. Sensitivity analyses showed little change in the results when adjusted. Sub-Saharan data are adjusted for age, relative wealth, urban/rural residence, birth order, maternal education and partner's education.*

 # Poobalan et al. (2009) restricted their review to nulliparous women.

This is an interesting finding because the context of a caesarean delivery is often rather different in Sub-Saharan Africa to in high-income settings. Most Sub-Saharan countries have caesarean rates below the 15% rate suggested by the WHO guidelines [87]; however the proportion of caesareans performed for absolute maternal indications (complications which are likely to result in death without surgical intervention) is not routinely aggregated [331]. A

systematic review by Dumont *et al.* (2001) showed that around three quarters of caesarean births took place for maternal reasons due to severe complications such as prolonged labour or haemorrhage [89]. For comparison, whilst most women who had a caesarean in NHS Trusts in England in 2008 have at least one clinical risk factor, many of these were indicated for reasons such as a previous caesarean delivery, pre-existing hypertension or diabetes [332] which are medically less urgent procedures.

I subsequently investigated the impact of maternal obesity on the neonatal death. In the pooled Sub-Saharan dataset, babies born to obese mothers had 34% increased odds of death during the neonatal period compared to those born to mothers of optimal weight (OR: 1.34; 95% CI: 1.02-1.75). However, the multivariable model showed that there was also a three-fold increase in neonatal deaths amongst babies delivered by caesarean compared to those born vaginally (OR: 2.96; 95% CI: 2.27-3.87) and a significant interaction was observed between the effect of maternal BMI and mode of delivery. This is likely to be a product of reverse causation.

Maternal obesity did not have a statistically significant effect amongst women who delivered by caesarean section. This may have been due to lack of statistical power due to the small numbers in this group; however (although not significant) there is an apparent trend in the effect estimates and the direction hints at maternal obesity having a protective effect on neonatal death amongst babies delivered by caesarean (all of whom have three times increased odds of death compared to vaginal deliveries). I suggest that this may be due to either residual confounding or a selection bias caused by maternal survival. It is plausible that the very richest mothers pre-book a caesarean delivery, which would have a protective effect on neonatal survival; these elite women are also more likely to be obese. Although I have controlled for wealth in the analysis I have done so through use of wealth quintiles which may not distinguish the very rich and so cause residual confounding. Unfortunately, the DHS does not contain any information relating to whether a caesarean was an emergency or an elective procedure. Alternatively, as previously mentioned, in Sub-Saharan Africa caesarean delivery is a risk factor for neonatal mortality because the operation is performed too late to save the babies' life. However, if the procedure was also performed too late to save the mother and she died at delivery I have no information that she ever existed, due to the cross-sectional design of the DHS. If it were true that obese mothers in this subgroup were more likely to die then this selection bias could create the appearance of a protective effect.

Amongst vaginal births the odds of death during the neonatal period were 50% higher for infants born to obese mothers (OR: 1.54; 95% CI: 1.16-2.05). The excess daily hazard of death

was greatest in the early neonatal period. During the first week of life amongst infants born vaginally, maternal obesity was associated with a 2-fold increase in neonatal mortality (Days 0-1 OR: 2.35, 95% CI: 1.59-3.48; Days 2-6 OR: 2.34, 95% CI: 1.47-3.74). Graphing the daily hazard and survivorship of infants during the first month of life showed that the excess risk of death due to maternal obesity declined throughout the neonatal period.

Few previous studies had examined the effect of maternal obesity and neonatal death and these findings represent an important contribution to the literature. A cohort study of singleton pregnancies in Denmark found that maternal obesity more than doubled the odds of neonatal death (OR: 2.6; 95% CI: 1.2-5.8) compared to optimal weight women, although no statistically significant effect was observed amongst the pre-obese category [126], similar to my results. Results from the Danish National Birth Cohort study have also shown that infants born to overweight mothers are at increased risk of neonatal death (Pre-Obese HR: 1.7, 95% CI: 1.2-2.5; Obese HR: 1.6, 95% CI: 1.0-2.4) [127].

However, only one published study to date has attempted to investigate the impact of obesity on the timing of death within the neonatal period. A population-based cohort study of 167,750 births from Sweden did not find a significant association between early neonatal death and obesity (OR: 1.2; 95% CI 0.7-1.7) [124]. The reported effect estimates were adjusted for maternal age, parity, education, smoking behaviour, height and whether the mother was living with the father. My study had much better power (the Swedish study had just 309 cases of early neonatal death [124], although the total number of women included was more than twice that my study) and I was able to examine the timing of neonatal death in much greater detail than has ever been published previously.

Particularly interesting, is the finding that maternal obesity acts as a risk factor primarily in the early neonatal period. Whilst the DHS data does not contain data on cause of death for infants, the timing is indicative of deaths due to birth injuries [15]. This would be consistent with what is known about the effect of maternal obesity on neonatal outcomes in high-income countries; maternal obesity is a risk factor for prolonged and obstructed labour [105, 108]. Furthermore, evidence from high-income settings has demonstrated a relationship between maternal obesity and increased admission to neonatal intensive care [110] and lower neonatal Apgar scores [125]. Most babies in the Sub-Saharan context will not have access to anything like the same level of intensive care that is available to most infants in high-income settings where previous research has been conducted, therefore it is concerning but unsurprising that we see a significant increase in neonatal deaths amongst babies born to obese mothers in Sub-Saharan Africa.

9.2 Strengths and Limitations

Analysing the DHS in this thesis allowed me to produce the first nationally-representative estimates of the effect of overweight and obesity on reduced fecundity and adverse pregnancy outcomes in Sub-Saharan Africa.

A particular strength of the DHS is the standardised sampling design and questionnaire structure. This allowed me to pool national surveys to create a large dataset with sufficient power to investigate rare outcomes such as neonatal death in greater detail than has been achieved previously.

The DHS has more than twenty years experience of conducting surveys in low-income settings and, as such, the quality of the data collected is good for a low-income setting [210, 220]. In particular, the height and weight information is measured by the interviewer, rather than relying on self-report or recall, which enhances the validity of the data [322].

However, the study also has limitations, many of which relate to the cross-sectional design of the DHS and the fact that in using a secondary data source, I was limited by the variables available to me in what research questions it was possible to analyse and which variables it was possible to control for. These limitations are discussed below.

1. **Temporal Direction of Associations**

One of the most important limitations of this work is the cross-sectional design of the DHS; since exposure and outcome data are collected simultaneously it is not possible to prove that the exposure pre-dates the outcome. The temporality assumption is an established criterion for causal inference [333] and this is a well-known limitation of cross-sectional studies; it is for example potentially possible that the associations are a product of reverse causation.

Nevertheless, there is still a strong case to be made that the findings of this thesis are causal. A monotonic biological gradient is observable for each outcome I investigated in this thesis; linear in the case of caesarean delivery and neonatal death and either linear or a possible threshold effect in the case of subfertility which strengthens the case for causality [333]. In addition, the associations were reasonably consistent across each geographic region investigated. All of the associations observed within this thesis are also biologically plausible. Evidence from high-income setting supports the hypothesis that increased adiposity reduces female fecundity through mechanisms such as anovulatory infertility and menstrual disruption [69, 291, 323]. Furthermore the findings for the caesarean outcome are very similar to those

observed in two previous systematic reviews [41-42]. Whilst the existing evidence on an association between maternal obesity and neonatal death is less conclusive, the association is supported by evidence such as increased admission to neonatal intensive care and lower Apgar scores for infants born to obese mothers [110, 125], outcomes which are likely to be associated with death in a low-income setting such as Sub-Saharan Africa. There is thus a good case for biological plausibility.

2. Validity of the Outcome Measures

The data quality for each of the main outcomes analysed in this thesis was discussed in detail in Chapter 3. This section summarises the important points in light of the study results.

The subfertility outcome is the most problematic of the outcomes investigated in this thesis in terms of face validity because the DHS collects data on existing births. Infertility is not a priority health concern for policy makers in most low-income countries because historically the focus has been on issues of over-population. The necessary variables to reliably determine whether the absence of a birth means that a woman is infertile, or if she is intentionally preventing a birth, are not collected in the DHS. There were two main concerns with construct validity that I raised in Chapter 3; first of all the length of the exposure period which should be used to define subfertility. A sensitivity analysis, presented in Chapter 7, showed that using 48 months, 60 months or 72 months made a negligible difference to the results, despite potential birth displacement issues.

The second area of concern was how best to define who was at risk of conceptions, i.e. which women were regularly exposed to intercourse and were not intentionally controlling their fertility. In an ideal study, I would have restricted my analysis to women who were actively attempting to become pregnant; unfortunately this data was not available. I therefore restricted the analysis to ever-partnered women who had not been sterilised and were not continuous contraceptive users, and excluded those women who said they did not want any further births. However, a sensitivity analysis restricted to never-users of contraception indicated that contraceptive use was likely to be producing residual confounding in my estimates. I did not consider it appropriate to completely exclude contraceptive users from the analysis, as doing so would have caused an important selection bias due to their higher average fecundity [18, 334]. Therefore my main results represent a conservative estimate on the effect of obesity on the odds of subfertility.

The survival analysis of time from first marriage to first conception analysis had much higher validity. I had monthly data on contraceptive usage and restricted the sample to recently married nulliparous women, who were highly likely to be attempting conception. However, I ultimately did not have sufficient power to investigate this outcome. Nevertheless the methods showed potential and as more countries are now including the full reproductive calendar in the DHS, so it would be interesting to repeat this analysis once more data becomes available.

The validity of the caesarean delivery outcome depends on the accuracy of each woman's self-report. The coding and skip pattern of the questionnaire was designed so that only women who delivered within a health facility could be coded as having had a caesarean delivery, however there will still be some likely small degree of misclassification where women who did deliver in a health facility confused a caesarean operation with another procedure [216]. Anecdotal evidence has suggested that some women may confuse a caesarean delivery with an episiotomy [88]. Not all health facilities will be capable of conducting a caesarean procedure [215-216]. Recall bias is unlikely to represent a substantial concern to these results because only the most recent birth of deliveries occurring in the five years preceding data collection were considered in the analysis.

The neonatal death variable could potentially be invalidated by under-reporting of deaths (or the misreporting of deaths in the neonatal period as still births) or by recall errors in the timing of death [15, 218]. Chapter 3 showed that there was heaping of neonatal deaths reported on days seven, fourteen and twenty-one; on each of these days there were close to twice the number of deaths recorded that would be expected if deaths were equally distributed with the adjacent days. This is finding only presents a risk to misclassification in this study at day seven as in the discrete-time survival model deaths between days seven to twenty-seven were included in the same category; however, the as the greatest burden of neonatal deaths occurs earlier in life any subsequent bias in the results is likely to be relatively small.

The omission of infants who were died on day zero (i.e. an early neonatal death) but were classified as still births and so not recorded in the birth history section or alternatively omitted completely is much harder to detect. A potential solution to this concern will be discussed below in Section 9.3 on future work.

3. Validity of the Primary Exposure (BMI)

Height and weight are measured by the interviewer in the DHS. However, BMI category may potentially be misclassified due to the cross-sectional design of the survey: I am implicitly assuming throughout this thesis that the exposure pre-dates the outcome, if this is not the case my BMI variable will be incorrect.

In Chapter 5 I used several different approaches to attempt to assess the degree of exposure misclassification; however I was not able to obtain reliable estimates of likely specificity or sensitivity due to data limitations. There is no appropriate external data source which could be used to obtain such information.

Therefore, as a sensitivity analysis, I used the Stata command *-episens-* [289-290] to calculate the change in the crude odds ratio which would occur for each outcome over a range of sensitivities and specificities (Table 9.2, Table 9.3 and Table 9.4). Sensitivity here refers to the probability that a woman who is recorded as being overweight is truly overweight (a true positive) whilst specificity is the probability that someone recorded as being of optimal weight is truly of optimal weight (a true negative).

Table 9.2 Exposure misclassification sensitivity analysis for the subfertility logistic regression model

		SENSITIVITY [Corrected OR (% Bias)]									
		0.80		0.85		0.90		0.95		1	
SPECIFICITY [Corrected OR (% Bias)]	0.80	*Could not be calculated as would produce negative cell counts*									
	0.825	13.08	-86%	12.85	-85%	12.67	-85%	12.51	-85%	12.38	-85%
	0.85	5.05	-63%	4.96	-62%	4.89	-62%	4.83	-61%	4.78	-61%
	0.875	3.51	-46%	3.45	-46%	3.40	-45%	3.35	-44%	3.32	-43%
	0.90	2.85	-34%	2.80	-33%	2.76	-32%	2.73	-31%	2.70	-30%
	0.925	2.49	-25%	2.45	-23%	2.41	-22%	2.38	-21%	2.36	-20%
	0.95	2.26	-17%	2.22	-15%	2.19	-14%	2.16	-13%	2.14	-12%
	0.975	2.10	-11%	2.06	-9%	2.03	-8%	2.01	-7%	1.99	-6%
	1	1.98	-5%	1.95	-4%	1.92	-2%	1.90	-1%	**1.88**	

Table 9.3 Exposure misclassification sensitivity analysis for the caesarean deliveries logistic regression model

	SENSITIVITY [Corrected OR (% Bias)]									
SPECIFICITY [Corrected OR (% Bias)]	0.80		0.85		0.90		0.95		1	
0.80	190.1	-98%	181.8	-98%	175.2	-98%	169.9	-98%	165.5	-98%
0.825	14.81	-80%	14.16	-79%	13.65	-79%	13.24	-78%	12.89	-77%
0.85	8.44	-65%	8.07	-64%	7.78	-62%	7.54	-61%	7.35	-60%
0.875	6.22	-53%	5.94	-51%	5.73	-49%	5.55	-47%	5.41	-46%
0.90	5.08	-43%	4.86	-40%	4.68	-38%	4.54	-36%	4.42	-34%
0.925	4.40	-34%	4.20	-31%	4.05	-28%	3.93	-26%	3.83	-24%
0.95	3.93	-26%	3.76	-22%	3.63	-19%	3.52	-17%	3.42	-15%
0.975	3.60	-19%	3.45	-15%	3.32	-12%	3.22	-9%	3.14	-7%
1	3.35	-13%	3.21	-9%	3.09	-6%	3.00	-3%	**2.92**	

Table 9.4 Exposure misclassification sensitivity analysis for the neonatal deaths logistic regression model

	SENSITIVITY [Corrected OR (% Bias)]									
SPECIFICITY [Corrected OR (% Bias)]	0.80		0.85		0.90		0.95		1	
0.80	7.58	-82%	7.52	-82%	7.47	-82%	7.43	-82%	7.39	-82%
0.825	2.85	-53%	2.83	-52%	2.81	-52%	2.79	-52%	2.78	-51%
0.85	2.11	-36%	2.09	-35%	2.08	-35%	2.07	-35%	2.06	-34%
0.875	1.81	-25%	1.80	-25%	1.79	-24%	1.77	-24%	1.77	-23%
0.90	1.65	-18%	1.64	-17%	1.62	-17%	1.62	-16%	1.61	-16%
0.925	1.55	-13%	1.53	-12%	1.52	-11%	1.52	-11%	1.51	-10%
0.95	1.48	-8%	1.47	-8%	1.46	-7%	1.45	-7%	1.44	-6%
0.975	1.43	-5%	1.41	-4%	1.41	-4%	1.40	-3%	1.39	-3%
1	1.39	-2%	1.38	-2%	1.37	-1%	1.36	-0%	**1.35**	

Specificity is a lot more important than sensitivity in terms of the amount of bias produced in this population as obesity is still relatively rare. Fortunately, as work in Chapter 5 indicated, on average, women are more likely to have gained weight than lost weight during the five year reference period prior to data collection in which the outcome could potentially have occurred in this study, due to ageing and possible background population shifts under the nutrition transition. Therefore the likelihood is that specificity is better than sensitivity in this study which is reassuring.

This sensitivity analysis serves to demonstrate the difference that uncertainty in the bias parameters can make to the effect estimates obtained. Whilst it is the norm for epidemiologists to attempt to quantify the uncertainty in their estimate caused by random error (though the presentation of p-values and/or confidence intervals), the biases caused by systematic errors are often ignored [289]. Everything else being equal, non-differential

exposure misclassification will tend to bias the observed result towards the null, but this is not uniformly the case [289, 335-336].

In this study, inferences from the best data available suggest that the crude odds ratio may be underestimated but without further validation work and longitudinal data on the weight trajectory for women in low-income settings it can only be an estimate.

4. Residual Confounding

Residual confounding may occur if confounding is still present after a covariate has been included in the model nominally adjusted for its effect. This may potentially occur because of missing data or measurement error, for example if the variable if it exists in the dataset does not accurately represent what it purports to measure. In this thesis, there is a risk that this occurred with variables such as age (due to misreporting) or relative wealth (if the variable constructed through principal components analysis based on household asset-ownership did not truly measure the underlying concept of wealth). Alternatively, "over-adjustment" may have occurred if one of the variables which I controlled for in my analyses was acting as a proxy for an unmeasured intermediate variable on the exposure-outcome causal pathway [337].

5. Unmeasured Variables

One of the limitations of secondary data analysis is the restriction of potential hypotheses imposed by reliance on the availability of pre-existing variables.

I constructed a proxy variable for infertility on the basis of each woman's birth history. It was not possible to adequately determine paternity on the basis of the pre-existing data, so I was not able to investigate the relationship between obesity and male infertility in this thesis.

Ideally, I would have controlled for HIV status of the mother in the analyses contained in this thesis. As explained in section 3.2, HIV-infection is related to subfertility, caesarean delivery, neonatal mortality and body weight so potentially is an important confounder in this thesis. DHS collects HIV data through voluntary, anonymous testing of women aged 15-49 years. However, the DHS are cross-sectional and each outcome investigated in this thesis could have occurred at any point during an exposure period up to five years prior to data collection; thus I cannot ascertain HIV status prior to the occurrence of the outcome. There is no way to determine who are the incident cases that have sero-converted within the five years preceding data collection.

An unmeasured confounder that would have been interesting to explore particularly in the neonatal mortality analysis is maternal diabetes. Whilst maternal obesity is known to have an independent effect on neonatal outcomes [109], much of the effect may well be due to diabetes. Diabetes is increasing in Sub-Saharan Africa; although a substantial proportion of women will be undiagnosed [44, 162]. Therefore the effect of maternal obesity as a risk factor for neonatal death is of interest in its own right, since height and weight simpler to measure in a survey or under-resourced antenatal clinic and could be used to screen patients at high risk of adverse pregnancy outcomes.

9.3 Implications of the Findings and Recommendations for Future Research

The key message of this thesis is that overweight/obesity is associated with adverse reproductive outcomes in the Sub-Saharan context. This is not widely recognised at present, yet is likely to become an increasing concern during the twenty-first century. For example, the adjusted odds ratios obtained for effect of maternal obesity on neonatal death were similar in magnitude to that mentioned by Lawn et al. (2005) for underweight (a pre-pregnancy weight <47kg) in the Lancet series on neonatal survival[15].

The findings of this thesis make a start towards filling a clear research gap in obesity research in Sub-Saharan Africa and as such will be useful as baseline data and to inform the design of future studies. Future research projects identified by this thesis include:

- To investigate the effect of BMI on reduced fecundity using the reproductive calendar module on a larger sample. The methods used in this thesis showed potential; however I had insufficient power to investigate obesity as an exposure. More African countries are now collecting monthly contraceptive data so an increased sample size will become available.

- To investigate the cause of neonatal deaths amongst obese mothers. The timing of neonatal deaths was suggestive of birth injuries as a potential cause; however to investigate this, studies investigating neonatal deaths in the hospital setting would be needed.

- To use the DHS calendar data to obtain information on pregnancy terminations and still births and investigate the association between maternal obesity and foetal outcome as a continuum along with neonatal deaths.

- To investigate the relationship between male obesity and low fecundity in the Sub-Saharan setting.
- To design a prospective cohort study that will allow the interaction between obesity, HIV and reproductive outcomes to be explored.

My thesis findings also have wider implications for public health policy. Obesity is a modifiable risk factor. Public health professionals working in diabetes care in Africa have reported that women are resistant to the idea losing weight, for fear that their neighbour will assume they are HIV+ [162]. If this belief is widespread, combined with perceptions of a larger body size as a positive attribute [160, 338], Africa potentially faces a future challenge in obesity control even greater than that of high-income countries [339]. The findings of this thesis should be of use to policy makers and health professionals in Sub-Saharan Africa who wish to design effective obesity education and prevention campaigns. Women of reproductive age are the population group most likely to be overweight or obese; they also typically control household nutrition and diet. Promotion of the finding that overweight/obesity is associated with adverse reproductive outcomes may be particularly effective and influential due to the immense cultural and social importance placed on child-bearing in this setting.

Infertility can carry a very large social, psychological and economic burden in African countries [20, 22-23, 340-341]. However, assisted conception is either unavailable or inaccessible to most women in this context and implementing such programmes is unlikely to be a priority of governments or international non-profit organisations in the near future [342-343]. Overweight women who do attempt to access infertility treatment should be made aware of the associated risk, and given appropriate dietary and lifestyle advice to lose weight should they want it. For overweight and obese women weight loss represents a cost-effective way of improving their conception chances, which has been demonstrated in high-income settings to be effective [344]. Obesity in the male partner is also likely to have a detrimental effect on fertility [84-85], although this has not been investigated in this thesis. Male obesity is currently very low (around 3%) in Sub-Saharan Africa [1]. Nevertheless, it is recognised that this is a limitation of this thesis and that the findings cannot be generalised to the male population.

Overweight women also need to be made aware of the adverse pregnancy outcomes associated with a high BMI, and encouraged to lose weight before conception if possible; identifying and targeting obese women in family planning clinics or during antenatal care could be a good strategy. The importance of obese women making plans to deliver in a health facility equipped to provide emergency obstetric care, should it become necessary, should be emphasised during routine antenatal care. In Sub-Saharan Africa obesity is associated with

increased wealth and education, so a substantial proportion of obese women will be sufficiently empowered and in a capacity to act upon this information if given to them. Guidance should ideally also include dietary and lifestyle advice to lose weight post-pregnancy. Current research underway in high-income countries, such as the UK and USA, is investigating the effectiveness of interventions to prevent excessive weight gain in pregnant women and to manage the effects of maternal obesity [271, 345-347]. Culturally-specific and appropriate interventions will ultimately need to be trialled in low-income settings

One additional interesting implication of the thesis which should also be mentioned here, is that the levels of excess adiposity amongst the population of women examined in this thesis remains relatively low compared to the current BMI distribution in most high-income countries where all prior research has been conducted. Even amongst women classified as obese, most had BMI values in the lower spectrum of obesity (30-35kg/m^2); just 1.64% of women in the study had a BMI over 35 kg/m^2 and only 0.43% would be classified as morbidly obese (≥40 kg/m^2). It is therefore perhaps surprising and concerning that a clear negative effect on health outcomes was observed, even at levels of overweight/obesity which have come to be seen as "normal" by many in the UK and USA [348-349].

To conclude, this thesis has produced the first nationally-representative quantitative estimates of the effect of BMI on reduced fecundity and adverse pregnancy outcomes in the Sub-Saharan setting. A particularly clear effect was observed for outcomes occurring around the intrapartum period. Overweight/obesity should be recognised as a risk factor for adverse reproductive outcomes in Sub-Saharan Africa.

References

1. Kelly, T., et al., *Global burden of obesity in 2005 and projections to 2030.* International Journal of Obesity, 2008. **32**(9): p. 1431-1437.
2. World Health Organization. *WHO Health Topics: Reproductive Health Home.* 2011 [Accessed 9th March 2011]; Available from: http://www.who.int/topics/reproductive_health/en/.
3. World Health Organization, *Trends in maternal mortality: 1990 to 2008. Estimates developed by WHO, UNICEF, UNFPA and The World Bank.* 2010, WHO: Geneva.
4. Hogan, M.C., et al., *Maternal mortality for 181 countries, 1980-2008: a systematic analysis of progress towards Millennium Development Goal 5.* Lancet, 2010. **375**(9726): p. 1609-1623.
5. Khan, K.S., et al., *WHO analysis of causes of maternal death: a systematic review.* Lancet, 2006. **367**(9516): p. 1066-1074.
6. Ronsmans, C., W.J. Graham, and S. Lancet Maternal Survival, *Maternal Survival Series 1: Maternal mortality: who, when, where, and why.* Lancet, 2006. **368**(9542): p. 1189-1200.
7. Murray, C. and A. Lopez, *Health Dimensions of Sex and Reproduction: the global burden of sexually transmitted diseases, HIV, maternal conditions, perinatal disorders, and congenital anomalies.* 1998: Harvard University Pres.
8. Filippi, V., et al., *Health of women after severe obstetric complications in Burkina Faso: a longitudinal study.* Lancet, 2007. **370**: p. 1329-1337.
9. Storeng, K.T., et al., *Paying the price: The cost and consequences of emergency obstetric care in Burkina Faso.* Social Science & Medicine, 2008. **66**(3): p. 545-557.
10. Filippi, V., et al., *Effects of severe obstetric complications on women's health and infant mortality in Benin.* Tropical Medicine & International Health, 2010. **15**(6): p. 733-742.
11. Borghi, J., et al., *Costs of near-miss obstetric complications for women and their families in Benin and Ghana.* Health Policy and Planning, 2003. **18**(4): p. 383-390.
12. Storeng, K.T., et al., *Beyond body counts: A qualitative study of lives and loss in Burkina Faso after 'near-miss' obstetric complications.* Social Science & Medicine, 2010. **71**(10): p. 1749-1756.
13. Rajaratnam, J.K., et al., *Neonatal, postneonatal, childhood, and under-5 mortality for 187 countries, 1970-2010: a systematic analysis of progress towards Millennium Development Goal 4.* Lancet, 2010. **375**(9730): p. 1988-2008.
14. Lawn, J., K. Shibuya, and C. Stein, *No cry at birth: global estimates of intrapartum stillbirths and intrapartum-related neonatal deaths.* Bulletin of the World Health Organization, 2005. **83**(6): p. 409-417.
15. Lawn, J.E., et al., *Neonatal Survival Series 1: 4 million neonatal deaths: When? where? why?* Lancet, 2005. **365**(9462): p. 891-900.
16. Belsey, M., *The epidemiology of infertility: a review with particular reference to sub-Saharan Africa.* Bulletin of the World Health Organization, 1976. **54**(3): p. 319-341.
17. Ericksen, K. and T. Brunette, *Patterns and predictors of infertility among African women: A cross-national survey of twenty seven nations.* Social Science & Medicine, 1996. **42**(2): p. 209-220.
18. Larsen, U., *Primary and secondary infertility in sub-Saharan Africa.* International Journal of Epidemiology, 2000. **29**(2): p. 285-291.
19. Walraven, G., et al., *The burden of reproductive-organ disease in rural women in The Gambia, West Africa.* Lancet, 2001. **357**(9263): p. 1161-1167.

20. Hollos, M. and U. Larsen, *Motherhood in sub-Saharan Africa: The social consequences of infertility in an urban population in northern Tanzania.* Culture Health & Sexuality, 2008. **10**(2): p. 159-173.
21. Tilson, D. and U. Larsen, *Divorce in Ethiopia: The impact of early marriage and childlessness.* Journal of Biosocial Science, 2000. **32**(3): p. 355-372.
22. Dyer, S.J., et al., *Infertility in South Africa: women's reproductive health knowledge and treatment-seeking behaviour for involuntary childlessness.* Human Reproduction, 2002. **17**(6): p. 1657-1662.
23. Dyer, S.J., *The value of children in African countries - Insights from studies on infertility.* Journal of Psychosomatic Obstetrics and Gynecology, 2007. **28**(2): p. 69-77.
24. Metwally, M., T.C. Li, and W.L. Ledger, *The impact of obesity on female reproductive function.* Obesity Reviews, 2007. **8**(6): p. 515-523.
25. Sebire, N.J., et al., *Maternal obesity and pregnancy outcome: a study of 287 213 pregnancies in London.* International Journal of Obesity, 2001. **25**(8): p. 1175-1182.
26. World Health Organization, *Physical Status: the use and interpretation of anthropometry. Report of a WHO expert committee.*, in *WHO Technical Report Series: 854*. 1995: Geneva.
27. Martorell, R., et al., *Obesity in women from developing countries.* European Journal of Clinical Nutrition, 2000. **54**(3): p. 247-252.
28. Popkin, B.M. and P. Gordon-Larsen, *The nutrition transition: worldwide obesity dynamics and their determinants.* International Journal of Obesity, 2004. **28**: p. S2-S9.
29. Prentice, A.M., *The emerging epidemic of obesity in developing countries.* International Journal of Epidemiology, 2006. **35**(1): p. 93-99.
30. World Health Organization, *Obesity: preventing and managing the global epidemic. Report of a WHO Consultation.*, in *WHO Technical Report Series: 894*. 2000: Geneva.
31. Fernald, L.C. and L.M. Neufeld, *Overweight with concurrent stunting in very young children from rural Mexico: prevalence and associated factors.* European Journal of Clinical Nutrition, 2007. **61**(5): p. 623-632.
32. Lee, J., et al., *Disentangling nutritional factors and household characteristics related to child stunting and maternal overweight in Guatemala.* Econ Hum Biol, 2010. **8**(2): p. 188-96.
33. World Health Organization, *Global health risks: mortality and burden of disease attributable to selected major risks.* 2009, WHO: Geneva.
34. Gomes, A., et al., *Body mass index and waist circumference in Mozambique: urban/rural gap during epidemiological transition.* Obesity Reviews, 2010. **11**(9): p. 627-634.
35. Abubakari, A.R., et al., *National prevalence of obesity: Prevalence and time trends in obesity among adult West African populations: a meta-analysis.* Obesity Reviews, 2008. **9**(4): p. 297-311.
36. Population Reference Bureau, *World Population Data Sheet*. 2010, PRB.
37. Pettigrew, R. and D. HamiltonFairley, *Obesity and female reproductive function.* British Medical Bulletin, 1997. **53**(2): p. 341-358.
38. Metwally, M., W.L. Ledger, and T.C. Li, *Does high body mass index increase the risk of miscarriage after spontaneous and assisted conception? A meta-analysis of the evidence.* Fertility and Sterility, 2008. **90**(3): p. 714-726.
39. Metwally, M., et al., *Body mass index and risk of miscarriage in women with recurrent miscarriage.* Fertility and Sterility, 2010. **94**(1): p. 290-295.
40. Stothard, K.J., et al., *Maternal Overweight and Obesity and the Risk of Congenital Anomalies A Systematic Review and Meta-analysis.* Jama-Journal of the American Medical Association, 2009. **301**(6): p. 636-650.
41. Chu, S.Y., et al., *Maternal obesity and risk of cesarean delivery: a meta-analysis.* Obesity Reviews, 2007. **8**(5): p. 385-394.

42. Poobalan, A.S., et al., *Obesity as an independent risk factor for elective and emergency caesarean delivery in nulliparous women - systematic review and meta-analysis of cohort studies.* Obesity Reviews, 2009. **10**(1): p. 28-35.
43. Levitt, N.S., *Diabetes in Africa: epidemiology, management and healthcare challenges.* Heart, 2008. **94**(11): p. 1376-1382.
44. Mbanya, J.C.N., et al., *Diabetes in sub-Saharan Africa.* Lancet, 2010. **375**(9733): p. 2254-2266.
45. Bovet, P., et al., *Distribution of blood pressure, body mass index and smoking habits in the urban population of Dar es Salaam, Tanzania, and associations with socioeconomic status.* International Journal of Epidemiology, 2002. **31**(1): p. 240-247.
46. Mensah, G.A., *Epidemiology of stroke and high blood pressure in Africa.* Heart, 2008. **94**(6): p. 697-705.
47. Rutstein, S.O. and I.H. Shah, *Infecundity, Infertility and Childlessness in Developing Countries*, in *DHS Comparative Reports No. 9.* 2004, ORC Macro & the World Health Organization: Calverton: Maryland.
48. Ronsmans, C., S. Holtz, and C. Stanton, *Socioeconomic differentials in caesarean rates in developing countries: a retrospective analysis.* Lancet, 2006. **368**(9546): p. 1516-1523.
49. Lawn, J.E., et al., *Reducing intrapartum-related deaths and disability: Can the health system deliver?* International Journal of Gynecology & Obstetrics, 2009. **107**: p. S123-S142.
50. Lawn, J.E., et al., *3.6 Million Neonatal Deaths - What Is Progressing and What Is Not?* Seminars in Perinatology, 2010. **34**(6): p. 371-386.
51. Uauy, R. and J. Kain, *The epidemiological transition: need to incorporate obesity prevention into nutrition programmes.* Public Health Nutrition, 2002. **5**(1A): p. 223-229.
52. Miranda, J.J., et al., *Non-communicable diseases in low- and middle-income countries: context, determinants and health policy.* Tropical Medicine & International Health, 2008. **13**(10): p. 1225-1234.
53. Leridon, H., *Studies of fertility and fecundity: comparative approaches from demography and epidemiology.* C R Biol, 2007. **330**(4): p. 339-46.
54. Baird, D.D., A.J. Wilcox, and C.R. Weinberg, *Use of Time to Pregnancy to Study Environmental Exposures.* Am. J. Epidemiol., 1986. **124**(3): p. 470-480.
55. Evers, J.L.H., *Female subfertility.* Lancet, 2002. **360**(9327): p. 151-159.
56. Marchbanks, P.A., et al., *Research on Infertility: Definition makes a difference.* Am. J. Epidemiol., 1989. **130**(2): p. 259-267.
57. Larsen, U., *Research on infertility: which definition should we use?* Fertility and Sterility, 2005. **83**(4): p. 846-852.
58. Gnoth, C., et al., *Definition and prevalence of subfertility and infertility.* Human Reproduction, 2005. **20**(5): p. 1144-1147.
59. World Health Organization, *The Epidemiology of Infertility. Report of a WHO Scientific Group.* 1975, WHO: Geneva.
60. Larsen, U. and J. Menken, *Measuing sterility from incomplete birth histories.* Demography, 1989. **26**(2): p. 185-201.
61. Larsen, U. and J. Menken, *Individual-level sterility: a new method of estimation with application to sub-Saharan Africa.* Demography, 1991. **28**(2): p. 229-247.
62. Larsen, U. and H. Raggers, *Levels and trends in infertility in sub-Saharan Africa*, in *Women and infertility in sub-Saharan Africa: a multi-disciplinary persepective*, B.J. T. and Z. Mgalla, Editors. 2001, Royal Tropical Institute: Amsterdam, The Netherlands.
63. Mayaud, P., *The role of reproductive tract infections*, in *Women and infertility in sub-Saharan Africa: a multi-disciplinary persepective*, B.J. T. and Z. Mgalla, Editors. 2001, Royal Tropical Institute: Amsterdam, The Netherlands.

64. Stekelenburg, J., et al., *Health care seeking behaviour and utilisation of traditional healers in Kalabo, Zambia.* Health Policy, 2005. **71**(1): p. 67-81.
65. De Muylder, X., P. Buekens, and B. Dujardin, *Caesarean section and infertility: a case-control study from Zimbabwe*, in *Women and infertility in sub-Saharan Africa: a multi-disciplinary persepective*, B.J. T. and Z. Mgalla, Editors. 2001, Royal Tropical Institute: Amsterdam, The Netherlands.
66. Johnson, M.H. and B.J. Everitt, *Essential Reproduction*. 1995: Blackwell Science.
67. Pasquali, R., *Metabolic effects of obesity on reproduction.* Reproductive Biomedicine Online, 2006. **12**(5): p. 542-551.
68. Alvarez-Blasco, F., et al., *Prevalence and characteristics of the polycystic ovary syndrome in overweight and obese women.* Archives of Internal Medicine, 2006. **166**(19): p. 2081-2086.
69. Pasquali, R., A. Gambineri, and U. Pagotto, *The impact of obesity on reproduction in women with polycystic ovary syndrome.* Bjog-an International Journal of Obstetrics and Gynaecology, 2006. **113**(10): p. 1148-1159.
70. Gambineri, A., et al., *Obesity and the polycystic ovary syndrome.* International Journal of Obesity, 2002. **26**(7): p. 883-896.
71. Wang, Y.F., *Is obesity associated with early sexual maturation? A comparison of the association in American boys versus girls.* Pediatrics, 2002. **110**(5): p. 903-910.
72. Kato, I., et al., *Prospective study of factors influencing the onset of natural menopause.* Journal of Clinical Epidemiology, 1998. **51**(12): p. 1271-1276.
73. Henderson, K.D., et al., *Predictors of the timing of natural menopause in the multiethnic cohort study.* American Journal of Epidemiology, 2008. **167**(11): p. 1287-1294.
74. Kato, I., et al., *Epidemiologic correlates with menstrual cycle length in middle aged women.* European Journal of Epidemiology, 1999. **15**(9): p. 809-814.
75. Lake, J.K., C. Power, and T.J. Cole, *Women's reproductive health: The role of body mass index in early and adult life.* International Journal of Obesity, 1997. **21**(6): p. 432-438.
76. Wilcox, A.J., et al., *Incidence of early loss in pregnancy.* New England Journal of Medicine, 1988. **319**(4): p. 189-194.
77. Weinberg, C.R. and A.J. Wilcox, *Methodologic Issues in Reproductive Epidemiology*, in *Modern Epidemiology*, K.J. Rothman, S. Greenland, and T.L. Lash, Editors. 2008, Lippincott Williamns & Wilkins.
78. Maheshwari, A., L. Stofberg, and S. Bhattacharya, *Effect of overweight and obesity on assisted reproductive technology - a systematic review.* Human Reproduction Update, 2007. **13**(5): p. 433-444.
79. Lashen, H., K. Fear, and D.W. Sturdee, *Obesity is associated with increased risk of first trimester and recurrent miscarriage: matched case-control study.* Human Reproduction, 2004. **19**(7): p. 1644-1646.
80. Sheiner, E., et al., *Maternal obesity as an independent risk factor for caesarean delivery.* Paediatric and Perinatal Epidemiology, 2004. **18**(3): p. 196-201.
81. Turner, M.J., et al., *Body Mass Index and spontaneous miscarriage.* European Journal of Obstetrics & Gynecology and Reproductive Biology, 2010. **151**(2): p. 168-170.
82. Nohr, E.A., et al., *Pre-pregnancy obesity and fetal death - a study within the Danish National Birth Cohort.* Obstetrics and Gynecology, 2005. **106**(2): p. 250-259.
83. Akingbemi, B.T., *Estrogen regulation of testicular function.* Reprod Biol Endocrinol, 2005. **3**: p. 51.
84. Du Plessis, S.S., et al., *The effect of obesity on sperm disorders and male infertility.* Nat Rev Urol, 2010. **7**(3): p. 153-61.
85. Hammoud, A.O., et al., *Impact of male obesity on infertility: a critical review of the current literature.* Fertil Steril, 2008. **90**(4): p. 897-904.
86. Macro International Inc. *MEASURE DHS STATcompiler*. 2011 [Accessed March 12 2011]; Available from: http://www.measuredhs.com.

87. Stanton, C.K. and S.A. Holtz, *Levels and trends in cesarean birth in the developing world.* Stud Fam Plann, 2006. **37**(1): p. 41-8.
88. Stanton, C.K., et al., *Reliability of data on caesarean sections in developing countries.* Bulletin of the World Health Organization, 2005. **83**(6): p. 449-455.
89. Dumont, A., et al., *Caesarean section rate for maternal indication in sub-Saharan Africa: a systematic review.* Lancet, 2001. **358**(9290): p. 1328-33.
90. Shah, A., et al., *Cesarean delivery outcomes from the WHO global survey on maternal and perinatal health in Africa.* International Journal of Gynecology & Obstetrics, 2009. **107**(3): p. 191-197.
91. Buekens, P., *Over-medicalisation of Maternal Care in Developing Countries.* Studies in HSO&P, 2001. **17**: p. 191-202.
92. Souza, J.P., et al., *Caesarean section without medical indications is associated with an increased risk of adverse short-term maternal outcomes: the 2004-2008 WHO Global Survey on Maternal and Perinatal Health.* Bmc Medicine, 2010. **8**: p. -.
93. Sahu, M.T., et al., *Impact of maternal body mass index on obstetric outcome.* Journal of Obstetrics and Gynaecology Research, 2007. **33**(5): p. 655-659.
94. Nahmias, P., *The Social Epidemiology of Maternal Obesity in Egypt*, in *Department of Sociology*. 2010, Princeton University.
95. Pongthai, S., *Labor and delivery of obese parturients.* Journal of the Medical Association of Thailand, 1990. **73**(SUPPL. 1): p. 52-56.
96. Djrolo, F., et al., *Influence of maternal weight on pregnancy outcome in Cotonou (Benin).* J Gynecol Obstet Biol Reprod (Paris), 2002. **31**(3): p. 243-7.
97. Institut National de la Statistique et de l'Analyse Économique (INSAE) and Macro International Inc., *Enquête démographique et de santé (EDSB-III) Bénin 2006.* 2007, Macro International Inc.: Calverton: Maryland.
98. Edomwonyi, N.P. and P.E. Osaigbovo, *Incidence of obesity in parturients scheduled for caesarean section, intra-operative complications, management and outcome.* East Afr Med J, 2006. **83**(4): p. 112-9.
99. Basu, J.K., C.M. Jeketera, and D. Basu, *Obesity and its outcomes among pregnant South African women.* International Journal of Gynecology & Obstetrics, 2010. **110**(2): p. 101-104.
100. O'Brien, T.E., J.G. Ray, and W.S. Chan, *Maternal body mass index and the risk of preeclampsia: A systematic overview.* Epidemiology, 2003. **14**(3): p. 368-374.
101. Villamor, E. and S. Cnattingius, *Interpregnancy weight change and risk of adverse pregnancy outcomes: a population-based study.* Lancet, 2006. **368**(9542): p. 1164-1170.
102. Bellamy, L., et al., *Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis.* Lancet, 2009. **373**(9677): p. 1773-1779.
103. Torloni, M.R., et al., *Prepregnancy BMI and the risk of gestational diabetes: a systematic review of the literature with meta-analysis.* Obesity Reviews, 2009. **10**(2): p. 194-203.
104. Verdiales, M., C. Pacheco, and W.R. Cohen, *The effect of maternal obesity on the course of labor.* Journal of Perinatal Medicine, 2009. **37**(6): p. 651-655.
105. Cedergren, M.I., *Non-elective caesarean delivery due to ineffective uterine contractility or due to obstructed labour in relation to maternal body mass index.* European Journal of Obstetrics & Gynecology and Reproductive Biology, 2009. **145**(2): p. 163-166.
106. Pevzner, L., et al., *Effects of Maternal Obesity on Duration and Outcomes of Prostaglandin Cervical Ripening and Labor Induction.* Obstetrics and Gynecology, 2009. **114**(6): p. 1315-1321.
107. Jensen, H., A.O. Agger, and K.L. Rasmussen, *The influence of prepregnancy body mass index on labor complications.* Acta Obstetricia Et Gynecologica Scandinavica, 1999. **78**(9): p. 799-802.

108. Zhang, J., et al., *Poor uterine contractility in obese women.* Bjog-an International Journal of Obstetrics and Gynaecology, 2007. **114**(3): p. 343-348.
109. Ehrenberg, H.M., B.M. Mercer, and P.M. Catalano, *The influence of obesity and diabetes on the prevalence of macrosomia.* American Journal of Obstetrics and Gynecology, 2004. **191**(3): p. 964-968.
110. Kalk, P., et al., *Impact of maternal body mass index on neonatal outcome.* European Journal of Medical Research, 2009. **14**(5): p. 216-222.
111. Chen, G., S. Uryasev, and T.K. Young, *On prediction of the cesarean delivery risk in a large private practice.* American Journal of Obstetrics and Gynecology, 2004. **191**(2): p. 617-624.
112. Saravanakumar, K., S.G. Rao, and G.M. Cooper, *Obesity and obstetric anaesthesia.* Anaesthesia, 2006. **61**(1): p. 36-48.
113. CMACE, *Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006–2008.* BJOG: An International Journal of Obstetrics & Gynaecology, 2011. **118**: p. 1-203.
114. World Health Organization, *Neonatal and perinatal mortality: country, regional and global estimates.* 2006, WHO: Geneva.
115. Hyder, A.A., S.A. Wali, and J. McGuckin, *The burden of disease from neonatal mortality: a review of South Asia and Sub-Saharan Africa.* Bjog-an International Journal of Obstetrics and Gynaecology, 2003. **110**(10): p. 894-901.
116. Wall, S.N., et al., *Reducing Intrapartum-Related Neonatal Deaths in Low- and Middle-Income Countries-What Works?* Seminars in Perinatology, 2010. **34**(6): p. 395-407.
117. Schiffman, J., et al., *Community-Based Intervention Packages for Improving Perinatal Health in Developing Countries: A Review of the Evidence.* Seminars in Perinatology, 2010. **34**(6): p. 462-476.
118. Waller, D.K., et al., *Prepregnancy obesity as a risk factor for structural birth defects.* Archives of Pediatrics & Adolescent Medicine, 2007. **161**(8): p. 745-750.
119. Rasmussen, S.A., et al., *Maternal obesity and risk of neural tube defects: a metaanalysis.* American Journal of Obstetrics and Gynecology, 2008. **198**(6): p. 611-619.
120. Biggio, J.R., et al., *Fetal Anomalies in Obese Women The Contribution of Diabetes.* Obstetrics and Gynecology, 2010. **115**(2): p. 290-296.
121. Kiran, T.S.U., et al., *Outcome of pregnancy in a woman with an increased body mass index.* Bjog-an International Journal of Obstetrics and Gynaecology, 2005. **112**(6): p. 768-772.
122. Michlin, R., et al., *Maternal obesity and pregnancy outcome.* Israel Medical Association Journal, 2000. **2**(1): p. 10-13.
123. Yu, C.K.H., T.G. Teoh, and S. Robinson, *Obesity in pregnancy.* Bjog-an International Journal of Obstetrics and Gynaecology, 2006. **113**(10): p. 1117-1125.
124. Cnattingius, S., et al., *Pre-pregnancy weight and the risk of adverse pregnancy outcomes.* New England Journal of Medicine, 1998. **338**(3): p. 147-152.
125. Chen, M.H., et al., *Maternal obesity and neonatal Apgar scores.* Journal of Maternal-Fetal & Neonatal Medicine, 2010. **23**(1): p. 89-95.
126. Kristensen, J., et al., *Pre-pregnancy weight and the risk of stillbirth and neonatal death.* Bjog-an International Journal of Obstetrics and Gynaecology, 2005. **112**(4): p. 403-408.
127. Nohr, E.A., et al., *Maternal obesity and neonatal mortality according to subtypes of preterm birth.* Obstetrics and Gynecology, 2007. **110**(5): p. 1083-1090.
128. Chen, A., et al., *Maternal Obesity and the Risk of Infant Death in the United States.* Epidemiology, 2009. **20**(1): p. 74-81.
129. United Nations. *United Nations Millennium Development Goals*. 2011 [Accessed 9th March 2011]; Available from: www.un.org/millenniumgoals/

130. Tanumihardjo, S.A., et al., *Poverty, obesity, and malnutrition: An international perspective recognizing the paradox.* Journal of the American Dietetic Association, 2007. **107**(11): p. 1966-1972.
131. Finucane, M.M., et al., *National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants.* Lancet, 2011. **377**(9765): p. 557-567.
132. Zheng, L., et al., *The association between body mass index and incident hypertension in rural women in China.* European Journal of Clinical Nutrition, 2010. **64**(8): p. 769-775.
133. Marins, V.M.R., et al., *The association between socioeconomic indicators and cardiovascular disease risk factors in Rio de Janeiro, Brazil.* Journal of Biosocial Science, 2007. **39**(2): p. 221-229.
134. Ntandou, G., et al., *Abdominal obesity explains the positive rural-urban gradient in the prevalence of the metabolic syndrome in Benin, West Africa.* Nutrition Research, 2009. **29**(3): p. 180-189.
135. Idemyor, V., *Diabetes in Sub-Saharan Africa: Health Care Perspectives, Challenges, and the Economic Burden of Disease.* Journal of the National Medical Association, 2010. **102**(7): p. 650-653.
136. Mendez, M.A., C.A. Monteiro, and B.M. Popkin, *Overweight exceeds underweight among women in most developing countries.* Am J Clin Nutr, 2005. **81**(3): p. 714-721.
137. Popkin, B.M., *Nutritional paterns and transitions.* Population and Development Review, 1993. **19**(1): p. 138-157.
138. Popkin, B.M., *The nutrition transition in low-income countres - an emerging crisis.* Nutrition Reviews, 1994. **52**(9): p. 285-298.
139. Popkin, B.M. and C.M. Doak, *The obesity epidemic is a worldwide phenomenon.* Nutrition Reviews, 1998. **56**(4): p. 106-114.
140. Drewnowski, A. and B.M. Popkin, *The nutrition transition: New trends in the global diet.* Nutrition Reviews, 1997. **55**(2): p. 31-43.
141. Omran, A.R., *The epidemiologic transition - A theory of the epidemiology of population change (Reprinted from The Milbank Memorial Fund Quarterly, vol 49, pg 509-538, 1971).* Bulletin of the World Health Organization, 2001. **79**(2): p. 161-170.
142. Popkin, B.M., *The nutrition transition: An overview of world patterns of change.* Nutrition Reviews, 2004. **62**(7): p. S140-S143.
143. Du, S.F., et al., *A new stage of the nutrition transition in China.* Public Health Nutrition, 2002. **5**(1A): p. 169-174.
144. Monteiro, C.A., et al., *Socioeconomic status and obesity in adult populations of developing countries: a review.* Bulletin of the World Health Organization, 2004. **82**(12): p. 940-946.
145. Wang, Y.F., C. Monteiro, and B.M. Popkin, *Trends of obesity and underweight in older children and adolescents in the United States, Brazil, China, and Russia.* American Journal of Clinical Nutrition, 2002. **75**(6): p. 971-977.
146. Walker, A.R.P., F. Adam, and B.F. Walker, *World pandemic of obesity: the situation in Southern African populations.* Public Health, 2001. **115**(6): p. 368-372.
147. Popkin, B.M., *Part II. What is unique about the experience in lower- and middle-income less-industrialised countries compared with the very-high-income industrialised countries? The shift in stages of the nutrition transition in the developing world differs from past experiences!* Public Health Nutrition, 2002. **5**(1A): p. 205-214.
148. Ezzati, M., et al., *Rethinking the "diseases of affluence" paradigm: Global patterns of nutritional risks in relation to economic development.* Plos Medicine, 2005. **2**(5): p. 404-412.
149. Rose, D. and K.E. Charlton, *Prevalence of household food poverty in South Africa: results from a large, nationally representative survey.* Public Health Nutrition, 2002. **5**(3): p. 383-389.

150. Caballero, B., *A nutrition paradox - Underweight and obesity in developing countries.* New England Journal of Medicine, 2005. **352**(15): p. 1514-1516.
151. Drewnowski, A., N. Darmon, and A. Briend, *Replacing fats and sweets with vegetables and fruits - A question of cost.* American Journal of Public Health, 2004. **94**(9): p. 1555-1559.
152. Drewnowski, A. and N. Darmon, *The economics of obesity: dietary energy density and energy cost.* American Journal of Clinical Nutrition, 2005. **82**(1): p. 265s-273s.
153. Temple, N.J., et al., *Price and availability of healthy food: A study in rural South Africa.* Nutrition, 2011. **27**(1): p. 55-58.
154. Monteiro, C., et al., *Obesity and inequities in health in the developing world.* International Journal of Obesity, 2004. **28**(9): p. 1181-1186.
155. The World Bank. *The World Bank Data Catalog.* 2011 [Accessed 15th March 2011]; Available from: http://data.worldbank.org/.
156. Doak, C.M. and B.M. Popkin, *The Rapid Emergenec of Obesity in Developing Countries*, in *Nutrition and Health: Nutrition and Health in Developing Countries*, R.D. Semba and M.W. Bloem, Editors. 2008, Humana Press: Totowa, NJ.
157. Brug, J. and K. Knut-Inge, *Children and adolescents*, in *Public Health Nutrition: From principles to practice*, M. Lawrence and T. Worsley, Editors. 2007, McGraw Hill & Open University Press.
158. MacKeown, J.M., T.M. Pedro, and S.A. Norris, *Energy, macro- and micronutrient intake among a true longitudinal group of South African adolescents at two interceptions (2000 and 2003): the Birth-to-Twenty (Bt20) Study.* Public Health Nutrition, 2007. **10**(6): p. 635-643.
159. Mendis, S., *The policy agenda for prevention and control of non-communicable diseases.* British Medical Bulletin, 2010. **96**(1): p. 23-43.
160. Puoane, T., L. Tsolekile, and N. Steyn, *Perceptions about body image and sizes among Black African girls living in Cape Town.* Ethnicity & Disease, 2010. **20**(1): p. 29-34.
161. Holdsworth, M., et al., *Perceptions of healthy and desirable body size in urban Senegalese women.* International Journal of Obesity, 2004. **28**(12): p. 1561-1568.
162. Awah, P.K., N. Unwin, and P. Phillimore, *Cure or control: complying with biomedical regime of diabetes in Cameroon.* Bmc Health Services Research, 2008. **8**.
163. Ziraba, A.K., J.C. Fotso, and R. Ochako, *Overweight and obesity in urban Africa: A problem of the rich or the poor?* Bmc Public Health, 2009. **9**.
164. United Nations Population Fund, *State of the World Population 2007: Unleasing the Potential of Urban Growth.* 2007, UNFPA.
165. UN-HABITAT, *The State of African Cities 2010: Governance, Inequalities and Urban Land Markets.* 2010, UN-HABITAT.
166. Caballero, B. and B.M. Popkin, *The Nutrition Transition: diet and disease in the developing world.* 2002, London: Academic Press.
167. Jeemon, P., et al., *Double burden of underweight and overweight among children (10-19 years of age) of employees working in Indian industrial units.* National Medical Journal of India, 2009. **22**(4): p. 172-176.
168. Ntandou, G., et al., *Physical activity and socioeconomic status explain rural-urban differences in obesity: A cross-sectional study in Benin (West Africa).* Ecology of Food and Nutrition, 2008. **47**(4): p. 313-337.
169. Sodjinou, R., et al., *Obesity and cardio-metabolic risk factors in urban adults of Benin: Relationship with socio-economic status, urbanisation, and lifestyle patterns.* Bmc Public Health, 2008. **8**.
170. Amorim, T.C., M.R. Azevedo, and P.C. Halle, *Physical Activity Levels According to Physical and Social Environmental Factors in a Sample of Adults Living in South Brazil.* Journal of Physical Activity & Health, 2010. **7**: p. S204-S212.

171. Cogswell, M.E., et al., *Gestational weight gain among average weight and overweight women - what is excessive?* American Journal of Obstetrics and Gynecology, 1995. **172**(2): p. 705-712.
172. Lopez, R.P., *Neighborhood risk factors for obesity.* Obesity, 2007. **15**(8): p. 2111-2119.
173. Bourne, L.T., E.V. Lambert, and K. Steyn, *Where does the black population of South Africa stand on the nutrition transition?* Public Health Nutrition, 2002. **5**(1A): p. 157-162.
174. van't Riet, H., et al., *The role of street foods in the dietary pattern of two low-income groups in Nairobi.* European Journal of Clinical Nutrition, 2001. **55**(7): p. 562-570.
175. van't Riet, H., A.P. den Hartog, and W.A. van Staveren, *Non-home prepared foods: contribution to energy and nutrient intake of consumers living in two low-income areas in Nairobi.* Public Health Nutrition, 2002. **5**(4): p. 515-522.
176. Nago, E.S., et al., *Food, energy and macronutrient contribution of out-of-home foods in school-going adolescents in Cotonou, Benin.* British Journal of Nutrition, 2010. **103**(2): p. 281-288.
177. Wareham, N.J., *Commentary: Measuring physical activity in Sub-Saharan Africa.* International Journal of Epidemiology, 2001. **30**(6): p. 1369-1370.
178. Sobngwi, E., et al., *Development and validation of a questionnaire for the assessment of physical activity in epidemiological studies in Sub-Saharan Africa.* International Journal of Epidemiology, 2001. **30**(6): p. 1361-1368.
179. Abubakari, A.R., et al., *Prevalence and time trends in diabetes and physical inactivity among adult West African populations: The epidemic has arrived.* Public Health, 2009. **123**(9): p. 602-614.
180. Tesfaye, F., P. Byass, and S. Wall, *Population based prevalence of high blood pressure among adults in Addis Ababa: uncovering a silent epidemic.* BMC Cardiovasc Disord, 2009. **9**: p. 39.
181. Cook, I., M. Alberts, and E.V. Lambert, *Relationship between adiposity and pedometer-assessed ambulatory activity in adult, rural African women.* International Journal of Obesity, 2008. **32**(8): p. 1327-1330.
182. Demographic & Health Surveys. *About DHS.* 2011 [Accessed 9th March 2011]; Available from: http://www.measuredhs.com/aboutdhs/history.cfm.
183. Macro International Inc., *Sampling Manual. DHS-III Basic Documentation No. 6.* 1996: Calverton: Maryland.
184. Levy, P.S. and S. Lemeshow, *Chapter 5: Stratification and Stratified Random Sampling,* in *Sampling of Populations. Methods and Applications.* 1999.
185. ORC Macro, *Interviewer's Manual. MEASURE DHS Basic Documentation No. 2.* 2006: Calverton: Maryland.
186. ORC Macro, *Supervisor's and Editor's Manual. MEASURE DHS Basic Documentation No. 3.* 2006: Calverton: Maryland.
187. Macro International Inc., *DHS Model Questionnaire - Phase 5 (2003-2008) (DHSQ5). Available from http://www.measuredhs.com/pubs.*
188. Croft, T., *DHS Data Editing and Imputation (DHSG3). Available from http://www.measuredhs.com/pubs.*
189. Ali, M.M., J. Cleland, and I.H. Shah, *Trends in reproductive behavior among young single women in Colombia and Peru: 1985-1999.* Demography, 2003. **40**(4): p. 659-673.
190. Becker, S. and S. Ahmed, *Dynamics of contraceptive use and breastfeeding during the post-partum period in Peru and Indonesia.* Population Studies-a Journal of Demography, 2001. **55**(2): p. 165-179.
191. Leone, T. and A. Hinde, *Sterilization and union instability in Brazil.* Journal of Biosocial Science, 2005. **37**(4): p. 459-469.
192. United Nations Statistics Division. *Composition of macro geographical (continental) regions, geographical sub-regions, and selected economic and other groupings* 2011

[Accessed 9th March 2011]; Available from: http://unstats.un.org/unsd/methods/m49/m49regin.htm.
193. Caldwell, J.C., *The delayed western fertility decline: An examination of English-speaking countries.* Population and Development Review, 1999. **25**(3): p. 479-+.
194. Augood, C., K. Duckitt, and A.A. Templeton, *Smoking and female infertility: a systematic review and meta-analysis.* Human Reproduction, 1998. **13**(6): p. 1532-1539.
195. Bolumar, F., et al., *Smoking reduces fecundity: A European multicenter study on infertility and subfecundity.* American Journal of Epidemiology, 1996. **143**(6): p. 578-587.
196. Rutstein, S.O., *Change in the Desired Number of Children: A Cross-Country Cohort Analysis of Levels and Correlates of Change*. 1998, Macro International Inc: Calverton: Maryland.
197. Garenne, M., *Fertility Changes in Sub-Saharan Africa*, in *DHS Comparative Reports No. 18*. 2008, Macro International Inc: Calverton: Maryland.
198. Kirkwood, B.R. and J.A.C. Sterne, *Essential Medical Statistics*. 2nd ed. 2003: Blackwell Science.
199. Waters, L., C. Gilling-Smith, and F. Boag, *HIV infection and subfertility.* Int J STD AIDS, 2007. **18**(1): p. 1-6.
200. Lewis, J.J., et al., *The population impact of HIV on fertility in sub-Saharan Africa.* AIDS, 2004. **18 Suppl 2**: p. S35-43.
201. Gray, R.H., et al., *Population-based study of fertility in women with HIV-1 infection in Uganda.* Lancet, 1998. **351**(9096): p. 98-103.
202. Delvaux, T. and C. Nostlinger, *Reproductive choice for women and men living with HIV: contraception, abortion and fertility.* Reprod Health Matters, 2007. **15**(29 Suppl): p. 46-66.
203. Chen, W.J. and N. Walker, *Fertility of HIV-infected women: insights from Demographic and Health Surveys.* Sex Transm Infect, 2010. **86 Suppl 2**: p. ii22-7.
204. Oguntibeju, O.O., W.M. van den Heever, and F.E. Van Schalkwyk, *The interrelationship between nutrition and the immune system in HIV infection: a review.* Pak J Biol Sci, 2007. **10**(24): p. 4327-38.
205. Jones, C.Y., et al., *Overweight and human immunodeficiency virus (HIV) progression in women: associations HIV disease progression and changes in body mass index in women in the HIV epidemiology research study cohort.* Clin Infect Dis, 2003. **37 Suppl 2**: p. S69-80.
206. Keithley, J.K., et al., *HIV infection and obesity: a review of the evidence.* J Assoc Nurses AIDS Care, 2009. **20**(4): p. 260-74.
207. Meekers, D., *Sexual Initiation and Premarital Childbearing in Sub-Saharan Africa.* Population Studies-a Journal of Demography, 1994. **48**(1): p. 47-64.
208. Harwood-Lejeune, A., *Rising age at marriage and fertility in southern and Eastern Africa.* European Journal of Population-Revue Europeenne De Demographie, 2001. **17**(3): p. 261-280.
209. Meekers, D., *The Process of Marriage in African Societies - a Multiple Indicator Approach.* Population and Development Review, 1992. **18**(1): p. 61-78.
210. Pullum, T.W., *An Assessment of Age and Date Reporting in the DHS Surveys, 1985-2003*, in *DHS Methodological Reports mo. 5*. 2006, Macro International Inc: Calverton, Maryland, USA.
211. Brown, M.S., *Coitus, the proximate determinant of conception: Inter-country variance in sub-Saharan Africa.* Journal of Biosocial Science, 2000. **32**(2): p. 145-159.
212. Blanc, A.K. and S. Grey, *Greater than expected fertility decline in Ghana: Untangling a puzzle.* Journal of Biosocial Science, 2002. **34**(4): p. 475-495.
213. Read, J.S. and M.K. Newell, *Efficacy and safety of cesarean delivery for prevention of mother-to-child transmission of HIV-1.* Cochrane Database Syst Rev, 2005(4): p. CD005479.

214. Thorne, C. and M.L. Newell, *Prevention of mother-to-child transmission of HIV infection.* Curr Opin Infect Dis, 2004. **17**(3): p. 247-52.
215. Gabrysch, S., et al., *The influence of distance and level of care on delivery place in rural Zambia: a study of linked national data in a geographic information system.* PLoS Med, 2011. **8**(1): p. e1000394.
216. Holtz, S.A. and C.K. Stanton, *Assessing the quality of cesarean birth data in the demographic and health surveys.* Studies in Family Planning, 2007. **38**(1): p. 47-54.
217. Brocklehurst, P. and R. French, *The association between maternal HIV infection and perinatal outcome: a systematic review of the literature and meta-analysis.* British Journal of Obstetrics and Gynaecology, 1998. **105**(8): p. 836-848.
218. Hill, K. and Y. Choi, *Neonatal mortality in the developing world.* Demographic Research, 2006. **14**(18): p. 429-452.
219. Loaiza, E., *Maternal Nutritional Status*, in *DHS Comparative Reports No. 24*. 1997, Macro International Inc.: Calverton: Maryland.
220. Pullum, T.W., *An Assessment of the Quality of Data on Health and Nutrition in the DHS Surveys, 1993-2003*, in *DHS Methodological Reports No. 6*. 2008, Macro International Inc.: Calverton: Maryland.
221. Schmitt, N.M., W.K. Nicholson, and J. Schmitt, *The association of pregnancy and the development of obesity - results of a systematic review and meta-analysis on the natural history of postpartum weight retention.* International Journal of Obesity, 2007. **31**(11): p. 1642-1651.
222. Prentice, A.M. and S.A. Jebb, *Beyond body mass index.* Obesity Reviews, 2001. **2**(3): p. 141-7.
223. Deurenberg, P., M. Yap, and W.A. van Staveren, *Body mass index and percent body fat: a meta analysis among different ethnic groups.* Int J Obes Relat Metab Disord, 1998. **22**(12): p. 1164-71.
224. Barba, C., et al., *Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies.* Lancet, 2004. **363**(9403): p. 157-163.
225. Jackson, A.S., et al., *The effect of sex, age and race on estimating percentage body fat from body mass index: The Heritage Family Study.* International Journal of Obesity, 2002. **26**(6): p. 789-796.
226. Gallagher, D., et al., *How useful is body mass index for comparison of body fatness across age, sex, and ethnic groups?* American Journal of Epidemiology, 1996. **143**(3): p. 228-239.
227. Rutstein, S.O. and K. Johnson, *The DHS Wealth Index*, in *DHS Comparative Reports No. 6*. 2004, ORC Macro: Calverton: Maryland.
228. Bollen, K.A., J.L. Glanville, and G. Stecklov, *Socioeconomic status and class in studies of fertility and health in developing countries.* Annual Review of Sociology, 2001. **27**: p. 153-185.
229. Fotso, J.C. and B. Kuate-Defo, *Measuring socioeconomic status in health research in developing countries: Should we be focusing on households, communities or both?* Social Indicators Research, 2005. **72**(2): p. 189-237.
230. Filmer, D. and L.H. Pritchett, *Estimating wealth effects without expenditure data - Or tears: An application to educational enrollments in states of India.* Demography, 2001. **38**(1): p. 115-132.
231. Manly, B.F.J., *Multivariate Statistical Methods: a primer*. 2nd ed. 1994, London: Chapman & Hall.
232. Wagstaff, A. and N. Watanabe, *What difference does the choice of SES make in health inequality measurement?* Health Economics, 2003. **12**(10): p. 885-890.
233. Howe, L.D., et al., *Is the wealth index a proxy for consumption expenditure? A systematic review.* Journal of Epidemiology and Community Health, 2009. **63**(11): p. 871-U21.

234. Vyas, S. and L. Kumaranayake, *Constructing socio-economic status indices: how to use principal components analysis.* Health Policy and Planning, 2006. **21**(6): p. 459-468.
235. Houweling, T.A., A.E. Kunst, and J.P. Mackenbach, *Measuring health inequality among children in developing countries: does the choice of the indicator of economic status matter?* Int J Equity Health, 2003. **2**(1): p. 8.
236. Rutstein, S.O., *The DHS Wealth Index: Approaches for Rural and Urban Areas*, in *DHS Working Papers. No. 60.* 2008, Macro International Inc.: Calverton: Maryland.
237. Ferguson, B.D., et al., *Estimating Permanent Income Using Indicator Variables*, in *Health Systems Performance Assessment: Debates, Methods and Empiricism*. 2003, WHO: Geneva.
238. Kolenikov, S. and G. Angeles, *Socioeconomic Status Measurement with Discrete Proxy Variables: Is Principal Component Analysis a Reliable Answer?* Review of Income and Wealth, 2009. **55**(1): p. 128-165.
239. Howe, L.D., J.R. Hargreaves, and S.R. Huttly, *Issues in the construction of wealth indices for the measurement of socio-economic position in low-income countries.* Emerg Themes Epidemiol, 2008. **5**: p. 3.
240. Booysen, F., et al., *Using an asset index to assess trends in poverty in seven Sub-Saharan African countries.* World Development, 2008. **36**(6): p. 1113-1130.
241. StataCorp, *Stata Statistical Software: Release 11*. 2009, StataCorp LP: College Station, TX.
242. Rabe-Hesketh, S. and A. Skrondal, *Chapter 8: Discrete-time survival*, in *Multilevel and Longitudinal Modeling Using Stata*. 2008, StataCorp LP: College Station, Texas.
243. Archer, K.J. and S. Lemeshow, *Goodness-of-fit test for a logistic regression model fitted using survey sample data.* The Stata Journal, 2006. **6**(1): p. 97-105.
244. Archer, K.J., S. Lemeshow, and D.W. Hosmer, *Goodness-of-fit tests for logistic regression models when data are collected using a complex sampling design.* Computational Statistics & Data Analysis, 2007. **51**: p. 4450-4464.
245. StataCorp, *Stata Survey Data Reference Manual. Release 11.* 2009: College Station, Texas.
246. The NHS Information Centre: Lifestyle Statistics, *Statistics on obesity, physical activity and diet: England, 2010.* 2010, The NHS Information Centre for Health & Social Care.
247. World Food Programme, *WFP in Africa : 2009 Facts and Figures*. 2009, WFP Liason Office to the AU & ECA; Addis Ababa, Ethiopia.
248. Li, L., et al., *Child-to-Adult Body Mass Index and Height Trajectories: A Comparison of 2 British Birth Cohorts.* American Journal of Epidemiology, 2008. **168**(9): p. 1008-1015.
249. Adair, L.S., *Size at birth and growth trajectories to young adulthood.* Am J Hum Biol, 2007. **19**(3): p. 327-37.
250. Stein, A.D., et al., *Growth patterns in early childhood and final attained stature: data from five birth cohorts from low- and middle-income countries.* Am J Hum Biol, 2010. **22**(3): p. 353-9.
251. Ong, S.K., et al., *Longitudinal study of the socio-demographic determinants of changes in body weight and waist circumference in a multi-ethnic Asian population.* International Journal of Obesity, 2009. **33**(11): p. 1299-1308.
252. Baltrus, P.T., et al., *Race/ethnicity, life-course socioeconomic position, and body weight trajectories over 34 years: The Alameda County Study.* American Journal of Public Health, 2005. **95**(9): p. 1595-1601.
253. Zajacova, A. and S.A. Burgard, *Body Weight and Health from Early to Mid-Adulthood.* Journal of Health and Social Behavior, 2010. **51**(1): p. 92-107.
254. Mujahid, M.S., et al., *Cross-sectional and longitudinal associations of BMI with socioeconomic characteristics.* Obesity Research, 2005. **13**(8): p. 1412-1421.
255. Williamson, D.F., et al., *The 10 year incidence of overweight and major weight gain in US adults.* Archives of Internal Medicine, 1990. **150**(3): p. 665-672.

256. Margetic, S., et al., *Leptin: a review of its peripheral actions and interactions.* International Journal of Obesity, 2002. **26**(11): p. 1407-1433.
257. Cummins, S. and S. Macintyre, *Food environments and obesity - neighbourhood or nation?* International Journal of Epidemiology, 2006. **35**(1): p. 100-104.
258. Weinsier, R.L., et al., *The etiology of obesity: Relative contribution of metabolic factors, diet, and physical activity.* American Journal of Medicine, 1998. **105**(2): p. 145-150.
259. Palou, A., et al., *Obesity: molecular bases of a multifactorial problem.* European Journal of Nutrition, 2000. **39**(4): p. 127-144.
260. Winkvist, A., K.M. Rasmussen, and L. Lissner, *Associations between reproduction and maternal body weight: examining the component parts of a full reproductive cycle.* European Journal of Clinical Nutrition, 2003. **57**(1): p. 114-127.
261. Kuehn, B.M., *Guideline for Pregnancy Weight Gain Offers Targets for Obese Women.* JAMA, 2009. **302**(3): p. 241-242.
262. Ludwig, D.S. and J. Currie, *The association between pregnancy weight gain and birthweight: a within-family comparison.* The Lancet, 2010. **376**(9745): p. 984-990.
263. Scott, J., D. Campbell, and M. Davies, *Mothers and infants*, in *Public Health Nutrition: From principles to practice*, M. Lawrence and T. Worsley, Editors. 2007, McGraw Hill & Open University Press.
264. Durnin, J.V., *Energy requirements of pregnancy. An integrated study in five countries: background and methods.* Lancet, 1987. **2**(8564): p. 895-6.
265. Durnin, J.V., *Energy requirements of pregnancy: an integration of the longitudinal data from the five-country study.* Lancet, 1987. **2**(8568): p. 1131-3.
266. Olson, C.M., et al., *Gestational weight gain and postpartum behaviors associated with weight change from early pregnancy to 1y postpartum.* International Journal of Obesity, 2003. **27**(1): p. 117-127.
267. Huang, T.T., H.S. Wang, and F.T. Dai, *Effect of pre-pregnancy body size on postpartum weight retention.* Midwifery, 2010. **26**(2): p. 222-231.
268. Mamun, A.A., et al., *Associations of excess weight gain during pregnancy with long-term maternal overweight and obesity: evidence from 21 y postpartum follow-up.* American Journal of Clinical Nutrition, 2010. **91**(5): p. 1336-1341.
269. Amorim, A.R., et al., *Does excess pregnancy weight gain constitute a major risk for increasing long-term BMI?* Obesity, 2007. **15**(5): p. 1278-1286.
270. Harris, H.E., G.T. Ellison, and M. Holliday, *Is there an independent association between parity and maternal weight gain?* Ann Hum Biol, 1997. **24**(6): p. 507-19.
271. Streuling, I., A. Beyerlein, and R. von Kries, *Can gestational weight gain be modified by increasing physical activity and diet counseling? A meta-analysis of interventional trials.* American Journal of Clinical Nutrition, 2010. **92**(4): p. 678-687.
272. Lyu, L.C., et al., *A prospective study of dietary intakes and influential factors from pregnancy to postpartum on maternal weight retention in Taipei, Taiwan.* British Journal of Nutrition, 2009. **102**(12): p. 1828-1837.
273. Baker, J.L., et al., *Breastfeeding reduces postpartum weight retention.* American Journal of Clinical Nutrition, 2008. **88**(6): p. 1543-1551.
274. Okechukwu, A.A., E.C. Okpe, and A.A. Okolo, *Exclusive breastfeeding and postnatal changes in maternal anthropometry.* Nigerian Journal of Clinical Practice, 2009. **12**(4): p. 383-388.
275. Janney, C.A., D.W. Zhang, and M. Sowers, *Lactation and weight retention.* American Journal of Clinical Nutrition, 1997. **66**(5): p. 1116-1124.
276. Gigante, D.P., C.G. Victora, and F.C. Barros, *Breast-feeding has a limited long-term effect on anthropometry and body composition of Brazilian mothers.* J Nutr, 2001. **131**(1): p. 78-84.
277. Butte, N.F. and J.C. King, *Energy requirements during pregnancy and lactation.* Public Health Nutrition, 2005. **8**(7A): p. 1010-1027.

278. Butte, N.F. and J.M. Hopkinson, *Body composition changes during lactation are highly variable among women.* Journal of Nutrition, 1998. **128**(2): p. 381S-385S.
279. Adair, L.S. and B.M. Popkin, *Prolonged lactation contributes to depletion of maternal energy reserves in Filipino women.* Journal of Nutrition, 1992. **122**(8): p. 1643-1655.
280. Mbofung, C.M.F. and T. Atinmo, *Zinc, copper and iron concentrations in the plasma and diets of lactating Nigerian women.* British Journal of Nutrition, 1985. **53**(3): p. 427-439.
281. Coitinho, D.C., R. Sichieri, and M.H.D. Benicio, *Obesity and weight change related to parity and breast-feeding among parous women in Brazil.* Public Health Nutrition, 2001. **4**(4): p. 865-870.
282. Winikoff, B. and M.A. Castle, *Defining maternal depletion syndrome.* American Journal of Public Health, 1993. **83**(7): p. 1052-1052.
283. Winkvist, A., K.M. Rasmussen, and J.P. Habicht, *A new definition of maternal depletion syndrome.* Am J Public Health, 1992. **82**(5): p. 691-694.
284. Kim, S.A., A.D. Stein, and R. Martorell, *Country development and the association between parity and overweight.* International Journal of Obesity, 2007. **31**(5): p. 805-812.
285. Koch, E., et al., *Impact of parity on anthropometric measures of obesity controlling by multiple confounders: a cross-sectional study in Chilean women.* Journal of Epidemiology and Community Health, 2008. **62**(5): p. 461-470.
286. Kim, S.A., et al., *The relationship between parity and overweight varies with household wealth and national development.* International Journal of Epidemiology, 2007. **36**(1): p. 93-101.
287. Prentice, A.M., et al., *Long-term energy balance in childbearing Gambian women.* American Journal of Clinical Nutrition, 1981. **34**(12): p. 2790-2799.
288. Shell-Duncan, B. and S.A. Yung, *The maternal depletion transition in northern Kenya: the effects of settlement, development and disparity.* Social Science & Medicine, 2004. **58**(12): p. 2485-2498.
289. Fox, M.P., T.L. Lash, and S. Greenland, *A method to automate probabilistic sensitivity analyses of misclassified binary variables.* International Journal of Epidemiology, 2005. **34**(6): p. 1370-1376.
290. Orsini, N., et al., *A tool for deterministic and probabilistic sensitivity analysis of epidemiologic studies.* Stata Journal, 2008. **8**(1): p. 29-48.
291. Grodstein, F., M.B. Goldman, and D.W. Cramer, *Body mass index and ovulatory infertility.* Epidemiology, 1994. **5**(2): p. 247-250.
292. Almroth, L., et al., *Primary infertility after genital mutilation in girlhood in Sudan: a case-control study.* Lancet, 2005. **366**(9483): p. 385-391.
293. Tielemans, E., et al., *Sources of bias in studies among infertility clients.* American Journal of Epidemiology, 2002. **156**(1): p. 86-92.
294. Higgins, J.P.T. and S. Green, *Cochrane Handbook for Systematic Reviews of Interventions. Version 5.0.1 [updated September 2008].* 2008, The Cochrane Collaboration, 2008.
295. Egger, M., G. Davey Smith, and D.G. Altman, *Systematic Reviews in Health Care. Meta-analysis in context.* 2nd ed. 2001: BMJ Books.
296. Deeks, J.J., et al., *Evaluating non-randomised intervention studies.* Health Technology Assessment, 2003. **7**(27): p. iii-x, 1-173.
297. Wells, G.A., et al. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.* Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm (Accessed 1st Sept. 2009).
298. Phillips, A.N. and G.D. Smith, *How independent are "independent" effects? relative risk estimation when correlated exposures are measured imprecisely.* Journal of Clinical Epidemiology, 1991. **44**(11): p. 1223-1231.

299. Egger, M., M. Schneider, and G.D. Smith, *Meta-analysis Spurious precision? Meta-analysis of observational studies.* BMJ, 1998. **316**(7125): p. 140-144.
300. *Pregnancy and Obesity: an analytic study and review of the literature.* J. Obstet. Gynaec. India, 1963. **13**(2): p. 213-223.
301. Kaku, M., N. Mori, and I. Miyagawa, *[Disturbance of sexual function and the adipose tissue in obese women].* Sanfujinka No Jissai, 1969. **18**(3): p. 212-8.
302. Kaneshiro, B., et al., *The relationship between body mass index and unintended pregnancy: results from the 2002 National Survey of Family Growth.* Contraception, 2008. **77**(4): p. 234-238.
303. Noci, I., et al. *Menstrual disturbances and fertility in obese patients.* in *Conference on Physiopathological Principles of Endocrine Dysfunctions in Women.* 1994. Siena, Italy: Monduzzi Editore.
304. Koloszar, S., J. Szollosi, and G. Bartfai, *Association between body mass index and ovulatory infertility in Hungarian women.* Human Reproduction, 1998. **13**: p. P265.
305. Gesink Law, D.C., R.F. Maclehose, and M.P. Longnecker, *Obesity and time to pregnancy.* Human Reproduction, 2007. **22**(2): p. 414-420.
306. Jensen, T.K., et al., *Fecundability in relation to body mass and menstrual cycle patterns.* Epidemiology, 1999. **10**(4): p. 422-428.
307. Bolumar, F., et al., *Body mass index and delayed conception: A European multicenter study on infertility and subfecundity.* American Journal of Epidemiology, 2000. **151**(11): p. 1072-1079.
308. Richman, S., *Obesity and Time to Conception.* Clinical Medicine: Reproductive Health, 2008. **1**: p. 3-8.
309. Hassan, M.A. and S.R. Killick, *Negative lifestyle is associated with a significant reduction in fecundity.* Fertil Steril, 2004. **81**(2): p. 384-92.
310. Kelly-Weeder, S. and C.L. Cox, *The impact of lifestyle risk factors on female infertility.* Women & Health, 2006. **44**(4): p. 1-23.
311. Ramlau-Hansen, C.H., et al., *Subfecundity in overweight and obese couples.* Hum Reprod, 2007. **22**(6): p. 1634-7.
312. Wellons, M.F., et al., *Racial differences in self-reported infertility and risk factors for infertility in a cohort of black and white women: The CARDIA Women's Study.* Fertility and Sterility, 2008. **90**(5): p. 1640-1648.
313. Yilmaz, N., et al., *The relationship between obesity and fecundity.* Journal of Women's Health (15409996), 2009. **18**(5): p. 633-636.
314. Hollander, D., *Risk of delayed conception is sharply elevated among obese women who smoke.* Family Planning Perspectives, 2000. **32**(6): p. 313-314.
315. Juul, S., W. Karmaus, and J. Olsen, *Regional differences in waiting time to pregnancy: pregnancy-based surveys from Denmark, France, Germany, Italy and Sweden.* Human Reproduction, 1999. **14**(5): p. 1250-1254.
316. Law, D.C.G. and M.P. Longnecker. *Does obesity reduce fecundity for specific subgroups?* in *2nd North American Congress of Epidemiology.* 2006. Seattle, WA: Oxford Univ Press Inc.
317. Kelly, S.S., *The impact of life style risk factors on female fertility status: An application of the interaction model of client health behavior.* 2004, University of Massachusetts Lowell. p. 262 p.
318. Nohr, E.A., et al., *Waiting time to pregnancy according to maternal birthweight and prepregnancy BMI.* Human Reproduction, 2009. **24**(1): p. 226-232.
319. Cox, D.R., *Regression Models and Life-Tables.* Journal of the Royal Statistical Society. Series B (Methodological), 1972. **34**(2): p. 187-220.
320. Kalbfleisch, J.D., *The statistical analysis of failure time data.* 1980, John Wiley & Sons: New York. p. 35-8.

321. Basso, O., S. Juul, and J. Olsen, *Time to pregnancy as a correlate of fecundity: differential persistence in trying to become pregnant as a source of bias.* International Journal of Epidemiology, 2000. **29**(5): p. 856-861.
322. Palta, M., et al., *Comparison of self-reported and measured height and weight.* Am. J. Epidemiol., 1982. **115**(2): p. 223-230.
323. Brewer, C.J. and A.H. Balen, *The adverse effects of obesity on conception and implantation.* Reproduction, 2010. **140**(3): p. 347-364.
324. Brody, S., *Slimness is associated with greater intercourse and lesser masturbation frequency.* Journal of Sex & Marital Therapy, 2004. **30**(4): p. 251-261.
325. Trischitta, V., *Relationship between obesity-related metabolic abnormalities and sexual function.* J Endocrinol Invest, 2003. **26**(3 Suppl): p. 62-4.
326. Bajos, N., et al., *Sexuality and obesity, a gender perspective: results from French national random probability survey of sexual behaviours.* British Medical Journal, 2010. **340**.
327. Chen, E.Y. and M. Brown, *Obesity stigma in sexual relationships.* Obesity Research, 2005. **13**(8): p. 1393-1397.
328. Aruguete, M.S., J.L. Edman, and A. Yates, *Romantic interest in obese college students.* Eating Behaviors, 2009. **10**(3): p. 143-145.
329. Duda, R.B., et al., *Assessment of the ideal body image of women in Accra, Ghana.* Tropical Doctor, 2007. **37**(4): p. 241-244.
330. Dapi, L.N., et al., *I Eat to be Happy, to be Strong, and to Live." - Perceptions of rural and urban adolescents in Cameroon, Africa.* Journal of Nutrition Education and Behavior, 2007. **39**(6): p. 320-326.
331. Stanton, C. and C. Ronsmans, *Recommendations for routine reporting on indications for cesarean delivery in developing countries.* Birth, 2008. **35**(3): p. 204-11.
332. Bragg, F., et al., *Variation in rates of caesarean section among English NHS trusts after accounting for maternal and clinical risk: cross sectional study.* BMJ, 2010. **341**.
333. Rothman, K.J., et al., *Causation and Causal Inference*, in *Modern Epidemiology*, K.J. Rothman, S. Greenland, and T.L. Lash, Editors. 2008, Lippincott Williamns & Wilkins.
334. Menken, J., J. Trussell, and U. Larsen, *Age and infertility.* Science, 1986. **233**(4771): p. 1389-1394.
335. Jurek, A.M., et al., *Proper interpretation of non-differential misclassification effects: expectations vs observations.* International Journal of Epidemiology, 2005. **34**(3): p. 680-687.
336. Jurek, A.M., S. Greenland, and G. Maldonado, *How far from non-differential does exposure or disease misclassification have to be to bias measures of association away from the null?* International Journal of Epidemiology, 2008. **37**(2): p. 382-385.
337. Schisterman, E.F., S.R. Cole, and R.W. Platt, *Overadjustment Bias and Unnecessary Adjustment in Epidemiologic Studies.* Epidemiology, 2009. **20**(4): p. 488-495.
338. Swami, V., et al., *The Attractive Female Body Weight and Female Body Dissatisfaction in 26 Countries Across 10 World Regions: Results of the International Body Project I.* Personality and Social Psychology Bulletin, 2010. **36**(3): p. 309-325.
339. Cecchini, M., et al., *Chronic Diseases: Chronic Diseases and Development 3 Tackling of unhealthy diets, physical inactivity, and obesity: health effects and cost-effectiveness.* Lancet, 2010. **376**(9754): p. 1775-1784.
340. Dhont, N., et al., *'Mama and papa nothing': living with infertility among an urban population in Kigali, Rwanda.* Human Reproduction, 2011. **26**(3): p. 623-629.
341. Larsen, U., et al., *Suffering Infertility: the impact of infertlity on women's life experiences in two Nigerian communities.* Journal of Biosocial Science, 2010. **42**(6): p. 787-814.
342. Sharma, S., S. Mittal, and P. Aggarwal, *Management of infertility in low resource countries.* Bjog-an International Journal of Obstetrics and Gynaecology, 2009. **116**: p. 77-83.

343. Ombelet, W., et al., *Infertility and the provision of infertility medical services in developing countries.* Human Reproduction Update, 2008. **14**(6): p. 605-621.
344. Nelson, S.M. and R.F. Fleming, *The preconceptual contraception paradigm: obesity and infertility.* Human Reproduction, 2007. **22**(4): p. 912-915.
345. Kramer, M.S. and S.W. McDonald, *Aerobic exercise for women during pregnancy.* Cochrane Database of Systematic Reviews, 2006(3).
346. Polley, B.A., R.R. Wing, and C.J. Sims, *Randomized controlled trial to prevent excessive weight gain in pregnant women.* International Journal of Obesity, 2002. **26**(11): p. 1494-1502.
347. Streuling, I., et al., *Physical activity and gestational weight gain: a meta-analysis of intervention trials.* Bjog-an International Journal of Obstetrics and Gynaecology, 2011. **118**(3): p. 278-284.
348. Perkins, J.M., H.W. Perkins, and D.W. Craig, *Peer weight norm misperception as a risk factor for being over and underweight among UK secondary school students.* European Journal of Clinical Nutrition, 2010. **64**(9): p. 965-971.
349. Burke, M.A., F.W. Heiland, and C.M. Nadler, *From "Overweight" to "About Right": Evidence of a Generational Shift in Body Weight Norms.* Obesity, 2010. **18**(6): p. 1226-1234.

Appendix A

Precise wording of the question relating to caesarean delivery extracted from the country-specific survey.

Survey (year)	Question Wording
Benin (2006)	Avez-vous accouché de (NOM) par césarienne?
Burkina Faso (2003)	Avez-vous accouché de (NOM) par césarienne?
Cameroon (2004)	Avez-vous accouché de (NOM) par césarienne?
Chad (2004)	Avez-vous accouché de (NOM) par césarienne?
Congo-Brazzaville (2005)	Avez-vous accouché de (NOM) par césarienne, c'est-à-dire avez-vous été opérée?
DRC (2007)	Avez-vous accouché de (NOM) par césarienne?
Ethiopia (2005)	Was (NAME) delivered by caesarean section?
Ghana (2008)	Was (NAME) delivered by caesarean section?
Guinea (2005)	Avez-vous accouché de (NOM) par césarienne?
Kenya (2008-09)	Was (NAME) delivered by caesarean section?
Lesotho (2004)	Was (NAME) delivered by caesarean section?
Liberia (2007)	Was (NAME) delivered by C-section?
Madagascar (2008-09)	Avez-vous accouché de (NOM) par césarienne?
Malawi (2004)	Was (NAME) delivered by caesarean section?
Mali (2006)	Avez-vous accouché de (NOM) par césarienne?
Mozambique (2003)	O parto de (NOME) foi normal, com ventosa ou cesariana?
Namibia (2006-07)	Was (NAME) delivered by caesarean section?
Niger (2006)	Avez-vous accouché de (NOM) par césarienne?
Nigeria (2008)	Was (NAME) delivered by caesarean section (operation)?
Rwanda (2005)	Was (NAME) delivered by caesarean section?
Senegal (2005)	Avez-vous accouché de (NOM) par césarienne?
Sierra Leone (2008)	Was (NAME) delivered by caesarean section?
Swaziland (2006)	Was (NAME) delivered by caesarean section?
Tanzania (2004)	Was (NAME) delivered by caesarean section?
Uganda (2006)	Was (NAME) delivered by caesarean section?
Zambia (2007)	Was (NAME) delivered by caesarean section?
Zimbabwe (2005-06)	Was (NAME) delivered by caesarean section?

Appendix B

Search Strategy (Chapter 6) as entered into PubMed

#1	"Overweight"[Mesh]
#2	"Obesity"[Mesh]
#3	"Body Mass Index"[Mesh]
#4	overweight
#5	obes*
#6	body mass index
#7	BMI
#8	#1 OR #2 OR #3 OR #4 #5 OR #6 or #7
#9	"Fertility"[Mesh]
#10	"Infertility, Female"[Mesh]
#11	fertil*
#12	infertil*
#13	subfertil*
#14	fecund*
#15	infecund*
#16	subfecund*
#17	pregnancy rate
#18	conception rate
#19	time to pregnancy
#20	time to conception
#21	delayed conception
#22	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#21	#8 AND #22

Appendix C

Newcastle-Ottawa Quality Assessment Scale [297]

(As modified to meet the needs of this review)

Selection:

1) Representativeness of the exposed cohort
   a) truly representative of the average woman of reproductive age in the community ✸
   b) somewhat representative of the average woman of reproductive age in the community ✸
   c) selected group of users e.g. nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✸
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (e.g. surgical records) ✸
   b) structured interview ✸
   c) written self report
   d) no description

Comparability:

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for women's age ✸
   b) study controls for one other confounding factor ✸

Outcome:

1) Assessment of outcome
   a) independent blind assessment ✸
   b) record linkage ✸
   c) self report
   d) no description

2) Participation rate
   a) participation> 20% ✸
   c) follow up rate < 20%
   d) no statement