LIFE COURSE DETERMINANTS OF OFFSPRING SIZE AT BIRTH: AN INTERGENERATIONAL STUDY OF ABERDEEN WOMEN

by

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Abstract

Offspring size at birth is the result of a complex interplay of biological and social variables acting over several generations. However much current epidemiological research tends either to focus on measures of size at birth as initial explanatory variables in the pathway between early life and later adult health outcomes or it limits the context of the determinants of offspring size at birth to concurrently measured adult parental characteristics. This ignores the temporally distal influences on fetal growth, in particular the intergenerational influence of the maternal intrauterine environment. Integrating the distinct periods of influence on offspring size at birth requires a lifecourse approach that allows for the cumulative influence of both proximal and distal biological and social factors.

The Aberdeen intergenerational cohort contains extensive parental, perinatal and developmental data on over 5000 females born between 1950 and 1955. Probabilistic record linkage to the Scottish Morbidity Record system linked 4000 females to over 7000 offspring delivery records. The linked intergenerational data were used to determine the effect of temporally ordered social and biological factors operating across a woman's lifecourse on her offspring's size at birth.

The lifecourse approach suggested that socioeconomic inequalities seen in offspring size at birth were largely generated by continuity of social environments across generations and the effect of the early childhood social environment in particular on differential maternal lifetime growth. Most notably maternal intrauterine growth had an enduring intergenerational effect on offspring growth that was not diminished by later adult maternal or paternal, biological or social characteristics.

Therefore interventions aimed at improving offspring size at birth on a population scale require intergenerational and lifecourse considerations, which acknowledge the long-term effect of the social environment, rather than just a short-term focus on the pre-pregnancy and pregnancy period.

Dedication

To the inspirational matriarchs in my family…

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Declaration that this thesis is my own work
(Re Sections 6.3.3 and 6.3.6 Degree Regulations)

I formally declare that the work contained in this thesis is the result of my own work. While the revitalisation of the Aberdeen Child Development Study is a co-operative project at the London School of Hygiene and Tropical Medicine, the Intergenerational component of the revitalisation has been solely my responsibility and all the work contained in this thesis is my own.

Susan M.B. Morton
July 2002

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Chapter 1:
Offspring Size at Birth

"Health is a phenomenon that illustrates the remaining social inequalities in a society" (Ostberg, 1996)

Introduction

Offspring size at birth is the primary focus for this thesis and the following overview summarises the rationale for considering it as the outcome of interest. The first section describes why size at birth is an important measure of population health and why it has recently gained renewed significance in epidemiological research due to the considerable interest in the fetal origins of adult disease hypothesis. Parallels will be drawn between pregnancy as an example of an adult health outcome and other chronic adult conditions commonly associated with size at birth in the fetal origins hypothesis. The second section concentrates on size at birth as an outcome in its own right rather than as an explanatory factor for population health. The determinants of size at birth will be reviewed, concentrating on intergenerational determinants as within generation determinants have been well established, however these will be summarised. In particular the socioeconomic inequalities in size at birth will be reviewed. Size at birth will be considered as an explanatory, an intermediate and an outcome variable in these discussions. Therefore the proposal will be made that a lifecourse approach is required to understand the effect of all the intergenerational, biological and social factors which are known to influence offspring size at birth.

1.1 Why is size at birth important?

An infant's birthweight is the strongest known single indicator of its risk of perinatal and infant mortality (Butler and Bonham, 1963). The lower the birthweight of an infant the greater its risk of both neonatal death and later developmental problems (Clark et al., 2000). Although less important in terms of absolute numbers affected, very large infants, at the other extreme of the birthweight distribution, also have an increased risk of death in the neonatal period (Wilcox and Russell, 1983). Within a population the prevalence of low birthweight in particular has been widely used as an indicator of that population's health status.

In the last decade indices of fetal growth have taken on a new significance in the light of a now substantial body of evidence linking indices of reduced fetal growth to an

increased risk of disease in adult life, in particular cardiovascular disease and its associated risk factors (Barker, 1994). Chronic adult diseases have been a major focus of public health in developed countries for the latter half of the twentieth century. During this time the aetiological model for these diseases emphasised adult risk factors, particularly aspects of lifestyle such as smoking, diet and lack of physical exercise. However the fetal origins hypothesis, proposed by Barker and his colleagues at the Southampton MRC group, challenged this focus and instead directed attention to intrauterine life as the key area for primary prevention of adult disease, although this relationship between early life and adult disease had been mooted earlier by Forsdahl (Forsdahl, 1977).

The renewed research interest in fetal life also extends to the political arena. The view that early life development is a crucial time for determining adult health status has recently emerged as a theme in the debate on health inequalities. In the report from the Independent Inquiry into Inequalities in Health, chaired by Sir Donald Acheson and for which Professor David Barker was a committee member, mothers were highlighted as being central to the task of reducing future inequalities in health (Independent Inquiry into Inequalities in Health, 1999). The report highlighted in particular the socioeconomic differentials seen in size at birth which have remained significant despite a recent general improvement in maternal and child health. The report recognised the contribution of the fetal origins hypothesis to the aetiology of adult health status and introduced an intergenerational theme by stating that an infant's birthweight is not only determined by the immediate environment of pregnancy but is also influenced by the mother's adult height and weight, her growth in childhood and indeed her own growth in utero (Barker, 1998; Independent Inquiry into Inequalities in Health, 1999).

Therefore size at birth has acquired a renewed significance in terms of its scope to determine the health status of a population. Not only is birthweight considered with respect to the proximate measures of infant mortality and morbidity but also with respect to the temporally removed determination of adult health status. The domain of fetal life has potentially become one in which researchers and politicians share a common interest as it may hold the key to reducing future health problems and the socioeconomic differentials in them.

1.1.1 The Fetal Origins of Adult Disease hypothesis

The renewed interest in fetal development comes largely as a result of the work by Barker and colleagues who proposed the fetal origins of adult disease hypothesis. This hypothesis suggests that the environment a fetus is subjected to in utero may play a key role in "programming" susceptibility to later adult disease. The term "programming" in this context is used to describe the process whereby stimuli or insults during critical periods of development have lasting effects on the structure or function of organs, tissues and body systems (Lucas, 1991). These effects may include altered gene expression, reduced cell numbers, imbalance between cell types, altered organ structure and changes in the pattern of hormonal release and of tissue sensitivity to hormones which persist and which potentially may be amplified in adult life. The assumption underlying the fetal origins hypothesis is that size at birth is a measure of fetal nutrition, or undernutrition, as the case may be. Studies in several countries, in both sexes and across authorship, have subsequently replicated the findings of the Southampton group and repeatedly confirmed that birthweight is inversely associated with later blood pressure or hypertension (Huxley et al., 2000). Inverse associations have also been established between size at birth and coronary heart disease (Rich-Edwards et al., 1997; Leon et al., 1998) non-insulin dependent diabetes (McKeigue et al., 1998; Rich-Edwards et al., 1999) and stroke (Rich-Edwards et al., 1997; Eriksson et al., 2000). Size at birth has also been linked to hormone dependent cancers in women, notably breast cancer, although here the hypothesised relationship is reversed with higher rates of fetal growth tending to be associated with higher rates of breast cancer (Michels et al., 1996).

Despite the now vast literature in support of the hypothesis that the in utero environment may play a role in "programming" susceptibility to later disease there remain some substantial questions regarding whether the association between size at birth and adult disease is causal. The most controversial issues include aspects of the thesis itself such as distinguishing fetal from maternal nutrition (Harding, 2001) and the validity of extrapolating the results of animal experiments to human experience (Gluckman, 2001). There have also been concerns related to the methodologies used in these studies. Notably there has been ongoing concern regarding the use of absolute birthweight as a single proxy measure for fetal growth, without consideration of length of gestation by many authors (Leon et al., 1998). There has also been much debate about the appropriateness of adjusting for current adult size which has been necessary in

some, but not all, studies before the relationship between birth size and adult disease becomes significant (Lucas et al., 1999; Gillman, 2002). Some authors suggest that if this adjustment for adult size is necessary that it is the change in relative size that is more critical than size at birth *per se* (Lucas et al., 1999). A further major concern has been the issue of confounding by socio-economic status since socioeconomic status is known to be strongly associated with both fetal growth and many of the potent risk factors for adult chronic disease, in particular smoking, diet, physical activity and other health-related behaviours (Kramer, 2000). Whilst some of the issues have been satisfactorily addressed the issue of causality is still largely unresolved and in particular the elucidation of the causal pathway from fetal life to adult health remains problematic (Terry and Susser, 2001).

These issues will not be explored further here as there has been much debate already elsewhere in the literature (Rich-Edwards and Gillman, 1997; Lucas et al., 1999; Williams and Poulton R, 1999; Hattersley and Tooke, 2001; Harding, 2001) and this hypothesis is not the key focus of this thesis, rather it illustrates the far reaching importance of fetal development for health outcomes beyond the perinatal period. However some of these ongoing methodological issues in particular are common to the understanding of the determinants of size at birth itself and will recur as themes during the thesis.

1.1.2 Offspring size at birth is predictive of maternal morbidity and mortality

For most women pregnancy occurs at the mid-point of her life between infancy and middle age. In this way pregnancy may be thought of as a specific adult health outcome to which the fetal origins hypothesis might be applied. Indeed, in relation to precursors of cardiovascular disease, the physiological stress of pregnancy in early adulthood may unmask the potential for later adult disease. Pregnancy is a state in which the potential for later chronic hypertension first manifests itself as gestational hypertension. Studies have also found that women are at greater risk of developing hypertension in pregnancy if they themselves had reduced intrauterine growth (Hennessy and Alberman, 1997). Further pre-eclampsia (gestational hypertension and significant proteinuria in the second half of pregnancy), a syndrome peculiar to human pregnancy (Taylor, 1998), which poses a significant threat to the health of the mother if severe, has in addition been associated with a high risk of reduced offspring size at birth. Women who have established hypertension prior to pregnancy are at increased risk of developing pre-

eclampsia and are at risk of delivering a growth retarded fetus whether they develop pre-eclampsia or not (Taylor, 1998). Indeed there is a suggestion that it is not only pathologically high blood pressure but also high normal blood pressure that is inversely associated with fetal growth (Churchill et al., 1997). Therefore the risk of developing hypertension in pregnancy is related to the mother's own size at birth, which fits neatly with the fetal origins hypothesis, but in addition it is associated with reduced offspring size at birth.

In addition to the recent increased interest in measures of size at birth due to the fetal origins hypothesis, there has been increasing investigation of the associations between maternal and offspring measures of size at birth. However there have been few studies, until much more recently, that have considered how these two research areas might complement each other. Davey Smith et al though have recently considered the association between offspring size at birth and later maternal morbidity and mortality in three populations, two from the United Kingdom and one from Finland (Davey Smith et al., 1997; Davey Smith et al., 2000a; Davey Smith et al., 2000b). As might be predicted from the intergenerational associations in size at birth and the fetal origins hypothesis the authors found in each study that the birth size of the offspring of a woman was predictive of her own later adult morbidity and mortality, particularly with respect to cardiovascular disease.

Therefore maternal size at birth is related to her risk of adult disease but her offspring size at birth is also important. It is important both as an outcome measure in pregnancies complicated by maternal hypertension but it may also be predictive of the risk of later adult heath problems in the mother, as well as potentially in the offspring themselves.

1.1.3 Size at birth – not just a starting point

Overall the fetal origins hypothesis has been largely responsible for refocusing attention on fetal growth and the importance of measures of size at birth. There is an argument which suggests that the fetal origins hypothesis has merely exchanged a focus on the narrow time interval of intrauterine life for the previous narrow focus on middle age in a search for the determinants of adult health status. Although in the last two years the link between fetal life and adult disease has been extended to consider aspects of early childhood development (Eriksson et al., 1999; Forsén et al., 1999; Eriksson et al., 2001).

What has been largely ignored to date in the fetal origins hypothesis is that size at birth, whatever measure is used, is itself the end result of a complex mixture of exposures (Paneth, 1994). Size at birth, whilst relatively simple to measure is itself a proxy measure for fetal development in its entirety. There are many reasons why an infant may be born small and infants who are born the same size are not a homogeneous group (Metcoff, 1994).

An infant's size at birth should not be regarded as only a starting point or a benchmark for current or later health. Rather to understand its importance in its associations with adult health it is necessary to consider in more depth the influences that have shaped it as a measurement of intrauterine growth. Size at birth is thus not just a starting point for an important hypothesis but an outcome that deserves further attention in its own right.

1.2 Determinants of size at birth – what is already known

There is a vast literature on the determinants of size at birth, but the traditional preoccupation in perinatal epidemiology has been to examine offspring size at birth in the context of concurrently measured adult maternal characteristics and the pregnancy course in particular. This has tended to ignore the distal temporal dimension in determinants of size at birth in a similar way that the preoccupation with adult risk factors for adult disease had, prior to the fetal origins hypothesis. However recently there has been an increased interest in intergenerational associations in size at birth. However it might be argued that like the fetal origins hypothesis these studies have merely shifted the emphasis from one period in time to an earlier one. Both these approaches tend to be temporally "flat" in that they do not capture any aspect of the life time development of the mother between two discrete time points. Nonetheless they do identify important influences on offspring size at birth which are reviewed here. Firstly the within generation, mainly adult, determinants of size at birth are considered.

There have been several extensive reviews of the literature in the last two decades including those by Kramer et al (Kramer, 1987; Kramer et al., 2000) and Robinson (Robinson, 1989). Therefore the intention is to provide a summary of the major findings reflecting the commonality in writings in this area rather than providing a further review of the many studies. However the review of the literature on intergenerational determinants of size at birth will be more substantial as it is particularly relevant to this aims of this thesis.

Size at birth is a measure of both fetal growth and time in utero although birthweight alone is often used as a proxy measure for size at birth given the paucity of reliable gestational age data in many studies, particularly in the earlier studies. Hence the majority of studies which have investigated determinants of size at birth have been concerned with elucidating the determinants of absolute birthweight rather than fetal growth. However birthweight and duration of gestation are not independent. The primary determinant of birthweight is gestational age. In particular if gestation is shortened then birthweight will be reduced although the reverse may not be the case. There is some debate about whether duration of gestation should be classified as a determinant of birthweight or whether it should be considered an outcome in its own right (Dougherty and Jones, 1982). For the purposes of this thesis absolute birthweight and duration of gestation will be treated as intermediary outcome variables, but the major outcome will be a measure of fetal growth or birthweight adjusted for gestational age (*Chapter 2*). In general the determinants of absolute size are much better understood than the determinants of maturity, which remain elusive. The review of determinants of size at birth will focus on the determinants of absolute birthweight with lesser discussion of the determinants of birthweight for gestational age, since the latter measure has been less extensively studied. The determinants of duration of gestation will be incidental rather than a focus of this discussion. Many, but not all, of the determinants of shortened gestation are in common with reduced fetal growth but in developed countries the majority of preterm delivery still remains unexplained (Kramer, 1987).

There have been two distinct approaches to the study of absolute birthweight. The most widely used approach chooses a threshold value, usually 2500 grams, and considers the determinants of the births that are under this limit (classified as Low Birth Weight). The second approach considers mean birthweight for populations. The major findings of these two approaches will be summarised.

1.2.1 Determinants of Low Birth Weight (LBW)

Focusing on the determinants of Low Birth Weight (LBW) is important because clinically infants born weighing less than 2500 grams are at increased risk of morbidity and mortality both perinatally (Butler and Bonham, 1963) and beyond (Goldstein and Peckham, 1976). LBW may be caused by either reduced gestation or reduced intrauterine growth or by a combination of both. In developed countries LBW is most

commonly the result of reduced gestation whereas in the less-developed countries it is most commonly due to reduced intrauterine growth (Kramer, 1987). The focus for the summary will be on developed countries since this thesis concerns a population in the United Kingdom.

A review of surveys of determinants of LBW in the United Kingdom (Robinson, 1989) consistently highlighted maternal smoking in pregnancy, low maternal pre-pregnancy weight, low parity and pre-eclampsia as the major factors associated with reduced intrauterine growth. These predictive factors were identified for and remained constant over two large birth cohorts in Britain born in 1958 and 1970, despite significant changes in obstetric practice during that time (Peters et al., 1983). In addition to these determinants of LBW maternal short stature, early pregnancy bleeding, young maternal age and lower socioeconomic status have also been consistently associated with an increased risk of LBW (Fedrick and Adelstein, 1978; Cnattingius et al., 1993; Meis et al., 1997).

There has been some controversy regarding the combined effects of these correlated determinants on LBW. With regard to socioeconomic status, Baird concluded that any changes in the incidence of low birthweight in an Aberdeen population between 1948 and 1972 could be largely related to concurrent changes in socioeconomic environment (Baird, 1974). Maternal smoking has subsequently been shown to be an important independent predictor of low birthweight after controlling for the influence of other possible mediating factors such as maternal age, parity and social class using data from the 1958 British Perinatal Survey (Butler et al., 1972) and data on 180,000 Scottish births between 1992 and 1994 (Bonellie, 2001). With respect to maternal age, younger age at pregnancy has consistently been associated with an increased risk of low birth weight, as well as other adverse reproductive outcomes. Teenage pregnancy in particular has been shown to have an association with an increased risk of LBW which is independent of other social and biological determinants in an American population where approximately 10% of girls aged 15 to 19 years become pregnant (Fraser et al., 1995). However women aged over 35 years, and 40 years in particular, have also been shown to be at increased risk of delivering low birthweight infants in a London population (Jolly et al., 2000).

A concern about considering the determinants of birthweight according to a set cut-off point is that the proportion of LBW infants in a population varies according to the overall population distribution of birthweight (Robinson, 1989), and not all LBW

infants in different populations carry the same perinatal risk (Wilcox, 2001). Wilcox has referred to this as the "low birthweight paradox" noting that while populations who have higher percentages of low birth weight infants tend to have higher infant mortality overall, individual low birth weight infants in populations with high rates of LBW tend to have a lower mortality than LBW babies of the same absolute birthweight in populations with a lower overall rate of LBW. Even within populations infants born to maternal smokers tend to be of lower birthweight on average than their peers born to mothers who are non-smokers, but weight for weight they have a lower mortality than infants born to non-smokers. This paradox is also evident for infants born at high altitude as compared to low altitude, African-American as compared to White U.S. infants, and twins compared to singletons (Wilcox, 2001). Essentially considering a fixed cut-off for low birthweight is a crude and often inaccurate way of assessing perinatal mortality risk across populations (Evans and Alberman, 1989). Nonetheless much of our knowledge about the determinants of birthweight comes from studies of low birthweight in particular. Fewer studies have considered the determinants of mean birthweight for populations across the entire birthweight range.

1.2.2 Determinants of mean birthweight on a population basis

Many of the factors which predispose to low birth weight also predict differences in mean size at birth over the whole birthweight range. Although many studies have considered birthweight and perinatal mortality one large scale population study in particular considered the determinants of mean birthweight for a well-defined population in the United Kingdom prior to 1980. The 1958 British Perinatal Survey collected extensive data on approximately 98% of all the births in the United Kingdom for the week of 3-9 March, 1958 (approximately 17,000 in total) and studied the joint effects of social, demographic and biological factors on birthweight and perinatal mortality (Goldstein, 1981). This large population study identified maternal age, parity, height, social class, previous reproductive history, pre-eclampsia, smoking after 20 weeks gestation and fetal sex as the main influences on the birthweight of singleton infants. Within a population mean birthweight tended to increase with increasing maternal age, height, parity and socioeconomic status, but be reduced in smokers and in mothers with pre-eclampsia. Male infants were heavier than female infants on average and singletons were heavier than multiple births. However considering the joint effects of these determinants was not straightforward at the time of this early study and the

authors relied largely on stratification rather than regression techniques to do so. Nevertheless they concluded that the major determinants of mean birthweight for the 1958 population were fetal sex, maternal parity, height, smoking and pre-eclampsia, but that overall these factors were less reliable in predicting birthweight than the previous sibling's birthweight (Butler and Bonham, 1963).

Since that early population study there have been several large, representative studies that have considered the determinants of mean birthweight for defined populations and there has been little dispute about the significant factors listed above (Hendricks, 1964; Love and Kinch, 1964; O'Sullivan et al., 1965; Dougherty and Jones, 1982; Kramer et al., 1990). One large, representative study of over 300,000 Scottish births between 1975 and 1988 (Maconochie, 1995) found the same determinants of mean birthweight as the 1958 study but was able to apply multivariate regression techniques to confirm the earlier findings obtained using stratification alone.

Unravelling the independent effects of these factors though is extremely difficult as many of the factors are highly correlated. If the correlated factors are entered into the same regression analysis the effect estimates may become distorted because of the association between the variables making it difficult to ascertain the independent effect of any single determinant. In addition population based studies of sufficient size to examine these joint effects further often lack sufficient detailed information or power to do so, so that reliable multivariate analyses remain uncommon (Maconochie, 1995).

One recent study used multilevel modelling in an attempt to disentangle the effects of individual and area level effects on mean birthweight using three geographically distinct areas in Finland (Jarvelin et al., 1997). The authors found the usual predictors of birthweight, but found an additional variation in mean birthweight due to an area level measure of wealth they called "Financial Capacity", leading them to suggest that there were as yet environmental factors that influenced size at birth that they could not define. Birthweight data from the United States, Denmark, Bavaria, Germany, Israel, Sweden, Japan, Norway, England, Wales and Scotland have also been compared in a report on trends of birthweight distributions over time by Evans and Alberman (Evans and Alberman, 1989). They noted that there was only a small variation in the birthweight distributions within these countries between 1970 and 1984 which they felt must be due to differences in the distribution of genetic factors and the biological and social factors previously identified as determinants of birthweight within a population. However the authors commented that given the social changes that had occurred on some of the

countries over the 15 year study period they had expected greater changes in birthweight measures. They speculated that the lack of change might reflect the strong influence of intergenerational factors. These factors will be reviewed in Section 1.2.5.

1.2.3 Determinants of birthweight adjusted for gestational age (fetal growth)

As more smaller preterm infants now survive the perinatal period (Alberman and Botting, 1991) it is increasingly realised that it is meaningless to consider determinants of birthweight without taking into account gestational age at delivery, unless births are restricted to term deliveries. The need to define birthweight adjusted for gestational age largely arose from the recognition that LBW infants, defined by absolute weight alone, were a heterogeneous group, comprised of both premature and small for gestational age infants, who had different levels of perinatal risk (Yerushalmy, 1967). In a similar way that birthweight has been grouped according to perinatal risk, birthweight for gestational age has also been divided into categories that are largely indicative of clinical perinatal risk. Typically categories consist of small for gestational age (SGA - usually less than the 10^{th} centile of birth weight for a given gestational age), appropriate for gestational age (AGA - between the 10^{th} and 90^{th} centile) and large for gestational age (LGA - greater than the 90^{th} centile of weight for gestational age) (Macfarlane and Mugford, 2000). The choice of appropriate population birthweight for gestational standards to compare birthweight to may however be problematic (*Chapter 2*) (Hobbins, 1997).

Most studies that have considered the determinants of birthweight adjusted for gestational age have been concerned only with the determinants in groups of small for gestational age infants or growth-retarded infants (IUGR[1]) rather than determinants of the distribution of birthweight for gestational age for a whole population. In general the determinants of reduced birthweight for gestational age are the same as for LBW (Robinson, 1989; Kramer, 1987). However in a study of all Swedish births between 1973 and 1986 (Elmén et al., 1996) it was noted that standardised birthweight adjusted for gestational age scores tended to be more strongly associated with perinatal mortality and later health measures than absolute birthweight alone.

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[1] IUGR= intrauterine growth retardation. It is defined according to birthweight at a particular gestational age being less than a defined centile of birthweight for gestational age (usually the 5^{th} or 10^{th} centile), but is not equivalent to small for gestational age.

Intrauterine growth retardation, like LBW, is an important cause of perinatal mortality (Burke et al., 1990) and it is a condition that receives a great deal of clinical attention both pre- and post- delivery. However for the purposes of this thesis the aim is to describe a measure of fetal growth for a whole population, rather than to discuss the complexities of definitions of growth retardation and small-for-gestational age, which has been done at length elsewhere (Robinson, 1989; Bakketeig et al., 1998; Hobbins, 1997) and which apply to only a small subset of all births. Birthweight for gestational age will be used throughout the thesis as a measure of individual fetal growth rather than an indicator of perinatal risk *per se* (*Chapter 2*).

1.2.4 Determinants of size at birth in consecutive deliveries

In an attempt to determine the relative importance of the correlated determinants of size at birth, whether the measure be absolute birthweight or birthweight adjusted for gestational age, it is of interest to consider a longitudinal approach rather than a cross-sectional one. Considering repeated births to the same mother may offer insights into the determinants of offspring size as many maternal variables which are known to contribute to differences in individual birth outcomes remain fixed throughout consecutive pregnancies. A mother's own intrauterine development, her childhood growth and attained adult height remain fixed throughout all her pregnancies as do contributors to adult socioeconomic position such as her education and the socioeconomic conditions she experienced in childhood and adolescence (Kline et al., 1989). Therefore when examining differences in consecutive birth outcomes for the same mother any differences should be largely independent of these variables. Few studies have looked at serial data for births to the same mother as most have tended to use more readily accessible cross-sectional data. However in the early 1970s Billewicz analysed the birthweights in consecutive pregnancies of nearly 7000 Aberdeen married women (Billewicz and Thomson, 1973). He concluded that individual women had a significant tendency to have pregnancies of similar gestation and size and estimated the full-sibling coefficient of correlation between consecutive birthweights to be greater than 0.5, which he suggested could not be explained on the grounds of maternal size alone. This figure was in line with estimates from earlier studies by Karn et al (Karn et al., 1951) and Morton (Morton, 1955) in the 1950s whose data gave correlation coefficients for siblings' birthweights of 0.4 and 0.5 respectively. They also found the now commonly accepted relationship that birthweights in consecutive pregnancies to

the same mother tend to increase. In 1995 the OPCS Longitudinal Study of over 10,000 women provided an opportunity to examine whether the tendency to repeat birthweight seen in the earlier studies was apparent in a large representative sample from England and Wales (Macran and Leon, 1995). The findings were consistent with the earlier studies but also illustrated regression to the mean effect observed in the birthweight of first and second births of the same sex with father's social class held constant. In the same year a large study was carried out on over 330,000 Scottish women which included not only live births but also perinatal deaths and reported spontaneous abortions as part of a women's reproductive history (Maconochie, 1995). In this study the tendency to repeat birthweight and gestational age in consecutive pregnancies was confirmed, and the phenomenon of regression to the mean was shown to extend beyond a woman's first two births. In addition if there was growth retardation of the fetus or the infant was born prematurely in an earlier pregnancy the risk of the same outcome in the following delivery was increased 5-6 fold. These findings were reproduced in a Swedish study (Winkvist et al., 1998) of familial patterns in birth characteristics where the risk of small for gestational age (SGA) delivery increased progressively with the number of previous SGA deliveries. The authors also described some wider familial patterns which extended to similarities in birth outcomes for siblings, in that if one sister had previously delivered a pre-term infant (that is with a gestational duration of less than 37 weeks) her sisters chance of a preterm delivery was increased by 80%.

This tendency for women to repeat similar birthweight and gestational age within a generation may reinforce the importance of her own development, in addition to concurrent pregnancy specific factors, for her reproductive success. One possible explanation for the continuity seen in her consecutive birth outcomes may be the important influence of her own intrauterine development.

1.2.5 Intergenerational determinants of size at birth

There is a growing body of literature describing the intergenerational continuities in measures of size at birth, suggesting that a mother's intrauterine environment and her early development directly influence her own reproductive outcomes. Evidence for this relationship originated over sixty years ago. A study by Kermack et al (Kermack et al., 1934) in the United Kingdom showed improvement in age-specific standardised mortality ratios from one generation to the next. The authors took this to be evidence that the health of adults was largely determined by their health as children and from this

they speculated that infant mortality might only be expected to fall when maternal health improved. Further they suggested that health in later life is determined to a large extent by health in early life, including childhood. After this study many studies followed by Baird and his colleagues which considered the perinatal outcomes of infants born in Aberdeen, largely between 1948 and 1972 in relation to the childhood environments of their mothers (Baird, 1949; Baird, 1952; Baird, 1974; Baird, 1977; Illsley, 1955; Illsley, 1966). Their collective findings are illustrated by a comment from Baird in his 1949 paper where he states that:

> "Efficient child-bearing is influenced by many factors, but none so much as the mother herself. The mother is the product of heredity and environment, and therefore so far as possible the whole woman should be studied. We wish to know something of her basic intelligence, her personality, and her home background. We wish to know about her standard of education, her occupation and that of her husband, and all that goes to make up her living conditions. We wish to know how she spends her money and what kind of housewife she is, what kind of food she eats, and what she thinks about childbirth and the rearing of children. We can then study how she behaves during pregnancy, labour and lactation, and not only in a first pregnancy but also in subsequent ones. In this way we may be able to build up a picture of various types and discover what psychological, social and physical influences affect reproductive performance and how they act." (Baird, 1949)

A study in the 1950s by Drillen lent support to these comments for a cohort of women in the United Kingdom (Drillien, 1957). He concluded in his 1957 paper that women from lower class backgrounds had higher "prematurity"* rates than women from middle class backgrounds regardless of their adult social status. However two studies, from outside the United Kingdom, published in 1970 did not find any evidence for a persistent effect of the maternal early environment on the risk of producing a low birthweight infant in adult life (Urdy et al., 1970; Legg et al., 1970).

As well as examining the influence of the early maternal postnatal environment, some early studies, and many later ones, considered the influence of the maternal intrauterine environment on the development of her offspring. In 1968 Ounsted and Ounsted compared the birthweight distributions for selected groups of mothers of

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* By "prematurity" Drillen was referring to a birthweight of less than 2500 grams

infants who were either small for dates, appropriate or large for dates (Ounsted and Ounsted, 1968). They noted that the birthweight distributions of the mothers of these infants were shifted upwards and downwards respectively for the large and small as compared to the appropriately grown group of infants. However at the time of that report the decision about appropriate size was based more on absolute birthweight than any measure of birthweight for gestational age. In terms of quantifying intergenerational associations of all measures of size at birth, including fetal growth and maturity, most studies which had sufficient detailed data on two generations have only been reported in the last twenty years. The major findings of these intergenerational studies are summarised in *Table 1.1.* The country of the source population is given together with the time periods of birth for the mothers and their offspring. Information is provided to identify whether the study began with the data on the mothers and then collected information on her deliveries or vice versa and on the source of the perinatal information in each generation. In the far right hand column the summarised intergenerational associations described in each study are shown. However these are only provided if the association referred to the same specific measure of size at birth (birthweight, gestational age and birthweight adjusted for gestational age) in both generations. The findings are presented according to analysis type and year of publication. Four studies reported crude and/or adjusted correlation coefficients (Hackman et al., 1983; Carr-Hill et al., 1987; Ounsted et al., 1988; Magnus et al., 1993). Eight studies reported linear regression coefficients, either crude or adjusted for other parental characteristics (Langhoff Roos et al., 1987; Little, 1987; Emanuel et al., 1992; Alberman et al., 1992; Coutinho et al., 1997; Hennessy and Alberman, 1998a; Hennessy and Alberman, 1998b; Ramakrishnan et al., 1999). Ten studies reported relative risk estimates of delivery of either low birthweight, preterm or small for gestational age infants as a function of maternal birth outcome (Klebanoff et al., 1984; Klebanoff et al., 1985; Klebanoff and Yip, 1987; Klebanoff et al., 1989; Sanderson et al., 1995; Klebanoff et al., 1997; Winkvist et al., 1998; Emanuel et al., 1999; Collins, Jr. et al., 2002) including Magnus et al who also reported correlation coefficients (Magnus et al., 1993). Two studies used analysis of variance to compare groups according to their mothers birth parameters (Ounsted and Ounsted, 1973; Lumey, 1992).

It has now been well established in many populations that there is an association between maternal absolute birthweight and numerous infant outcomes, including low birthweight, preterm delivery, relative intrauterine growth retardation as well as

perinatal mortality, infant mortality and other neonatal outcome measures such as respiratory distress syndrome (Hackman et al., 1983; Klebanoff et al., 1984; Klebanoff and Yip, 1987; Magnus et al., 1993; Skjaerven et al., 1997). In addition to associations between maternal birthweight and offspring size at birth, paternal birthweight has also been shown to have an influence on infant size at birth after adjusting for many other confounding variables including adult height and weight (Magnus et al., 1984; Carr-Hill et al., 1987; Alberman et al., 1992). However in studies where both maternal and paternal measures were available for each individual infant the paternal measures had much less influence on infant size at birth than the maternal measures (Little, 1987). Studies that have been carried out in developed countries have found the intergenerational association between maternal and infant size at birth to be positive with an average increase of between 10 and 20g of infant birthweight for every 100g increase in maternal birthweight. One recent study considered intergenerational effects on birthweight and birth length in Guatemala, a less well-developed country, for 215 intergenerational mother-infant pairs and found that infant birthweight increased by 29g on average for every 100g increase in mothers birthweight (Ramakrishnan et al., 1999). Additionally there was a positive significant effect of maternal birthweight on infant birth length (0.2 cm per 100gram of maternal weight) in this population. This suggests that the intergenerational relationship may be stronger in less-developed countries where maternal growth to adulthood may be restricted by poor environmental conditions throughout her infancy and childhood.

Studies in which gestational age information has been available for the second generation have concluded that maternal low birthweight is also associated with an increased risk of both reduced fetal growth and preterm delivery of her infants in addition to absolute birthweight. However these studies were not able to determine whether the continuity in size at birth acted through similarities in intrauterine growth rates or control of length of gestation, or perhaps both.

In terms of intergenerational continuities in measures of duration of gestation and fetal growth (birthweight adjusted for gestational age measures) there is less evidence for intergenerational continuity because there are less studies which have been able to collect reliable birthweight and gestational age information for both maternal and infant generations. The studies that have considered associations in these size at birth measures in the United Kingdom have largely relied on recall to obtain the second generation's gestational age (Hennessy and Alberman, 1998a; Hennessy and Alberman,

1998b), with mothers being from the 1958 British Perinatal Survey (98% of all births in England, Wales and Scotland during the week of the 3-9 March 1958). Inclusion of infants was subject to follow up of the mothers aged 33 years at most, with births limited to the most recent delivery. This may well have excluded more socially advantaged women who had not begun their child bearing until after this age. The authors acknowledge a follow up rate of 73% at 33 years, after excluding those who had emigrated, with an under representation of women from lower social environments. The studies did however have extensive information on other parental and grandparental characteristics known to influence size at birth. The authors concluded that there were six significant variables that consistently influenced offspring size at birth. In order of strength of association these were maternal fetal growth, maternal smoking in pregnancy, infant sex, maternal adult height and weight and early age at menarche (Hennessy and Alberman, 1998a). No grandparental or social class variables remained significant after adjustment for all characteristics, although with the selective loss to follow up and the exclusion of mothers older than 33 years at delivery parental social class was likely to have been depleted of numbers in the extreme categories. The same authors also considered the intergenerational association in length of gestation, although the second generation infants were limited to first-born, term deliveries (Hennessy and Alberman, 1998b). They nevertheless found a small, but significant, univariate relationship between parental gestational age and non-preterm gestational age of infants of 0.067 week per 1 week increase in maternal gestational age and 0.045 week per 1 week increase in paternal gestational age (for separate infants as maternal and paternal data were not available together). Prior to this study there had been inconsistent results in the intergenerational association in gestational age at delivery (*Table 1.1*).

Most other studies that were able to investigate the relationship in gestational age in addition to absolute size at birth were from Scandanavian countries were the systems for storing perinatal information are similar to those in Scotland. In the studies by Klebanoff et al in Sweden and Denmark (Klebanoff et al., 1989; Klebanoff et al., 1997), Magnus et al in Norway (Magnus et al., 1993)and Winkvist et al also in Sweden (Winkvist et al., 1998) internal record linkage was used to provide birthweight and gestational age data for a large number of mother-infant pairs. However unlike the large British (Hennessy and Alberman, 1998a) or American (Emanuel et al., 1999) studies they lacked extensive information on other potential parental determinants of offspring growth. Most analyses were restricted to determining continuity of risk of adverse birth

outcome in terms of risk of transmission of low birthweight or reduced intrauterine growth rather than considering if an association existed across the full range of population growth measures. These studies generally confirmed that mothers born small for gestational age themselves were up to three times as likely to deliver small for gestational age infants as appropriate or large for gestational age mothers (Klebanoff et al., 1989; Magnus et al., 1993; Klebanoff et al., 1997; Winkvist et al., 1998). However only one study (Klebanoff et al., 1989) found a non-significant 10 – 50% increased risk of a preterm mother delivering a preterm infant. Authors therefore tended to conclude that the mechanism by which infant fetal growth was related to maternal size at birth was through control of growth rate rather than through a genetic predisposition for preterm delivery. However gestational age is subject to much greater imprecision and measurement error than absolute birthweight which tends to weaken the chance of finding a significant relationship overall (Emanuel et al., 1999). In addition gestation at delivery is not always determined by spontaneous labour, but may be shortened iatrogenically because of medical concerns about the welfare of an infant, particularly for the second generation infants who were delivered at a time of greater provision of neonatal intensive care facilities (Klebanoff et al., 1993). Hence while there are many determinants of pregnancy outcome and therefore size at birth the significance of intergenerational factors is that they persist after adjustment for the known important risk factors contemporary to the pregnancy itself (Emanuel, 1997).

1.2.6 Genes versus environment

The close relationship between a mother's own size at birth and that of her offspring has been interpreted by some authors as an example of the genetic inheritance of birthweight. The classic study that partitioned birthweight into its components, including the genetic contribution, was that of Penrose in 1954 (Penrose, 1954). He concluded that some 38% of the variation between siblings size at birth could be attributed to genetic inheritance, of which fetal genes contributed 16%, 2% was due to fetal sex and 20% was due to maternal genes. The greater part of the variance, some 62%, he concluded, was attributable to environmental causes. Of these, 18% were derived from the mother's general health and nutrition, 6% from her pregnancy specific health, 7% from her parity, 1% from her age and the remaining 30% he attributed to "unknown intrauterine influences". Therefore while he concluded that the overwhelming contribution to fetal size was maternal, he attributed almost two-thirds to

environmental factors and much less to genetic factors. Historically Ounsted also found that clustering of birthweight in siblings was largely determined by non-genetic factors, including maternal childhood growth and her subsequent adult height (Ounsted and Ounsted, 1966). A later Aberdeen study, specifically considering whether birthweight was genetically determined, compared the birthweight of 505 intergenerational pairs of young mothers and their first born infants. They found residual correlations in birth weight of only 0.14 and 0.17 after adjustment for fetal sex, maternal height, gestational age and maternal pre-eclampsia, and also concluded that genetic factors play only a minor role in determining birth weight (Carr-Hill et al., 1987). However trying to determine what is a genetic and what is an environmental determinant may be creating a false dichotomy in what is really a close, interdependent relationship. The problems in trying to separate the effects of shared genes from shared environments both within and between generations, which are acknowledged by many eminent authors (Kline et al., 1989; Khoury et al., 1988), go beyond the current scope of this thesis. However the common theme seems to be that it is difficult to attribute all of the correlation between intergenerational birth size to a common genome when environmental conditions that may affect biological measures are also shared across generations.

1.2.7 Summary of determinants of size at birth

Therefore there are many correlated determinants of offspring size at birth, some biological and some social, some within a generation and others intergenerational. These may be summarised and divided into broad categories of maternal or fetal factors or factors which result from maternal and fetal interaction. The factors highlighted below are listed in Appendix 1.

a) Maternal factors

Maternal factors which influence birthweight may be further subdivided into fixed and pregnancy-specific factors. Maternal fixed characteristics include those that were established before her reproductive career began. These include her own intrauterine growth and development, her completed education and subsequent occupation, her health-related behaviours and her attained adult physical size, namely her height and pre-pregnancy weight.

Maternal pregnancy-specific factors include those contemporaneous to her current pregnancy. These include her age, her previous reproductive history including her parity

and previous abortions or infertility, her uterine size and capacity, her current social circumstances including her partner's status, her pregnancy weight gain and intercurrent health status together with any specific pregnancy related conditions, especially pre-eclampsia or gestational diabetes. It also includes behaviours such as smoking, alcohol intake and any other drug use plus other lifestyle influences such as her level of antenatal care, her nutrition and exercise habits.

b) Fetal factors

Fetal factors include the fetal genome which necessarily combines parental genetic material and subsequently defines fetal sex and any chromosomal anomalies, both of which are related to intrauterine growth. The other important fetal factor is whether the pregnancy is single or multiple.

c) Maternal-fetal interaction

These factors relate to the interaction between the mother and the fetus that intimately determine the exact nature of fetal growth. Usually they are thought of as relating to placentation but this may be overly simplistic. Certainly the size and function of the placenta is extremely important as it sits physically at the interface of the mother and the developing fetus. Placentation may be determined by both the maternal (eg pre-existing hypertension) and fetal (eg multiple gestation) determinants, in ways which are still not completely understood (Hay, 1991). However there are other mechanisms that operate to regulate fetal growth which are only beginning to be understood. For instance it used to be thought that the fetus was a passive recipient of nutrition from the mother via the placenta but there is emerging evidence that the fetus is also able to secrete hormones which influence the function of the placenta and perhaps even the maternal metabolism (Harding, 2001).

1.3 Socioeconomic inequalities in size at birth

Among the many determinants of size at birth, adult parental social class has consistently been associated with differential fetal growth. It has been established in many different populations that the lower the relative socioeconomic position of an individual the poorer their birth outcomes, including their birthweight, are likely to be (Andersson et al., 2000; Spencer et al., 1999; van de Mheen et al., 1996; Leon et al., 1992). The effect is not limited to the most disadvantaged groups but there is a gradient in mean birth size across the entire social strata (Macfarlane and Mugford, 2000).

Recently there has been increasing concern regarding socioeconomic inequalities in many health outcomes, of which birth outcomes are just one component. Socioeconomic inequalities have taken on heightened political significance in Britain in the last three decades after being initially highlighted in the Black Report of 1980 (Black Report, 1980). The report had a major impact on further research efforts directed at examining social inequalities, and the issues it raised have since been revisited and elaborated in the 1999 Acheson Report (Macintyre, 1997). Of particular concern is that infants born to women in disadvantaged socioeconomic groups are consistently more likely to be of lower birthweight than their more advantaged peers. On average infants born to fathers in Social Class IV or V in the United Kingdom currently have a birthweight that is 130 grams lighter than those born to fathers in Social Classes I or II (Office for National Statistics, 1997). Women in lower social classes are therefore much more likely to deliver an infant who is classified as low birthweight (that is born weighing less than 2500g) and at increased risk of perinatal and later adult morbidity, according to the fetal origins hypothesis. These statistics rely on classification of social class according to paternal occupation which is not applicable for single mothers. In single mothers the rate of low birthweight has been found to be either similar to or lower than for infants with fathers in the lowest social class (National Perinatal Epidemiology Unit Report, 1997). Additionally there is a tendency for a woman to repeat deliveries of small for gestational age infants in consecutive births if she is socially or economically disadvantaged (Read and Stanley, 1993). This suggests that there may be characteristics of the mother and her social class that exert a constant influence on all her pregnancies.

Social class categories cluster individuals together according to some broad measure of their education or occupation. One social group having more money or education than another probably has little or no direct effect on how fast a fetus grows in utero. In other words socioeconomic disadvantage cannot be a direct, independent determinant of fetal growth. Rather, socioeconomic disadvantage may be a proxy for or lead to adverse psychological, behavioural, or other environmental exposures that impair fetal growth (Kramer, 1998). Recent research has highlighted the broad nature of a social class category in terms of assigning relative risk of reduced birthweight. It has shown using three separate measures of status, at area and individual level, that it is possible to find finer gradations of risk within these broad categories suggesting that each class category

is indeed a proxy for an environment with multiple effects which are not all homogeneous (Pattenden et al., 2001).

Socioeconomic inequalities are not only evident in size at birth but also in its determinants as many of the maternal adult factors that influence offspring size at birth are themselves socially patterned. Rates of maternal smoking in pregnancy, for example, one of the most important influences on size at birth, vary according to social class. Women in the United Kingdom who are in the least advantaged groups tend to have the highest rates of smoking, both outside of (Cavelaars et al., 2000) and during pregnancy (Rush and Cassano, 1983). Further maternal adult height is associated with social status (Kuh et al., 1991) as is maternal age at first pregnancy (dos Santos Silva and Beral, 1997). In some studies the socioeconomic gradient in offspring size at birth appears to be explained by differences in these socially patterned maternal characteristics of age, parity and smoking (Nordstrom and Cnattingius, 1996) however this is by no means a universal finding (Spencer et al., 1999; Bonellie, 2001). A recent review of the socioeconomic determinants of intrauterine fetal growth by Kramer (Kramer, 1998) concluded that it is still not clear whether the socioeconomic gradient in infant growth can be fully explained by the other known maternal risk factors because most research has tended to focus on only a few factors at a time with social class measured at one point in time.

1.3.1 Social disadvantage – adding the temporal dimension

The research into socioeconomic differences in size at birth tends to largely ignored the evidence linking socioeconomic disadvantage throughout life to adult health and disease risk. Studies which have considered social position over a lifetime, rather than at just one point in time, find that an index combining data regarding social position from different stages of life is more strongly related to adult disease risk than any indicator relating to just one point in time (Kuh et al., 1997). It is suggested that to properly understand the origins of adult chronic disease a lifecourse perspective is required which takes account both the programming which may occur in fetal life and the wider social environment in which fetal and postnatal growth take place (Lamont et al., 1998). Equally it might be appropriate in trying to understand the socioeconomic gradient in size at birth to consider the social environment throughout a woman's life that is likely to have shaped the adult biological characteristics that are known to influence her offspring's size at birth. In this way social factors are not just confounders but are

explanatory factors on the causal pathway of influence on maternal development and therefore on her reproductive potential (Gillman, 2002).

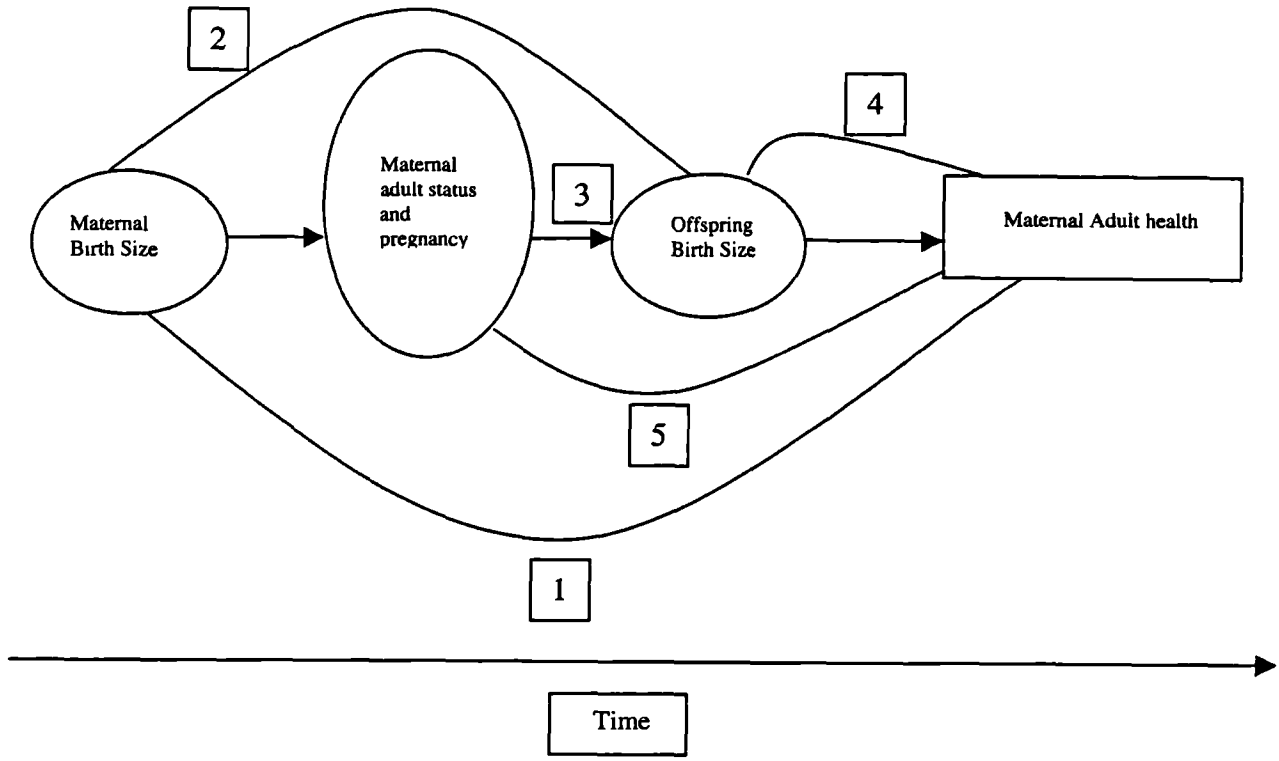
One of the aims of this thesis is to attempt to understand better the socioeconomic disparities that are seen in offspring size at birth using a large, rich data set with both biological and social information available at several points in a woman's lifecourse, rather than focussing on either one specific time or falsely dichotomising the biological and the social effects.

1.4 Size at birth in a temporal perspective

It is possible to consider the temporal dimension in all the determinants of size at birth and also to consider the associations of size at birth with later measures of adult health so that size at birth may be viewed as both an explanatory and an outcome variable over a lifecourse.

In the fetal origins hypothesis size at birth represents the beginning of the now well-established association with later adult health, represented by arrow 1 in *Figure 1.1*. However size at birth may be both the outcome variable and the explanatory variable as is the case with respect to the intergenerational associations in size at birth summarised in *Table 1.1,* (arrow 2 in *Figure 1.1*). Size at birth may only be the outcome, as is the case for the within generation determinants of size at birth discussed above (arrow 3 in *Figure 1.1*). Offspring size at birth may also be the starting point for an association with later maternal adult health, somewhat of a reversal of the traditional role of maternal adult characteristics determining offspring size at birth, as recently highlighted by Davey Smith et al in a series of studies (arrow 4, *Figure 1.1*). Further pregnancy at an intermediate point in the life of a woman may unmask the physiological potential for later adult disease, or it may promote it (arrow 5, *Figure 1.1*).

Figure 1.1 : **Size at birth as an explanatory and an outcome variable**



Each of these associations highlights the importance of size at birth as a correlate of or a possible determinant of health status throughout the life of a female beyond its immediate relationship with perinatal morbidity and mortality. However it is also indicative, but not an exhaustive list, of the complex inter-relationships between fetal growth and both earlier and later maternal health.

To integrate these pieces of information that link together distinct periods in a woman's life requires more than a cross-sectional or intergenerational approach to size at birth, it requires a lifecourse approach to offspring size at birth. This approach changes the emphasis for size at birth from the starting point for determining later morbidity or mortality risk to part of the continuum of influence of lifetime maternal development, and it allows for the influence of both proximal and distal biological and social factors across the lifecourse.

1.5 A lifecourse approach

The life course approach offers a way of integrating the knowledge that is currently available linking early life factors to adult health status. It suggests that throughout the lifecourse exposures or insults gradually accumulate, through episodes of illness, adverse environmental conditions and behaviours, increasing the risk of chronic disease

and mortality (Kuh and Ben-Shlomo, 1997). Accumulation of risk is different from biological programming in that it does not require the notion of a critical period but places more emphasis on a greater range of biological and social experiences in childhood, adolescence and early adulthood than either the middle age lifestyle or the fetal programming models. It however does not preclude the possibility of critical or sensitive periods during development.

This is not a novel idea. Indeed the influence of early life-development on later health was considered commonplace in the early part of the twentieth century (Davey Smith and Ebrahim, 2001). There was a common way of thinking about human biology which viewed the physical status of an individual as being the outcome of social processes but this tradition fell from favour after the Second World War. The work of Barker and his colleagues renewed the link between early life and adult disease, albeit in a largely biological way, which has opened the door for the merging of basic biological and sociological research with a greater consideration of how social and biological lifecourse experiences develop together.

1.5.1 Size at birth in a lifecourse perspective

Few studies to date looking at the determinants of size at birth have addressed biological and social factors acting together in relation to size at birth and rarely have they looked at their impact across a women's lifecourse and across generations. Those that have included both biological and social factors have tended to be restricted to one type of measurement controlling for the other at a fixed point in time considering it only as a potential confounder of any relationship elucidated (Koupilová et al., 1997). A major problem is that there are few longitudinal studies which have collected sufficient birth to birth information across generations to be able to attempt to quantify the effects of the different factors and the different effects they might have depending on their relative timing (Power and Hertzman, 1997a).

In order to address these issues cohorts are required which have collected not only high quality perinatal data but also socioeconomic and anthropometric measures throughout infancy, childhood and into early adult life over more than one generation. The National Birth cohorts of 1946, 1958 and 1970 have the potential to address some of these data issues but the collection of perinatal information across generations is not straightforward for these geographically diverse cohorts and information is currently incomplete for the second generation. With such data it is possible to explore the

continuities that exist in birth outcomes across generations and the possible determinants of these over a lifecourse.

1.5.2 An intergenerational and lifecourse approach – the way forward?

Socioeconomic inequalities continue to exist in size at birth despite a recent general improvement in the health of mothers and children (Macintyre, 1997). However social class in itself is not a sufficient explanation for the differentials. Studies have repeatedly shown the intra- and inter- generational links between measures of size at birth and usually in separate studies the impact of socioeconomic factors on size at birth and vice versa have been spelt out. However the challenge remains to integrate these components which requires a lifecourse and an intergenerational approach to explore the evidence both for programming during critical periods of growth and the development of risk attached to exposures throughout the lifecourse and across generations.

The fetal origins hypothesis has concentrated attention on size at birth as the starting point for the inverse association that has been found with later adult health status, but for any particular birth size there are maternal, fetal and intergenerational factors which exert influence. An offspring's size at birth is the result of a complex interaction of biological and social factors which act at different time points, for different durations with different impact depending on prior exposures over a lifecourse and in fact over the previous generation's lifecourse. In the lifecourse of an average woman pregnancy occurs in the midst of her life experience. It is influenced by her own intrauterine development, which in turn is dependent on her own mother's intrauterine development and by all the childhood and early adulthood experiences she has had since. It is a time which will have an impact on her own future health status (Green et al., 1988) and which will also impact immediately on her child's growth and through that fetal environment will influence the next generations birth outcomes and later adult health. The challenge is to look beyond one generation in an attempt to shed light on the complex inter-relationships between biological and social factors which act over women's lifecourses to perpetuate inequalities in offspring size at birth.

Appendix 1: Summary of the major determinants of size at birth

a) Maternal Factors

Fixed:

Maternal height*

Maternal pre-pregnancy weight

Nutritional status

Maternal genome

Social environment *(completed education, occupation, marital status, partners status)

Previous reproductive history*

Mothers own intrauterine development and size at birth *

Pregnancy Specific:

Maternal Age*

Pregnancy weight gain

Smoking status*

Gravidity*

Maternal disease* – hypertension*, antepartum haemorrhage, infection.

Paternal genome

Paternal height

b) Fetal factors

Infant sex*

Multiple vs. Singleton Gestation*

Fetal genome

c) Maternal-fetal interaction

Placentation

* Data available in the Aberdeen intergenerational study (Chapter 2)

Table 1.1 : **Summary of known intergenerational associations in maternal and offspring size at birth (restricted to singletons)**

Reference (Year)	Study population*				Data source				Intergenerational associations **		
	Source	N (pairs)	Mothers year of birth	Infants year of birth	Mothers		Infants		Birthweight (grams)	Gestational age (weeks)	Fetal growth measure
					Birthweight	Gestation at delivery	Birthweight	Gestation at delivery			
Correlation Analysis											
Hackman et al (1983)	US	748	After 1948	1977-79*	Birth certificates	-	Obstetric records	Obstetric records	0.11 (adjusted)	-	-
Carr-Hill et al (1987)	Scotland	505	1950-56*	1968-1981 (First born females)	Obstetric records	Obstetric records	Obstetric records	Obstetric records	0.14-0.18 (adjusted)	-	-
Ounsted et al (1988)	UK	986	Not stated	1964-75*	Recall	-	Birth records	-	0.10 0.30 (crude)	-	-
Magnus et al (1993)	Norway	11092	1967-69*	1986-89	Birth records	Birth records	Birth records	Birth records	0.24 (crude)	0.09 (crude)	Not reported
Multivariate Regression											
Langhoff-Roos et al (1987)	Sweden	276	Not fixed	Term, normal bwt*	Recall	-	Obstetric records	Obstetric records	0.19 (adjusted)	-	-

Little (1987)	U.S.	377	Not stated.	Not stated, 12 month period*	Recall	-	Obstetric records	-	0.11-0.17 (adjusted)	-	-
Emanuel et al (1992)	U.K.	880	3-9 March 1958*	Before 1982- most recent birth	Obstetric records	Obstetric records	Recall	-	0.12 –0.19 (crude)	-	-
Alberman et al (1992)	U.K.	1151	3-9 March 1958*	Before 1982- most recent birth	Obstetric records	Obstetric records	Recall	-	0.18 (adjusted)	-	-
Coutinho et al (1997)	U.S.	>100,000	1956-1975 Illinois born	1989-91 All Illinois infants*	Birth certificates	-	Birth certificates	-	0.24 – 0.27 (crude)	-	-
Hennessy et al (1998)	U.K.	2356 -2578	3-9 March 1958*	Term infants before 1991	Obstetric records	Obstetric records	Recall	Recall	0.27 (adjusted)	Not reported	0.26 (adjusted)
Hennessy et al (1998)	U.K.	3229	3-9 March 1958*	Term infants before 1991	Obstetric records	Obstetric records	Recall	Recall	Not reported	0.07 (adjusted)	0.01/per SD (adjusted)
Ramakrishnan et al (1999)	Guatemala	215	1969-77	1991-96* term births	Records	Recall	Records	Clinical Estimate	0.20 – 0.32 (adjusted)	-	-

Risk ratios											
Klebanoff et al (1984)	U.S.	1348	1930 - 45	1959-66*	Recall	-	Records - prospective	Records - prospective	3.5 LBW (adjusted)	-	-
Klebanoff et al (1985)	U.S.	1335	1930 - 45	1959-66*	Recall	-	Records - prospective	Records - prospective	1.2 LBW (adjusted)	-	-
Klebanoff et al (1987)	U.S.	43,891	1959-66 in State	1979-84*	Birth certificates	-	Birth certificates		3.0 LBW (crude)	-	-
Klebanoff et al (1989)	Sweden	1154	1955-65	1972-83*	Birth registry	Birth registry	Birth registry	Birth registry	Not reported	0.7 Preterm (adjusted) NS	2.0 SGA (adjusted)
Magnus et al (1993)	Norway	11092	1967-69*	1986-89	Birth records	Birth records	Birth records	Birth records	3.0 LBW (cf weight over 4000g)	1.46 Preterm NS	Not reported
Sanderson et al (1995)	U.S.	8248	Not stated	1988*	Birth Certificate Recall	-	Birth Certificate Recall	Birth Certificate Recall	2.5-2.8 LBW (adjusted)	-	-
Klebanoff et al (1997)	Denmark	2103	1959-61*	Up to 1989	Birth registry	Birth registry	Birth registry	Birth registry	Not reported	1.5 Preterm (adjusted)	2.0 SGA (adjusted)
Winkvist et al (1998)	Sweden	4746	1955-72*	1973-90	Birth registry	Birth registry	Birth registry	Birth registry	Not reported	1.1 Preterm (adjusted) NS	1.5 SGA (adjusted) NS

Emanuel et al (1999)	U.S.	38 513	In state after 1949	1987-95*	Birth certificates	-	Obstetric records	Obstetric records	2.3 LBW (adjusted)	-	-
Collins et al (2002)	U.S.	>100,000	1956-75 Illinois born	1989-91* All Illinois infants	Birth certificates	-	Birth certificates	-	Compares RRs in different ethnic groups		
ANOVA											
Ounsted et al (1973)	U.K.	315	Not stated	1958*	Records	-	Records	-	700grams (adjusted)	-	-
Lumey (1992)	Netherlands	575	1944-46*	1960 -85	Obstetric records	-	Interview	-	Varies according to maternal famine exposure		

Notes:

*Denotes the **origin** generation for the study, that is which generation data was collected first.

** **Estimate of offspring effect** - Summary results are presented according to the analysis type. They refer to the association between the same measures of maternal and offspring size at birth only. If the results are not for the entire range of size at birth then the groups being compared are provided (e.g. LBW or SGA in both generations). Estimates are for the effect on offspring size according to 1 unit of maternal measure (e.g. 1 gram or 1 week or 1SD of fetal growth) for correlation, regression and risk ratio estimates

NS = not significant at $p<0.05$ level, otherwise all results significant

Adjusted = refers to adjustment for contemporary maternal characteristics, notably age parity, height and weight for studies where applicable

Chapter 2:

Aims and Outcome Measures

This chapter has two purposes. The first is to document the aims and associated specific objectives of this thesis. The second is to describe the main outcome variable of the study and provide the rationale for choosing it.

2.1 Aim of study

AIM: To determine the contributions of biological and social variables acting across a woman's lifecourse that influence her offspring's size at birth.

In particular to:

1. Determine the influence of a woman's own intrauterine development on her offspring's size at birth;
2. Determine the contribution of social and biological factors operating across the lifecourse of a woman on:
   i. observed intergenerational continuities in offspring size at birth;
   ii. socioeconomic differences in offspring size at birth.

2.1.1 Specific objectives

These elaborate on the aim of the study, by presenting more detailed objectives structured largely according to the order in which they are addressed in the thesis. In Chapter 5 these specific objectives are used to structure the details regarding the statistical methodology used throughout.

A. Description of study population

i. To check that the mothers (first) and offspring (second) generations are representative of their contemporary Aberdeen and Scottish populations respectively in terms of measures of size at birth.
ii. To establish that both generations' size at birth measures are patterned in ways that are consistent with perinatal trends described in the relevant epidemiological literature.

B. Data quality assessment

i. To describe and evaluate the methods used in the linkage of the first generation females to their second generation deliveries.

ii. To evaluate the completeness of the linkage of the first generation females to their second generation deliveries and to determine if there is any selection bias in the first generation females who were linked to second generation deliveries.

C. Cross-sectional and intergenerational comparisons

i. To compare the distribution of size at birth measures in first and second generation infants in a cross-sectional manner to consider any changes over time, particularly in the light of changing obstetric and neonatal practises.

ii. To describe the intergenerational continuities in size at birth measures for first and second generation infants and in particular to examine the continuity in the intergenerational risks of adverse birth outcome (LBW, pre-term delivery and SGA).

iii. To further describe intergenerational continuities in the adult determinants of size at birth measures and to consider if the continuities in size at birth may be partly explained by the intergenerational continuity in parental biological and social characteristics.

D. Adding the temporal dimension

i. To consider how far second generation size at birth might be influenced by the development of the mother over her life course, using the example of differential maternal growth.

ii. To estimate statistically independent measures of change in maternal size over time to facilitate the determination of the independent effects of different time periods of development on second generation size at birth.

E. Towards a lifecourse and intergenerational approach to the data

i. To consider if social inequalities in second generation size at birth may be partly explained by continuity of the socioeconomic environment or social patterning of maternal lifecourse variables.

ii. To consider the joint effects of all the biological and social, lifecourse and intergenerational determinants of second generation size at birth using an approach that incorporates the temporal dimension of the data.

2.2 Size at birth – the outcome variable

Size at Birth is a function of two important variables – fetal growth rate and time in utero.

Therefore size at birth will be considered using three measures:

1. **Absolute birthweight** measured in grams will be used as a measure of absolute size, but will not be used as the sole outcome variable for the intergenerational analyses.
2. **Gestational age at delivery** measured in completed weeks since the first day of the mother's last menstrual period will be used as a measure of maturity. Gestational age at delivery is also considered to be the most important *determinant* of absolute birthweight. However it will be considered here as an outcome in its own right and as a necessary contributor to the main measure of size at birth (fetal growth).
3. **Fetal growth** measured as a Standard Deviation (SD score) or z-score of birthweight adjusted for gestational age and sex will be the main measure of size at birth. The reason for using this as the main outcome measure of size at birth is explained below.

2.2.1 Measuring size at birth

Historically the measurement of size at birth has been dependent on the measurement of birthweight alone. Interest in measuring birthweight developed amongst obstetricians from the seventeenth century onwards (Cone, 1961) but routine weighing of new-born infants only began in the nineteenth century. However in the late nineteenth and early twentieth century birthweight was not considered an important enough item of information to be included in vital statistics. Definitions regarding small size at birth were also based only on weight. For example in the early twentieth century all babies weighing below an arbitrary cut-off point of 2500g (5.5 pounds) were classified as premature without further consideration of length of gestation (Yerushalmy, 1967) a definition which persisted formally in Scotland until 1979 (Macfarlane and Mugford,

2000). In 1970 the Chief Medical Officer's annual report referred to the distinction between short gestation and slow fetal growth in response to increasing concern, largely from obstetricians, that definitions were required that pertained to low birth weight (defined then as currently at less than 2500g) and prematurity (born with a gestational age of less than 259 days) (Department of Health and Social Security, 1971). Definitions of low birth weight, prematurity and gestational age appeared in the International Classification of diseases only in the ninth revision, published in 1977 (World Health Organisation, 1977).

The measurement of birthweight, like most other measurements, is subject to measurement error. Variation may be due to the exact time of measurement of the newborn, either immediately after birth or in the following 24-48 hours when weight is likely to drop. Measurement error in terms of inaccuracies and limits of weighing scales or inaccurate reading of scales together with rounding up or down of birthweight may also contribute (Alberman, 1984). Gestational age is however subject to greater measurement error than absolute birthweight. It is traditionally calculated from the date of onset of the mother's last menstrual period. Assuming this date is accurate the gestational calculation is then based on the assumption that ovulation will occur exactly 14 days later, however cycle length varies within and between women considerably. Even with the advent of ultrasound assessment of gestational age the error limits are generally regarded as plus or minus one week. Postnatal assessments of gestational age may be made, using for example the Dubowitz Scale (Dubowitz et al., 1970), but these assessments tend to be limited to small, unwell, or premature infants.

However the error in treating absolute birthweight as an accurate marker of size at birth across a population of births may be greater altogether than these other measurement errors. An absolute weight alone is not sufficient when comparing infants size at birth across a wide range of gestational ages at delivery. For example a 2500g infant born at 40 weeks gestation has a different rate of fetal growth than a 2500g infant born at 34 weeks gestation. Using a measure of birthweight that is adjusted for gestational age is more appropriate.

2.2.2 Birthweight adjusted for gestational age

In addition to the measures of absolute birthweight and gestational age at delivery, a **fetal growth** score was therefore derived for all first and second generation singleton

males and females with complete birthweight and gestational age information. Fetal growth scores are standard deviation scores (SD scores) calculated by subtracting the sex-specific mean birthweight for each completed week of gestation from the individuals absolute birthweight and dividing by the standard deviation of all the sex-specific birthweight for that gestational age (that is the z-score standard normal transformation)[2]. The notion of using standard deviation or z-scores (SD scores) is to capture fetal growth rather than just absolute birthweight. Further SD scores allow gestational age to be considered as an independent variable from fetal growth – which is not the case for absolute birthweight because of the strong positive correlation between the two variables.

Fetal growth (SD) scores rely on an appropriately collected set of birthweights which are gestation and sex specific so that at each gestational age the distribution of birthweight is approximately normal to allow for transformation of absolute birthweights at appropriate gestational ages to the standard normal distribution.

The choice of appropriate population standards for birth weight for gestational age (fetal growth) is not straightforward. Most difficulty comes in defining normal fetal growth for premature infants (born at less than 37 weeks gestation). It might be reasonably argued that infants who are born at early gestations are not "normal" and therefore may not have normal fetal growth to the point at which they are delivered. Historically these measures tended to be based on autopsy findings (Alberman, 1984) but in the last decade standards have been based increasingly on ultrasound assessment of fetal growth in utero (Newnham and Evans, 2000). However using two-dimensional images to determine fetal weight requires several assumptions to be made and therefore considerable uncertainty is introduced particularly for fetuses at the extremes of the size distribution. The calculation relies on a formula that predicts fetal weight from biparietal diameter and femur length, both two dimensional measurements of a three-dimensional mass.

In this study two different reference populations and two different methods of standardisation are used. The first generation fetal growth scores are calculated using an internal standardisation process, whereas the second generation are standardised using

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[2] Fetal growth SD score = (Absolute birthweight – Mean birthweight for week of gestational age and sex)/ (Standard deviation for week of gestational age and sex)

an external standardisation process. The reference population for the second generation is all singleton livebirths for Scotland between 1975 and 1990, which is a population of over 800,000 births including sufficient deliveries at lower gestational ages to ensure normality of birthweight distribution. These standardisation processes will be described and justified further in Chapters 3 and 7 for the first and second generations' size at birth respectively.

Often when size at birth is the outcome cut-offs or threshold values are used to dichotomise the outcome. Clinically it may be appropriate to define cut-offs and categorise infants according to these categorical measures of size at birth because they identify different levels of perceived risk and therefore required levels of care. However in epidemiological studies considering the determination of size at birth in a whole population it may be more appropriate to treat the measures as continuous, so as to retain as much detailed information as possible, which is indeed how they will be treated in this thesis.

Appendix 1: Explanatory variables available in the Aberdeen intergenerational dataset

Grandparental Generation

A. General

Grandpaternal social class (according to occupational class –Registrar General 1951)

Maternal education (available for first born)

Maternal occupation – prior to marriage

Maternal adult height (centimetres)

Paternal social class at time of index child's birth (according to occupational class –Registrar General 1951)

B. Pregnancy Specific (Mothers of the First Generation)

Maternal age (years)

Marital status (single/married/widowed)

Maternal gravidity and parity (includes previous recognised early abortions)

Family size in 1962 (total number of living children)

Certainty of gestation (from known date of Last Menstrual Period)

Pregnancy complications (Antepartum haemorrhage, Gestational hypertension and/or Pre-eclampsia)

Obstetric history (Early miscarriage, pre-term delivery, perinatal death, small for gestational age)

First Generation

C. Perinatal Characteristics

Length of labour (< or > 24 hours)

Type of delivery (Spontaneous vaginal, Caesarean)

Birthweight (grams)

Gestational age at delivery (completed weeks)

Singleton/Multiple Pregnancy (yes/no)

Placental weight (grams)

Sex

Apgar at 1 and 5 minutes (clinical score at birth - out of 10)

Condition at birth (liveborn, stillborn, resuscitation required)

Any immediate neonatal complications (neonatal intensive care required, early death)

Any problems in the perperium (postpartum haemorrhage, later neonatal or maternal death)

D. Childhood

Age at measurement (months)

Height at measurement (in centimetres)

Weight at measurement (in kilograms)

Repeated height and weight up to 12 years (approx. 40% complete)

Visual acuity (Snellen test results and strabismus)

Hearing acuity

Reading test scores (in 1962)

Serial IQ test scores at 7,9 and 11 years (standardised to Scottish population)

Birth order and family size

E. Adulthood (Women Who Reproduced)

Adult height (in centimetres)

Marital status (single/married/widowed)

Premarital social class (by occupation – time specific Registrar General code)

Partner's social class (by occupation – time specific Registrar General code)

F. Pregnancy Specific (Mothers of Second Generation):

Maternal age (years)

Maternal gravidity and parity (i.e. includes previous recognised early abortions)
Certainty of gestation (from date of LMP and/or ultrasound assessment)

Pregnancy complications (Antepartum haemorrhage, Gestational hypertension and/or Pre-eclampsia) Smoking in pregnancy*

Obstetric history (Early miscarriage, pre-term delivery, perinatal death, small for gestational age)

Pregnancy outcome (spontaneous abortion, missed abortion, induced abortion, ectopic pregnancy)

<u>Second Generation</u>

G. Perinatal Characteristics

Length of labour (< or > 24 hours)

Type of Delivery (Spontaneous vaginal or Caesarean)

Birth weight (grams)

Gestational age at delivery (in completed weeks)

Placental weight* (grams)

Sex

Singleton/ Multiple birth

Apgar at 1 and 5 minutes (clinical score at birth – out of 10)

Condition at birth (livebirth, stillbirth, resuscitation required)

Any immediate neonatal complications (neonatal intensive care required, early death)

Immediate postpartum condition (postpartum haemorrhage, maternal death with relevant ICD code*)

* Available in Aberdeen Maternity and Neonatal Data but not Scottish Morbidity Records

Chapter 3:

Study Population: The First Generation (G1)

This chapter begins the description of the Study Population for the intergenerational analysis of offspring size at birth. It describes the historical study that provided the information on the early life characteristics of the first generation females.

The first generation was derived from the historical Aberdeen Child Development Study. This was a population based study of almost fifteen thousand Aberdeen school children carried out in the early 1960s by American and Scottish researchers. It was originally designed to determine the extent to which reading problems were related to parental and perinatal factors and to estimate the prevalence and aetiology of mental subnormality in a well defined community. Aberdeen was chosen as the location of the study because of the high standard of educational and obstetric records that formed an important source of data in the original study. From an epidemiological and public health perspective, very little has been done with or published about this extraordinarily rich source of data apart from two books that focused on the issue of mental subnormality (Richardson and Koller, 1996; Birch et al., 1970). In addition to a description of the original study the reasons why Aberdeen was a well-suited location for this type of research are highlighted. In particular a description of the perinatal record system set up in Aberdeen in the late 1940s, called the Aberdeen Maternity and Neonatal Databank (AMND) is included. This useful data source is used to validate the original perinatal data collected in the 1960s.

3.1 Aberdeen Child Development Study

The Aberdeen Child Development Study collected data on the perinatal, parental and childhood characteristics of all the 14,938 children who were in Aberdeen primary schools in 1962. In December 1962 these children, then aged 7-12 years, undertook standardised reading tests and provided information about parental occupation, circumstances and numbers of siblings. In March 1964 this cohort of school children was resurveyed using a sociometric instrument that provided information on friendship groups. At this point class teachers also completed a detailed behavioural inventory for each child (a pilot version of the Rutter scale B). Information was obtained retrospectively from school test records (IQ at 7 and 9 years) and school health records (height, weight, visual and hearing acuity). IQ scores at 11 years were obtained prospectively. For the 12,161 children born in Aberdeen between 1950 and 1955

comprehensive information was abstracted from the Aberdeen Maternity Hospital Records about the course of their mother's pregnancy and their physical characteristics at birth. For infants born at home or in Nursing homes information was also available from the Aberdeen Maternity Hospital where all this information was routinely stored. For a random 1 in 5 sample of the full Child Development Study population, (n=2510), detailed face to face interviews were conducted with the child's mother and a wide range of information was obtained including family circumstances, attitudes and more detail on behaviour (a pilot version of the Rutter scale A). All of this information was computerised. An outline of the nature and collection of this information is in *Appendix 1*.

3.1.1 The city of Aberdeen

The city of Aberdeen was felt to be an appropriate setting to pursue the original study firstly because the school and health authorities were co-operative and secondly because for more than a decade preceding this study standardised information had been systematically collected and recorded regarding the social, familial and health characteristics of almost all mothers and on the course and complications of nearly all the pregnancies and deliveries occurring in the community. In addition the population of Aberdeen was relatively stable in the 1960s with a high proportion of the children born in the city still in residence 10 years after the time of their birth.

In the 1960s Aberdeen was the third largest city in Scotland and had a population of 187,000. It was geographically isolated with no large suburbs outside the city limits and no large adjacent towns. In the 1950s Aberdeen had a birth rate of approximately 3,000 children per year and approximately 30,000 children enrolled in schools in any one year. The Director of Education at that time had responsibility for the general overview of both municipal and private schools so it was possible to contact all children through a single administrative authority. The Aberdeen Department of Education, in addition to maintaining complete records on every child's academic progress, also administered the standard achievement tests at ages 7, 9 and 11 years.

In 1971 British Petroleum announced large oil finds in the North Sea. This had a major effect upon Aberdeen and its population. Until then the city had been economically diverse, with fishing and shipbuilding in decline. The oil industry transformed the local economy, making Aberdeen the most affluent city in Scotland. Today the Grampian region, in which Aberdeen is located, has the lowest level of

deprivation in Scotland. This prosperity accounts in part for the stability of the study population.

Socioeconomic gradients in birth outcome and adult health were very evident in the 1950s and 1960s, at the time the Aberdeen cohort members were born and were growing up. This was well documented in the classic studies by Dugald Baird (Baird, 1974; Baird, 1974) and Illsley (Illsley, 1955). The affluence brought by the oil industry, however, did not eliminate socio-economic differences in health. For example, studies of birth outcome in Aberdeen in the late 1970s and early 1980s (Carr-Hill and Pritchard, 1992), showed relative socio-economic differences as large as those seen in the much more deprived area of South Wales. Strong effects of current social class on respiratory symptoms in a subset of the original cohort itself at ages 39-45 years have also been reported (Bodner et al., 1997).

3.2 Aberdeen Maternity and Neonatal Databank (AMND)

In addition to the perinatal data originally extracted from the Aberdeen Maternity Hospital records by researchers in the 1960s detailed information regarding pregnancy and birth outcome for the members of this cohort was extracted from the Aberdeen Maternity and Neonatal Databank (AMND). This extraction of perinatal data provided an opportunity for validation of the original Child Development perinatal records.

The AMND was set up in the 1940s, by Dugald Baird and his colleagues of the Medical Research Council (MRC) at the Obstetric Medicine Research Unit (then in Aberdeen but now in Glasgow and renamed as the Social and Public Health Sciences Unit), with the primary objective of providing high quality research data. It continues to be recognised internationally as unique in both its scope and its character as it comprises not only standardised data on pregnancies and routine obstetric information but also extensive social information recorded contemporaneously (Thompson et al., 1979).

Setting up such a database in Aberdeen was aided by the fact that the region had clearly defined geographic boundaries and a single obstetric/gynaecological unit, namely the Aberdeen Maternity Hospital. Initially the database only recorded information on the approximately 85% of births that occurred in the hospital but after 1948 non-hospital births were also integrated into the system. Until 1958 the information was stored on edge-punched (Cope-Chat) cards but at this time a Hollerith card record system was introduced to facilitate faster sorting and retrieval of information. The earlier records were also punched onto the Hollerith cards. In 1967 the

system underwent a further upgrade with additional facilities introduced for increased storage of data and in addition to singleton and legitimate births, multiple and illegitimate births were included. The geographical boundaries were also increased so that from 1967 details of all deliveries occurring to women resident in Aberdeen city and its suburbs were recorded.

In 1972 the decision was made to computerise all the records and in addition to link successive events occurring to individual women. From 1972 onwards this was relatively straightforward as women were allocated a unique hospital number for contact with all areas of the hospital system (obstetric or otherwise). However prior to 1972 women had a separate number assigned for each hospital episode. Whilst this identified the year, it was often the year before the birth date as the number was assigned according to the date of first antenatal contact. Records of events occurring between 1967 and 1971 were easier to link than those occurring earlier as they had a higher proportion of key linkage information such as mother's date of birth, surname, maiden name and initial of first name. As a fallback though there was a manual file index which cross-referenced all case records.

This system, unlike many clinical data recording systems was specifically designed with research in mind. It has been operational for over 50 years and the information collected spans two generations of mothers.

The AMND system was accessed to retrieve the computerised perinatal records for the members of the original Child Development Study.

3.2.1 Linkage of Child Development Study children to their AMND birth records

All the information from the Child Development Study is held in an anonymised form, with a unique numerical identifier for each record, and this was the form of the data available in London for this study. However, the original nominal file for the 14,938 Child Development Study children is kept by the Glasgow Social and Public Health Sciences (MRC) Unit entirely separate from the anonymised computerised data set (the MRC unit having moved from Aberdeen to Glasgow in 1986). This nominal file consists of three variables per child in the original study: surname of the child in 1962 at the time of original survey; child's sex; and date of birth. This nominal information was used by Aberdeen personnel to match each individual with their computerised birth records in the AMND, which also contains nominal information.

In order to carry out this match a file was created for the entire AMND births for the years 1950-1955 abbreviated to the corresponding three nominal variables which referred to the delivery record for the Child Development Study child's mother (surname of mother at delivery, baby sex, date of delivery). The AMND file was limited to singleton deliveries because multiple deliveries were not routinely included in the AMND system until after 1972 and because of problems identifying the birth order of multiple deliveries in the Child Development Study.

The file with the three nominal variables for each of the Child Development Study individuals was then read one line at a time and checked with each of the AMND records in turn. Date of delivery was allowed to vary by one day in either direction from the date of birth if the two other variables matched, but otherwise the match had to be exact.

This matching process provided a parallel set of anonymised perinatal data for 11367 of the 14938 original Child Development Study members. The 11367 AMND matched records however compared more favourably with the 11845 births from the original Child Development Study that were singleton deliveries and occurred in Aberdeen, being 96% of all those deliveries. Surname changes between the birth of the child and the survey in 1962 or, as this was an exact matching process, errors in dates of greater than 1 day or misspelling of surnames may have contributed to the 478/11845 (4%) failed singleton matches. It was not possible to match the 3093 other original cohort members to their obstetric records because they were largely born outside of Aberdeen (n=2777) or they were one of a multiple delivery (n=316).

This retrieval process provided an important check on the validity of the perinatal data recorded in the 1960s. In addition to validating the original Child Development Study obstetric data, the AMND was utilised to link the first generation females to their offspring delivery records as part of the linkage process to the second generation (see Chapter 4).

3.3 First generation females (G1)

In terms of defining a first generation for the intergenerational dataset it was only possible to link females from the original Child Development Study to second generation deliveries as linkage to second generation deliveries was dependent on common key maternal, but not paternal, variables (Chapter 4).

Of the 12161 children in the Aberdeen Child Development Study who were born in Aberdeen there were 5873 females who had perinatal data collected from their original maternity records by Child Development Study researchers in 1962. However 155 (2.6%) were multiple births and were therefore not considered further because of the difficulty of comparing size at birth between singletons and multiple births. All remaining 5718 singleton females had birthweight information and 5210 (91%) also had gestational age information. The 5210 singleton females who had data on both measures constitute what will be referred to as the **core** first generation females. The following paragraphs provide a basic description of the perinatal and childhood characteristics of these first generation females. In section 3.5 the size at birth measures of the core first generation females are compared to the size at birth measures of all liveborn female infants in Aberdeen from 1950 to1955 to determine how representative they were of all female births in that region over the same time period.

3.3.1 Size at birth of the first generation females (G1)

The size at birth of the first generation females was assessed by considering the distribution of absolute birthweight and the distribution of gestational age at delivery for the 5718 and 5210 females respectively who were singleton deliveries with complete measures at birth. Further a measure of fetal growth was calculated for all first generation infants, giving a measure of size at birth independent of gestational age and sex of the infant, as described in Chapter 2.

A. Birthweight

There were two sources of birthweight available, which were variable in their completeness and recording of the weight measures. The first birthweight measures were those from the original Child Development Study. These had been abstracted from the original obstetric records in 1962 for the 5718 singleton females who were singletons and born in Aberdeen. Weights were recorded in categories to the nearest half pound in the study, with the lowest category being a birthweight less than 2.5 pounds and the highest category a birthweight greater than 9.5 pounds. The categorical values were converted for the following analyses from pounds to grams* using the mid-point of each category for the conversion. For example in the birthweight category 3.50

* Conversion used was 1 pound = 453.6 grams

– 3.99 pounds all females were assigned the equivalent birthweight in grams of 3.75lbs. For the two extreme open-ended categories the measures were approximated in the same way (i.e. using 2.25lbs for the lowest and 9.75lbs for the highest categories) although this may have over- and under- represented respectively the true extreme values.

The second source of birthweight was the Aberdeen Maternity and Neonatal Databank (AMND). Perinatal data was obtained from the AMND for 5480 (95.8%) of the 5718 singleton females from the Child Development Study using the matching process described in section 3.2.1. The birthweight data in AMND was also entered in pounds and ounces, but values were recorded to the nearest ounce rather than to the nearest half pound. These values were also converted to grams using the same conversion factor as for the Child Development Study. Both sets of values were converted to grams so as to be comparable to the second generation birthweight information which was recorded in grams.

i. Validation of birthweight

Comparison of the two independently abstracted and converted birthweight distributions showed they were highly correlated, after allowing for the half pound categorisation, with a Pearson correlation coefficient equal to 0.993 ($p<0.001$). There were 15 females whose two birthweight values differed by greater than half a pound and who were not in either of the two extreme birthweight categories (i.e. less than 2.5 or greater than 9.5 pounds). In each case the two birthweight values were compared to the recorded gestational ages at delivery, which did not differ. In each of the 15 cases neither birthweight was incompatible with the gestational age therefore the AMND value was chosen, as it had more precise measures of birthweight (rather than having been converted from categorical values). For all matched females (n=5480) the AMND birthweight values were adopted as the variable of choice. For the 238(4.2%) first generation singleton females not matched to a birth record in the AMND but with a categorical birthweight recorded in the original Child Development Study this birthweight, converted to grams, was retained. The validity of all birthweight and gestational age combinations were again considered in the validation of gestational age (part B below).

ii. Distribution of birthweight

Absolute birthweight for the 5718 first generation singleton females was approximately normally distributed (*Figure 3.1*). The range of birthweight was 1049grams to 5557grams with a mean birthweight of 3257g and a standard deviation of 484g.

Birthweight may also be classified as low birthweight (less than 2500g) broken down into very low birthweight (less than 1500g) and extremely low birthweight (less than 1000g), appropriate birthweight (2500g – 4000g) and high birthweight (greater than 4000g) with cut-offs determined because of differential perinatal mortality risk between groups (Macfarlane and Mugford, 2000). The distribution of birthweight so categorised for the first generation females is shown in *Table 3.1*. For these singleton females born between 1950 and 1955, who survived infancy, there were 334/5718 (5.8%) born weighing less than 2500g, but no survivors born weighing less than 1000g, and 255/5718 (4.5%) born weighing greater than 4000grams.

B. Gestational age

Gestational age at delivery was also available from the two sources (Aberdeen Child Development Study and AMND). In the Child Development Study records length of gestation was defined as beginning from the first day of the last menstrual period (LMP) and recorded as the "nth week of gestation". For example the 10^{th} week of gestation referred to days 63-69 from the first day of the last menstrual period (LMP) rather than 10 weeks complete gestation (days 70-76). It was further classified by the attending obstetrician as certain or uncertain depending on his/her clinical assessment and on the woman's menstrual cycle regularity and her recall of her exact date of last menstruation. The current World Health Organization (WHO) definition of gestation at delivery is completed days or weeks of gestation measured from the first day of the woman's LMP (Macfarlane and Mugford, 2000). Therefore the Child Development Study gestations were adjusted to conform to this standard so that all gestational ages refer to completed weeks of gestation. Gestational age at delivery was available for 5210 (91.1%) of the 5718 first generation females from this study. The mean birthweight of the females with an uncertain gestation was however significantly lighter than those with gestational age information (3206g compared to 3262g, p=0.01).

In the Aberdeen Maternity and Neonatal Databank (AMND) gestational age at delivery was available for 5012 (96.2%) of the 5210 singleton females with gestational

age information from the Child Development Study. The AMND gestations were also coded as the nth week of gestation rather than completed weeks of gestation and were therefore similarly converted to completed weeks of gestation in accordance with the WHO definition.

i. Validation of gestational age

The gestational ages from the AMND file were used to validate the Child Development records. The correlation between the two data sources was high with a Pearson correlation coefficient of 0.995 ($p<0.001$). Gestational age was validated for all females with complete information, using recorded birthweight. Based on the assumption that birthweight was likely to be more robust than gestational age, birthweight was divided into 500g intervals and the gestational age range within each group was examined. Checks were made for any outlying gestations but if the gestations were in agreement and appropriate for the birthweight distribution the gestational age was retained. However if the gestations differed, which was the case for 30 females the gestational age which was closest to the mean value for the birthweight was retained, using all Aberdeen deliveries as the reference (Table 3.4). However for no pair did the gestations differ by more than 2 weeks.

ii. Gestational age distribution

The distribution of the gestational age at delivery for the 5210 first generation singleton females is skewed to the left, with a median gestational age at delivery of 40.0 weeks (*Figure 3.2*). The mean gestational age was 39.3 weeks with a standard deviation of 1.7 weeks. Most of the deliveries (87.7%) however occurred at term (37 to 41 completed weeks), with the range of gestations being 28 to 43 or more completed weeks.

In terms of the clinical categories of maturity at delivery, 312/5210 (6.0%) of the females were born at gestational ages of less than 37 completed weeks (pre-term) and 329/5210 (6.3%) were born at gestational ages greater than 41 completed weeks (post-term) (*Table 3.2*).

C. Fetal growth (Standard deviation (SD) scores)

In addition to the measures of absolute birthweight and gestational age at delivery, a fetal growth score[3] was derived for all first generation singleton males and females with complete birthweight and gestational age information (the core 5210 females and 5856 males). An internal standardisation process was used for this population-based group of infants who were all born in the same geographical area (namely Aberdeen, Scotland) over a defined 6 year period (1950 to 1955). The internally referenced SD scores of birthweight for gestational age will be referred to as a measure of fetal growth throughout the thesis. They are useful measures of size at birth because they assign a relative size score to all females which is independent of gestational age and of sex. The description of the distribution of fetal growth scores is limited here to the core first generation females (n=5210).

i. Distribution of first generation females fetal growth (SD scores)

Fetal growth for the 5210 core singleton first generation females is normally distributed as might be expected given the standard normal transformation used to calculate the scores (*Figure 3.3*). Similarly as would be expected from an internal standardisation process the mean fetal growth score is 0 with a standard deviation of 1. Further there are approximately 10% of infants in both the small for gestational age (less than tenth centile of birthweight for given gestational age) and the large for gestational age (greater than ninetieth centile of birthweight for given gestational age) groups. The range of fetal growth values is -3.8 to 4.4.

3.4 Comparison of the birthweight for gestational age distribution of the core first generation females to all Aberdeen singleton deliveries between 1950 and 1955

The 5210 core first generation females are the potential mothers of the second generation. Therefore before pursuing the linkage to second generation deliveries it is useful to understand how these females compare to all singleton females born in Scotland between 1950 and 1955 in terms of measures of size at birth. The core group of 5210 singleton females were the "survivors" to school entry of all those children

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[3] Fetal growth SD score = (Absolute birthweight – Mean birthweight for gestational age and sex)/ (Standard deviation for gestational age and sex)

born, and remaining in, Aberdeen between 1950 and 1955. Hence their perinatal characteristics might be expected to differ from those of all livebirths between 1950 and 1955. In particular their distribution of birthweight might be skewed towards the upper end of the range for each week of gestational age, largely because perinatal and infant mortality is influenced not only by gestational age but is also increased for lower birthweights at any length of gestation (Macfarlane and Mugford, 2000).

Ideally it would have been useful to compare this population of females with all females born in Scotland during the same time period. However there was a lack of population based perinatal data available for Scotland before 1967 when the SMR2 record system was initiated. The AMND record system was however operational and had collected data on gestational age and birthweight of all Aberdeen births from 1948 onwards. Therefore all female live births recorded in the AMND system between 1950 and 1955 were used as the reference group for the first generation perinatal information. There were 7251 liveborn, singleton female births recorded between 1950 and 1955 in the AMND. *Table 3.3* details the mean birthweight for each completed week of gestational age for the 5210 core first generation women and *Table 3.4* details the mean birthweight for each completed week of gestation for all Aberdeen births between 1950 and 1955. The two distributions are compared graphically in *Figure 3.4*. In general the two distributions are very similar, especially at term gestations. The greatest variation is seen in the size of female infants born before 37 weeks of gestation. The 5210 core first generation females had a lower mean birthweight than all Aberdeen female births at 30 and 31 weeks gestation, although the numbers of infants in both groups were relatively small, but a greater mean birthweight for gestational ages between 32 weeks and term (37 completed weeks). Beyond 32 weeks this is consistent with the expectation that survivors to school entry are likely to have higher mean birthweights for their gestational age, especially at the lower end of the gestational age distribution.

Potentially the fetal growth SD scores could have been calculated using all Aberdeen singleton births between 1950 and 1955 as an external reference population. However given the similarity between the two distributions of birthweight for gestational age at all but the lowest gestational ages where delivery numbers are relatively small, this made a negligible difference to the SD scores obtained (details not shown).

3.5 Childhood development of the first generation females

An advantage of using this historical cohort for an intergenerational study is that the original Child Development Study collected data from school medical and educational records as well as perinatal and extensive parental and family data (which will be referred to in greater detail in later chapters). In particular data obtained from school medical records in 1963 included measures of childhood height and weight recorded at school entry usually between the ages of four and six years (*Appendix 1).* School records accessed in 1962 also provided IQ test scores for the children at 7 years retrospectively whereas IQ test scores at 11 years were obtained prospectively for all children born before 1955 (*Appendix 1*).

The following section describes the distribution of these childhood measures for the 5210 core first generation females. Both childhood size and IQ scores will be considered as indicators of a females early development in later chapters and childhood size will be considered in particular in more detail in Chapter 11.

3.5.1 Childhood height and weight of the core first generation females

Analyses of size in childhood was restricted to females whose measurements were taken between the ages of 4 and 6 years (48 to 83 months inclusive), as variation in the rate of childhood growth is great, particularly as children approach puberty. Height and weight were available between these ages for 4871 (93.5%) of the 5210 core first generation females. The distribution of absolute height in centimetres shown in *Figure 3.5(a)* is approximately normal with a mean of 107.2cm and a standard deviation of 5.3cm. The range of height was 73.7 cm to 137.2cm. Similarly the distribution of weight in kilograms shown in *Figure 3.6(a)* is also approximately normal with a mean of 18.6 kg and standard deviation of 2.3kg. The range of weight was 10.9 kg to 34.9kg. These are very similar to the height and weight distributions of 5 year old girls living in London in the 1960s, published by Tanner and Whitehouse (Tanner, 1978). From their height and weight for age charts, the mean height of 5 year old girls in London at the same time was approximately 107cm, and their mean weight was approximately 18kg.

The variation in height and weight seen for the Aberdeen females was partly due to spread of ages at which the children were measured (48 to 83 months) and partly due to individual differences in genetic potential, environmental influences and rates of maturation (Rona, 1981). To remove the variation due to the difference in age at measurement height and weight standard deviation scores adjusted for the age of the

child at measurement were calculated, in a similar way that birthweight for gestational age measures of fetal growth were derived earlier. This allowed comparability of childhood size independent of age at measurement.

The height for age and weight for age scores were calculated for females of the same age via a normal transformation using the mean and standard deviation weight and height for all females calculated for each three month age range between 48 and 83 months of age. Single month intervals were not used because of the small numbers in the extreme age categories. The distribution of height for age scores are shown in *Figure 3.5(b)* and the weight for age scores are shown in *Figure 3.6(b).* In both cases the mean of the distribution was 0 and the standard deviation was 1.0.

3.5.2 Childhood IQ scores of the core first generation females

The results of the IQ tests administered to all Aberdeen school children at the age of 7 and 11 years were abstracted from the School Records by researchers in the Aberdeen Child Development Study. The test at 7 years was the Moray House Picture Intelligence Test carried out within 6 months of the child's seventh birthday. It was based entirely on pictures and aimed to test a child's perception and understanding of pictorial differences rather than being an assessment of formal educational achievement, hence it was called an IQ test. It was largely used as a broad screening tool to identify children who, in 1962, were classified as "mentally retarded" (defined as an IQ score of less than 60). Many studies have since shown a high degree of correlation between these early IQ test scores and later educational achievement and adult social status (Illsley, 2002). The IQ test at 11 years included a battery of Moray House tests, two of verbal reasoning and one each of arithmetic and English. The results of this test were largely used for allocation of secondary school places.

The test scores at 7 years were obtained retrospectively from the School records but the test scores at 11 years were only prospectively recorded for children born before 1955, because the youngest children did not reach the age of 11 during the study duration. The analyses will therefore be limited to the 4691 (90%) of the 5210 core females with IQ test results available at both ages.

Table 3.5 describes the key parameters of the distribution of IQ scores for the 4691 first generation females. The mean and standard deviation test score at 7 years is higher than at 11 although the IQ scores were reported to be standardised according to the Scottish population norms at both ages, with an overall mean of 100 and a standard

deviation of 15. These standardised scores were available from the original Child Development Study. In both cases the means for the Aberdeen females are greater than the Scottish average. This is probably because those children with the lowest scores (IQ <60) were not at mainstream primary schools and were not included in the original study.

The IQ scores will be referred to as explanatory variables in Chapter 6. In general they are used as indicators of childhood cognitive development and of later potential educational achievement.

3.6 Summary

This chapter has described the historical Aberdeen Child Development Study from which the 5210 core first generation (G1) females were defined. They were the females from the original study who were born in Aberdeen and who had complete perinatal information available from their original obstetric records. The distribution of their measures of size at birth and their childhood height, weight and IQ scores were also described.

These first generation females were necessarily survivors to at least the age of 7 years and enrolled at Aberdeen primary schools in 1962 to have been included in the original study. Nevertheless their distribution of size at birth was very similar to all liveborn deliveries that occurred in Aberdeen between 1950 and 1955, especially at gestational ages of greater than 36 completed weeks. In childhood their mean size was similar to that of females of the same age in London in the 1960s as described by Tanner and Whitehouse. Their IQ scores at 7 and 11 years were standardised to the Scottish population as a whole and were appropriate given that those children who were unable to attend primary school were excluded. Therefore these 5210 young girls, although geographically isolated in a stable population in the northeast of Scotland, were largely representative of other females born at the same time in the United Kingdom who survived into childhood and for whom comparable measurements were available between the ages of 4 and 6 years.

These females are the potential mothers of the second generation and in Chapter 6 the early life characteristics of the subset who reproduced will be compared to those who did not. However prior to that chapter the resource for and the linkage to the second generation will be described.

Figure 3.1 : **Distribution of absolute birthweight of first generation singleton females (n=5718)**

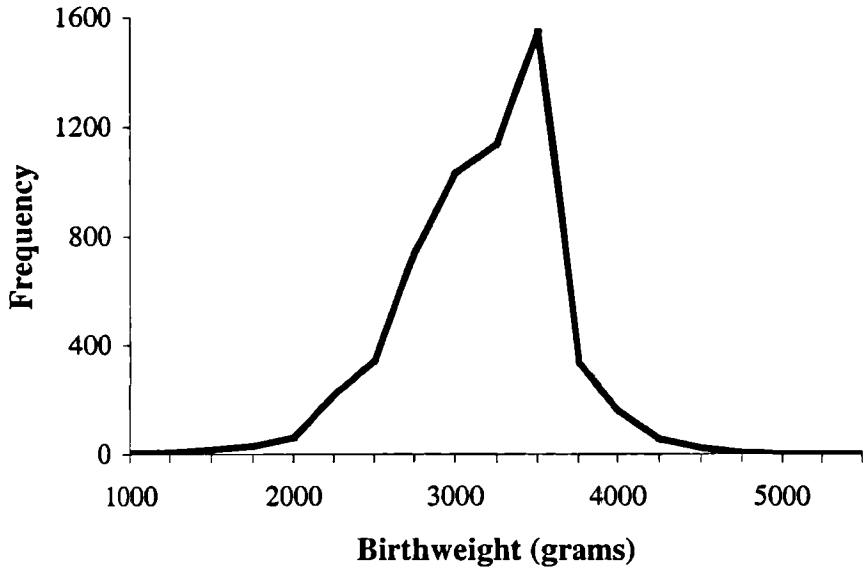

Table 3.1 : **Categorical distribution of absolute birthweight for first generation singleton females (n=5718)**

Birthweight category	Frequency	Percent (%)
ELBW	0	0
VLBW	11	0.2
LBW	323	5.6
Appropriate BWT	5129	89.7
High BWT	255	4.5
TOTAL	5718	100.0

ELBW = extremely low birthweight (<1000g)
VLBW = very low birthweight (1000g - 1499g)
LBW = low birthweight (1500g - 2499g)
Appropriate BWT = 2500g – 4000g
High BWT = birthweight greater than 4000g

Figure 3.2 : **Distribution of gestational age for singleton first generation females (n=5210)**

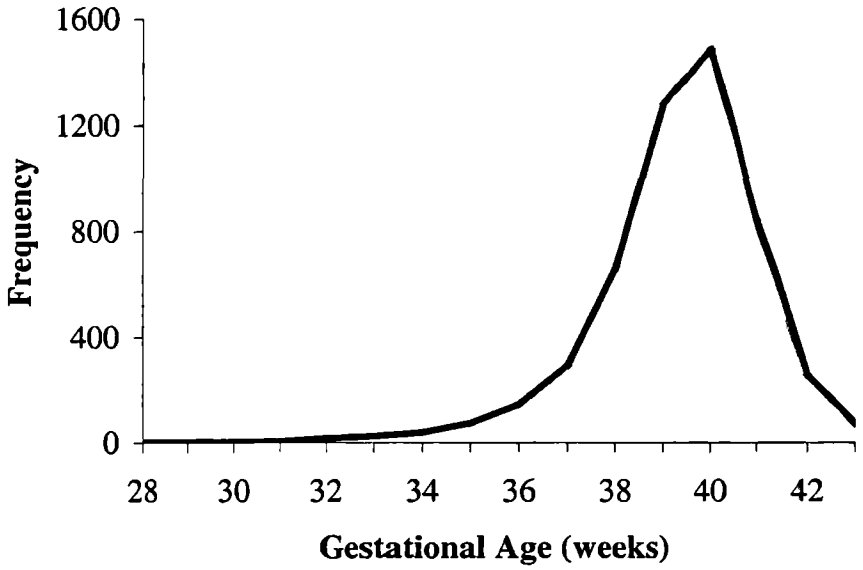

Table 3.2 : **Categorical distribution of gestational age for first generation singleton females (n=5210)**

Gestational Age Category	Frequency	Per cent (%)
Preterm	312	6.0
Term	4569	87.7
Post term	329	6.3
TOTAL	5210	100.0

Preterm = less than 37 completed weeks of gestation at delivery
Term = 37 to 41 completed weeks of gestation at delivery
Post term = greater than 41 completed weeks of gestation at delivery

Figure 3.3 : **Distribution of fetal growth for core first generation singleton females (n=5210)**

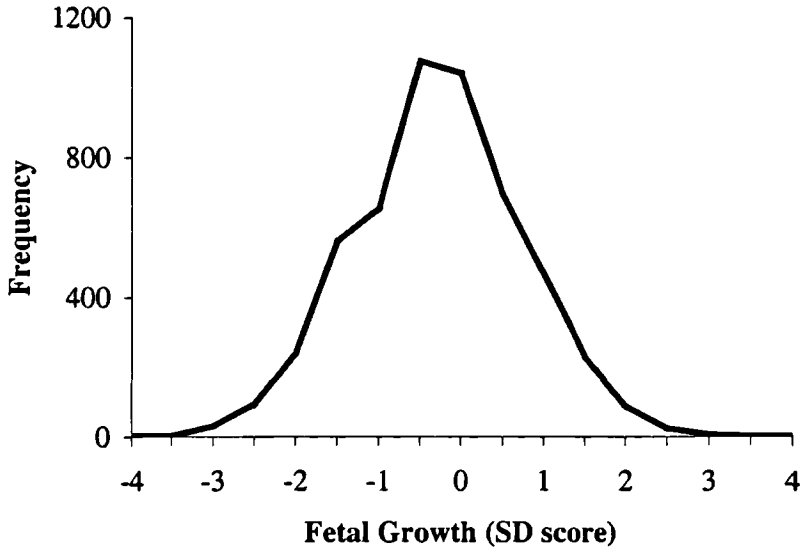

Table 3.3 : **Mean and standard deviation of birthweight for each completed week of gestation at delivery for the core singleton first generation females (n=5210)**

Gestational age (completed weeks)	Frequency	Birthweight (grams)	
		Mean	Std Deviation
28	2	1226	130
29	2	1340	190
30	2	2040	161
31	5	1837	203
32	17	2426	803
33	25	2350	662
34	39	2772	556
35	74	2759	510
36	146	2992	486
37	294	3070	437
38	662	3140	437
39	1285	3261	426
40	1488	3339	434
41	840	3411	453
42	257	3430	481
43	72	3357	514
Total	5210	3262	478

Table 3.4 : **Mean and standard deviation of birthweight for each completed week of gestation at delivery for all liveborn, singleton females born in Aberdeen 1950 – 1955.**

Gestational age (completed weeks)	Frequency	Birthweight (grams)	
		Mean	Std Deviation
28	6	1165	132
29	9	1386	467
30	8	2660	911
31	11	2179	741
32	18	2162	784
33	27	2313	729
34	56	2663	549
35	105	2710	519
36	202	2901	494
37	391	3041	452
38	969	3135	451
39	1730	3268	433
40	2121	3343	438
41	1213	3394	460
42	290	3399	485
43	95	3403	496
Total	7251	3251	512

Figure 3.4 : **Comparison of mean birthweight for each week of gestational age for all core first generation females to all female singleton livebirths in Aberdeen 1950 – 1955.**

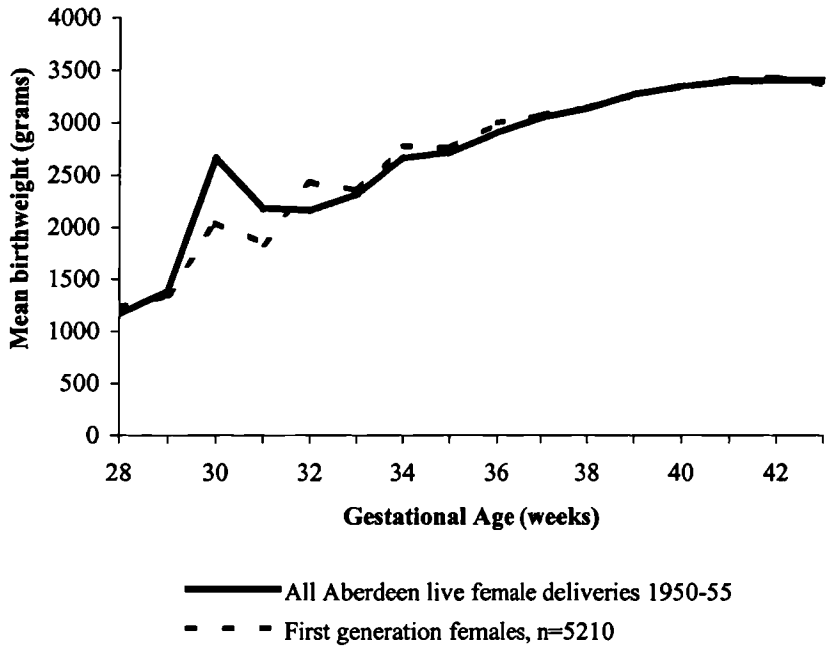

Figure 3.5(a) : **Distribution of height (in centimetres) at school entry for the core first generation singleton females (n=4871)**

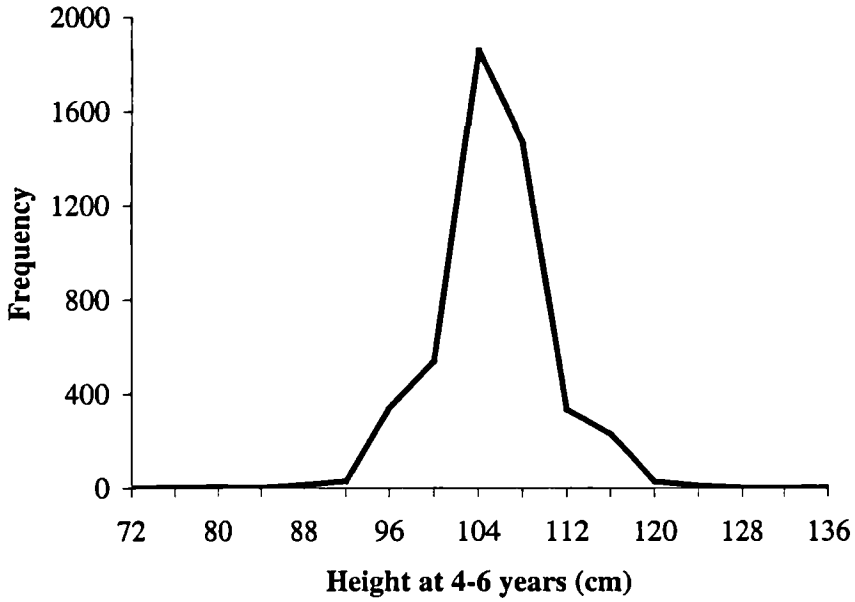

Figure 3.5(b) : **Distribution of height for age scores of core first generation females (n=4871)**

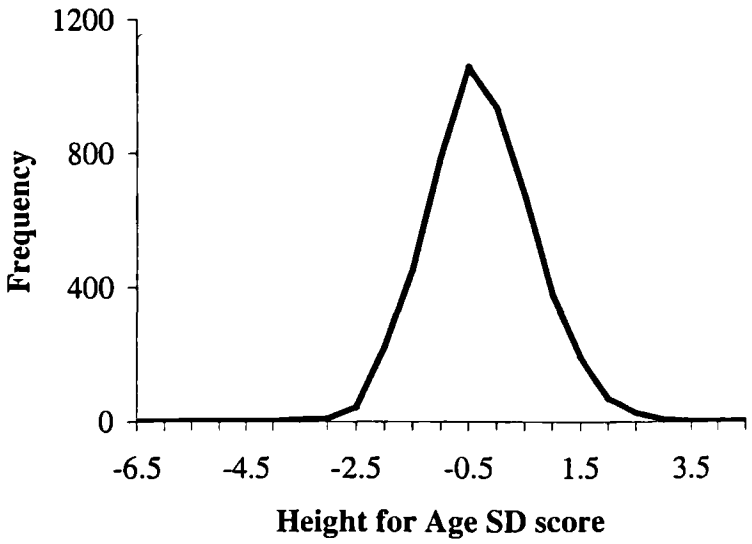

Figure 3.6(a) : **Distribution of weight (in kilograms) at school entry for core first generation singleton females (n=4871)**

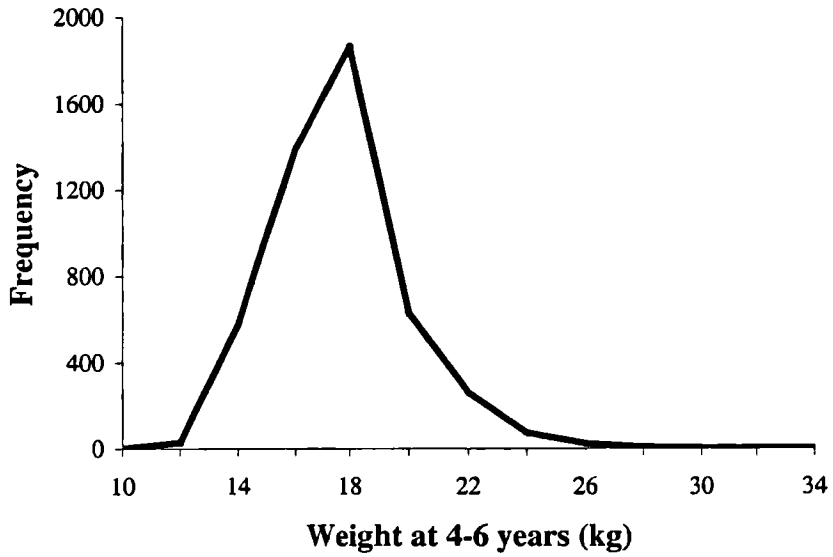

Figure 3.6(b) : **Distribution of weight for age scores of core first generation females (n=4871)**

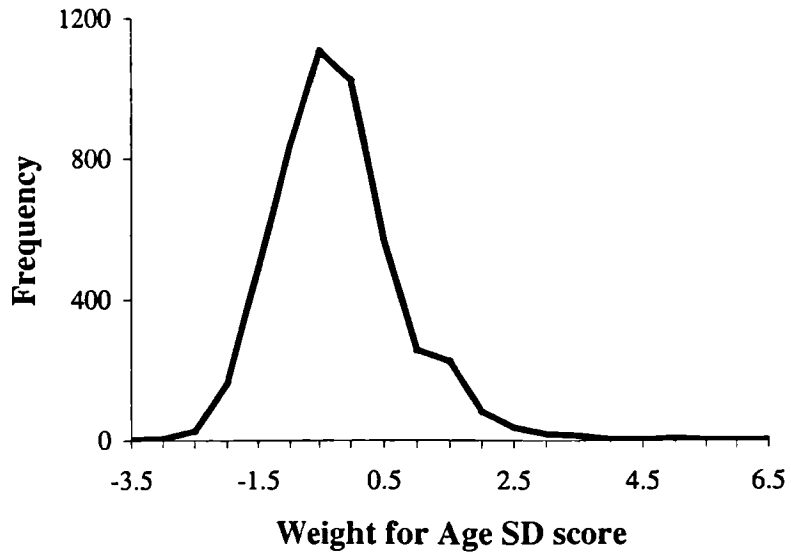

Table 3.5 : **Distribution of IQ test scores at 7 and 11 years for core first generation females (n=4691)**

IQ test score	7 years	11 years
Minimum	62	55
Maximum	166	142
Mean	108.7	104.9
Standard deviation	15.8	12.9

Appendix 1: Aberdeen Child Development Study : Sources and categories of data

Source	Population available for	Variables	Comment
Survey of primary school children aged 7-12 years conducted in December 1962	All school children in Aberdeen primary schools classes III to VII (born 1950-55), except for special schools for "subnormal", "handicapped" and deaf	Name, address, date of birth of child, occupation of father and number of older and younger sibs and whether twin or triplet *all as reported by child at time of test*	Excludes children absent and those deemed untestable because of handicap
		Battery of reading tests appropriate for each age group administered specifically for the purposes of the survey	
School records at December 1962	Information available on all children who attended surveyed schools even if they were not actually surveyed	7+ and 9+ IQ test results as routinely administered by schools. School class and attendance figures for each child.	
Aberdeen Maternity Hospital (AMH) obstetric records	All children who took part in the December 1962 school survey for whom obstetric records could be traced. Does NOT cover children included in population due to subsequent data collections.	Parity, parent's age delivery, mother's height, complications, delivery type, length labour, cause caesarean section, place upbringing of mother, time of first antenatal visit, length gestation, birthweight, puerperium, multiplicity, place of previous delivery	AMH records included information about those born at home and in nursing homes
		Occupation of mother and mother's father, mother's premarital occupation, education, marital status, interval between marriage and LMP, mother's age at marriage	Complete data for first pregnancies only
School medical records at July 1963	For most children information available at point of entry in primary school, and for a sub-set at subsequent points. Records created for all children even if they were not part of the original survey	Age at examination, height, weight, visual and hearing acuity, whether wearing glasses. For most children information on height and weight available at around age 5. Visual and hearing acuity tests conducted on different occasions .	Medical records kept by schools. After age 5 years, variable number of tests per child, related in part to changing schools - with new examination at each entry
		Laterality (handedness)	
		11+ scores (where relevant)	
		Previous primary schools and dates of entry to them	
		Info (not computerised) or various medical conditions	

Source	Population available for	Variables	Comment
Teachers' questionnaires conducted March 1964	All children in classes primary IV to secondary 2B (i.e. classes in which the original reading survey children would be in). Includes other children who were not part of December 1962 reading survey.	Scale of minor behavioural problems (yes/no). Scale of more serious behavioural problems (yes/no). List of children who were tidiest, best at sports, untidiest, most liable to tell tales and most helpful to teacher.	Instrument used was early version of the Rutter A scale
Brief questionnaire to children March 1964		Child's indication of 3 others they liked best in the class March 1964 - ID numbers of 3 best friends	Allows construction of friendship networks
Schools' 9+ and 11+ IQ scores	Obtained prospectively for all children aged 96 months or more in December 1962 who were included in one or other of the survey rounds who remained in Aberdeen up to relevant point	Verbal reasoning, arithmetic, English, teacher's estimate	Excludes almost all those born in 1955 i.e. only available for births 1950-54

Chapter 4:

Study Population: The Second Generation (G2)

This chapter continues the description of the Study Population for the intergenerational dataset by describing the sources for and the process of linkage of the first generation females to their second generation delivery records in Scotland.

Information regarding deliveries to first generation females was obtained from two sources. The Information and Statistics Division (ISD) of the Scottish Health Service Common Services Agency provided delivery records for Scottish-born offspring of first generation females originally in the Aberdeen Child Development Study using the routinely collected maternity discharge information from the Scottish Morbidity Record (SMR2). Offspring delivery information was also independently extracted from the Aberdeen Maternity and Neonatal Databank (AMND) for first generation mothers who delivered in Aberdeen.

Firstly the nature of the SMR2 record system and the process of linkage to the SMR2 records are described. An outline of the requirements for maintaining the anonymity of all the linked information is included. Secondly the extraction of the second generation deliveries from the AMND records is briefly reviewed and the merging of these two sets of second generation records is detailed.

The methods used to check and clean the data obtained by the linkages are outlined and finally the validity of the linkage is checked for a subset of the first generation women who have subsequently completed a postal questionnaire and given permission for their obstetric records to be deanonymised.

4.1 The Scottish Morbidity Record for maternity discharges – SMR2

The SMR2 records are the part of the Scottish Morbidity Record system which was designed for the routine collection of information about the antenatal period and delivery from maternity hospital case records onto computer. The origin of the system dates back to 1968 when a decision was taken that all Scottish hospital discharge records, cancer registrations and death records would be held centrally in machine readable form and would contain patient identifying information such as name, date of birth and area of residence so that linkage of records might be possible at a later date. Overall 99% of all

deliveries in Scotland take place in hospital, and it is claimed that the SMR2 forms have covered over 97% of all registered hospital births collected by each of the 15 Scottish Health Boards since 1976 (Information and Statistics Division, 1987). Home deliveries were not recorded in the SMR2 system until after 1991. A review by ISD of the few studies that have made use of data prior to 1976 confirms that the completeness of the SMR2 data was below 90% until 1976 and one study that used the pre-1976 records for Edinburgh births found that they were only 80% complete. This represented an average rate over the time period with completeness increasing with each year so that completeness in 1969 was estimated at only 65% (Information and Statistics Division, 1997).

The variables collected and stored on the SMR2 maternity discharge summaries include details of the woman's current pregnancy, her previous obstetric history, her adult height, area of residence, her own and her partner's occupation, a record of the labour and birth itself and a brief postnatal record for the infant/s. The exact nature of the variables stored on the SMR2 records have however undergone several changes between their inception in 1969 and 1999. In particular the nature of the socioeconomic information has changed over the thirty year period. Prior to 1997 information was collected on marital status and maternal and paternal occupations, but this has been dropped from the latest version of the form from 1997 onwards. In a contrary fashion smoking status was not collected with any consistency until after 1990. Given that the first generation females were born between 1950 and 1955 we would expect that they might have delivered their offspring over the entire period from 1969 to the present, but that most of the deliveries would have occurred prior to 1997, or at least first deliveries. Therefore obtaining adult socioeconomic information for the first generation females was feasible but ascertaining pregnancy smoking status from this source was not. Facsimiles of the three SMR2 forms used between 1969 and 1999 to collect the information are appended (Appendix 1).

4.2 Data protection issues – maintaining anonymity

Prior to describing the linkage itself the data protection issues that arose during the study are highlighted as they affected the process of recovery of second generation delivery records. In order to comply with the Data Protection Act and Ethical guidelines any SMR2 data that were provided by Information and Statistics Division (ISD) had to be anonymised.

This entailed any patient identifiable data being removed from the linked Scottish maternity records by ISD in Scotland. Patient identifiable data included any of the following:

- Surname/family name
- Community Health Index (CHI) number
- Hospital case reference number
- National Health Service (NHS) number
- Full postcode.

In addition mother's full date of birth was deemed an identifiable item so this was not available for validation of maternal linkage to her offspring. Mother's year of birth only was provided. These requirements complicated the process of linking maternal data to offspring data. The steps taken to comply with the requirement for an anonymised intergenerational dataset are detailed below in *section 4.2.1.*

4.2.1 The linkage process to SMR2

The second generation offspring delivery records obtained from ISD are the result of using probabilistic record linkage to match first generation maternal nominal and other identifying information with the complete SMR2 delivery files from 1969 to 1999, which also contain maternal identifying information. Whilst nominal information has been used for the ISD linkage the entire intergenerational dataset nevertheless remains anonymised. The steps involved in obtaining the anonymised second generation SMR2 records are summarised in *Figure 4.1.*

The original Child Development Survey information on the first generation females is anonymised so that records are only identifiable via a numerical identification key (ID key) assigned by the original researchers in 1962. The ID keys of all the 5873 first generation females with perinatal data were sent from London to Glasgow where the nominal information for all the Child Development Study children has been stored, separately from the original anonymised data, by the MRC Social and Public Health Sciences Unit since it moved there from Aberdeen in 1986. This unit in Glasgow provided the information on the date of birth and forename and surname of 5866 of the 5873[#] first generation females who

[#] Seven of the females ID keys did not match the ID numbers held with the nominal information in Glasgow

were born in Aberdeen, as it was recorded in 1962, together with the original ID key (as provided by London) to the General Registrars Office (GRO) in Edinburgh. The GRO used computer (National Health Service Central Register) and manual tracing methods to seek current adult surnames and the vital status of these females in 2001. They were able to trace 5634 (96%) of the 5866 first generation females and therefore provide updated names and current status and area of residence to ISD, still with the original ID key linked to the nominal data. Of the 5210 core first generation women described in Chapter 3, 4997 (96%) had updated nominal information sent to ISD for linkage to SMR2 records (*Figure 4.1).*

The first generation maternal nominal and identifying information available to ISD consisted of the following identifiers: her current surname (updated from GRO trace); her maiden name (assumed to be her surname in 1962); forename; her full date of birth; current area of residence characterised by postcode (at last tracing by GRO). Corresponding information on surname, maiden name, first and second initial, full date of birth and postcode stored on the SMR2 maternity discharge form were the five variables used for the probabilistic record linkage undertaken by ISD to identify delivery records belonging to first generation females.

The computerised probabilistic record linkage used by ISD involved the comparison of two files of records, the first contained the maternal identifying information from GRO and the second consisted of all the SMR2 delivery records containing corresponding maternal information.

4.2.2 Probabilistic record linkage – a general description

If the recording of identifying information in routinely collected data were perfect it would not be necessary to use this probabilistic linkage process. However studies have shown that for large routinely collected datasets the discrepancy rate is up to 3% in pairs of records belonging to the same person. Thus exact matching using five common identifiers may miss up to 15% of true links (Newcombe, 1988). The decision to link a pair of records depends on the similarity of the five common data fields being matched. Firstly the set of all possible record pairs is considered. Theoretically, each record on one file is compared to each record on the other file and each record pair is classified as a link or 'nonlink'. However, this is problematic with large files such as the ones in this study, as the total

number of possible record comparisons between files becomes excessively large (for example if we assume the first file of maternal information has 5,000 records and SMR2 contains approximately 2 million records, then there are around 10 billion possible comparisons). Variation and inconsistency in spelling of surnames make phonetic coding systems necessary for accurate and complete linkage of registry files. The two phonetic coding systems used by ISD are the NYSIIS (New York State Identification and Intelligence System) and Soundex codes (an adapted system designed to cope specifically with Scottish surnames). Both coding systems are able to convert surnames that are phonetically similar to the same code on the relevant files. In order to increase the efficiency and manageability of such a large scale linkage, the file with the identifying information is partitioned, or 'blocked', using one or more reliable personal identifiers (e.g. creating a blocking field consisting of the phonetic code of the surname) to limit the scope of the comparisons. It is estimated that the proportion of true links lost because of blocking is less than 0.5% (Kendrick and Clarke, 1993).

The odds in favour of a link between any two records are called 'weights'. In general, weights are assigned according to the relative frequency of the actual value of the identifying variable in the files and an estimate of how frequently each variable is misreported. This calculation assumes that the values of individual variables being compared are statistically independent.

In the case of the Aberdeen data where we have 5 variables for matching:

$$\textbf{Overall Weight} = \textbf{Weight}_1 + \textbf{Weight}_2 + \textbf{Weight}_3 + \textbf{Weight}_4 + \textbf{Weight}_5$$

If the values of the matching variables are not the same, the weight is negative. This reduces the overall weight in favour of a true link. In practise, each record pair that is brought together is classified into one of three categories: definite link, possible link, or a 'nonlink', based on overall weight, and agreed cut-off thresholds. The distribution of the overall weights is generally bimodal (*Figure 4.2*) and usually clusters around a high weight (i.e. a definite link with a weight above the upper threshold) and a low weight (i.e. a 'nonlink' with a weight below the lower threshold). The higher the overall weight, the greater the likelihood that the records belong to the same individual.

The middle area between the two modes contains the possible links and usually also contains the "cut-off" point, this is usually referred to as the "grey area". The records with overall weights in the grey area are reviewed manually by staff at ISD in order to minimise the number of false positive links (i.e. linked pairs that actually describe two different individuals) and false negative non-links (i.e. unlinked pairs that actually represent the same individual). This manual checking determines the appropriate "cut-off" point for a particular linkage.

4.2.3 Probabilistic record linkage – applied to the Aberdeen first generation data

This probabilistic record linkage method was applied to all SMR2 deliveries from 1969 to 1999 using the updated information on the 5634 Aberdeen first generation females supplied by GRO Scotland.

A linkage score (equal to the overall weight) was retained as one of the variables provided by ISD with the perinatal information (*Table 4.1*), which represented the "fit" of the match on maternal identifiers in general terms. A cut-off linkage score of 22 was chosen as appropriate for this linkage after manual checking by ISD personnel to maximise the false negatives and minimise the false positives. However exact details of this choice are not available as the manual checks involved access to nominal information. Providing the linkage score with the anonymised data aided the decision making involved in checking the quality of the linkage *(Section 4.5).*

The linked SMR2 offspring data were provided from ISD with all nominal and identifying information used in the linkage removed and the ID key replaced with another unrelated unique identifier to preserve maternal and offspring anonymity. The new identifier was unique to each of the 5634 first generation women traced by GRO and all second generation deliveries to the same first generation mother shared the same identification number.

The distribution of the linkage scores, both for all the SMR2 records initially linked and for the final cleaned dataset, which is described in section 4.5, are shown in *Figure 4.3.* The two distributions are very similar but most of the attrition in the cleaned data has occurred in the lower range of linkage scores as would be expected since these were the least probable matches statistically.

4.2.4 Creating the "Amalgamated SMR2 file" from the linked SMR2 data

The second generation deliveries were expected to occur over several decades, given that the first generation females were born between 1950 and 1955. However, the SMR2 records had undergone several changes between their inception in 1969 and 1999. There were three different SMR2 record systems used during the period 1969 to 1999. Accordingly the variables that were extracted from the SMR2 records varied over time. The exact time-specific variables extracted for each second generation delivery are detailed in *Table 4.1.* Correspondingly SMR2 information on second generation deliveries was received from ISD in three separate files relating to the different coding systems: pre-1975, 1975-March 1997 and April 1997 to December 1999. The file of deliveries prior to 1975 was a composite file for the delivery records for each of the years 1969 through 1974. The SMR2 records are known to be less complete in these years and therefore they had not been previously collated as they are not generally used in any analyses of trends in births because of their incompleteness (Information and Statistics Division, 1997). The second file contained information from the SMR2 records for deliveries between 1975 and March 1997. From April 1997 the SMR2 system was again modified (also known as the COPPISH SMR02 system – Core Patient Profile Information in Scottish Hospitals) so as to be compatible with the introduction of the tenth revision of the International Classification of Disease coding (ICD10) (Macfarlane and Mugford, 2000).

In total the probabilistic linkage matched 7217 second generation offspring delivery records to 3690 of the 5634 first generation women (*Figure 4.1*). For 1944 (34%) of the 5634 first generation females no maternity records were matched to their updated information from GRO. Deliveries before 1975 contributed 1411 (19.5%) of these while the majority were deliveries between 1975 and March 1997, being 5795 (80.3%), with only 11 (0.2%) occurred after March 1997.

The three separate files were amalgamated to create a large file of all the recorded SMR2 deliveries for the subset of the 5634 identified Child Development Study females who had delivered offspring between 1969 and 1999. This file which combines information from the three separate linked files is called the *Amalgamated SMR2 File.*

As the extended time period involved the extraction of obstetric data from schemes that did not remain consistent over the entire period, creating this involved converting and

creating common variable types and data labels. It also required the conversion of occupational codes to appropriate social class codes for the relevant time which was done for two separate periods: pre-1981 and 1981 onwards. In addition maternal pregnancy-related diagnostic codes required conversion to diagnostic categories using the appropriate ICD coding for the year of delivery. Hence ICD 8 was applied to all diagnostic codes for discharges between 1968 and 1979, ICD9 for discharges between 1980 and 1996 and ICD10 for deliveries after March 1996.

The SMR2 records included details of hospital admissions that did not result in delivery (for example spontaneous and therapeutic abortions, threatened abortions and other antenatal indications such as hyperemesis or pre-eclampsia) but these were removed from the *Amalgamated SMR2 file* as they represented different outcomes than offspring size at birth. The *Amalgamated SMR2 file* was restricted to singleton offspring viable deliveries. Viable deliveries were defined as those with a birthweight of greater than or equal to 500grams and a gestational age of greater than or equal to 24 completed weeks, as these are the currently accepted standard limits of infant viability (Allen et al., 1993).

However these 7217 second generation deliveries did not constitute the final second generation dataset as they required reconciliation with the delivery records obtained from the separate linkage undertaken using the Aberdeen Maternity and Neonatal Databank (AMND), followed by data-cleaning to check for the appropriate inclusion of all records.

4.3 The AMND offspring records

In addition to the ISD linkage an abstraction of the deliveries to singleton first generation females who were born in Aberdeen was also carried out separately using the Aberdeen Maternity and Neonatal Databank (AMND). As well as locating the first generation female's own delivery record (as described in Chapter 3) the AMND had an additional field which automatically linked the woman to her offspring delivery records. Thus the exact linkage described to obtain perinatal records for the first generation Child Development Study members in Chapter 3 was extended to provide 4318 Aberdeen second generation delivery records for 2110 (37.5%) of the 5634 GRO-traced first generation females. As for the SMR2 records these were restricted to singleton deliveries of viable infants with a birth weight of at least 500grams and a gestational age of at least 24

completed weeks. Initially the data had been linked using the anonymised ID key from the original Child Development Study as the identifier but ISD also converted this to the new identity key to match their own conversion allowing comparison of the two second generation linkages whilst preserving anonymity.

4.4 Creating the Merged file of second generation deliveries

Several stages were required to create the final second generation dataset suitable for intergenerational analysis. The first stage involved merging the *Amalgamated SMR2 file* containing the second generation data extracted from the SMR2 files with the second generation data obtained from the AMND linkage. Prior to merging the two independently linked second generation datasets consistency checks on key perinatal variables were carried out. Range checks lead to the exclusion of implausible values, for example impossible gestational ages of 49 or 99 weeks, and restricted the included records to viable*, singleton second generation deliveries between 1967 and 1999, as described earlier.

The *Amalgamated SMR2 file* was merged with the AMND delivery records by matching on the new maternal ID number (as assigned by ISD) and the year of delivery of the second generation offspring. This *Merged file* contained second generation delivery records that were in one of three categories: either they were identified in both SMR2 and AMND, so that there were potentially two independently coded records of the same birth, or they were found in only one of the datasets, SMR2 only or AMND only. Merging the SMR2 and the AMND files together yielded 8057 offspring delivery records in total, 3739(46.4%) came from SMR2 only, 840(10.4%) came from AMND only and 3478(43.2%) were identified in both AMND and SMR2 (*Figure 4.5*).

4.4.1 General check (all sources)

The first general check for the validity of the records in the *Merged file* involved a consideration of the theoretical reasons for a record being in one of these three categories compared to the actual proportions obtained from the linkages. This was to check in particular for any evidence of systematic bias in inclusion or exclusion of Aberdeen delivery records from SMR2.

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* Viable refers to a gestational age of 24 weeks or more and a birthweight of at least 500 grams

i. In theory

Theoretically we would expect records to be found only in SMR2 if a delivery had occurred in Scotland but outside of Aberdeen. A proportion might also be expected to be found only in SMR2 because of the less stringent matching process used to link first generation mothers to their offspring (that is the SMR2 probabilistic record linkage versus the exact matching used for the AMND linkage).

Theoretically we might expect between 1 and 3% of all Aberdeen deliveries to be found only in the AMND record system since the SMR2 system claims between 97 and 99% completeness. However prior to 1976 the SMR2 system was acknowledged to be less complete and therefore we might expect a change in the proportion in this category over time.

Similarly we might theoretically expect 97% or more of the AMND deliveries to also be found in SMR2 (that is in the BOTH category) as the Aberdeen deliveries should form a subset of all the Scottish deliveries to the first generation women.

ii. In practice

In practice just over half of all the SMR2 records were found in SMR2 only and were not matched to records in AMND. This was a higher proportion than expected and could not be attributed to those SMR2 only deliveries having occurred outside of Aberdeen since 77.6% of the SMR2 only deliveries came from Aberdeen maternity hospitals. It is likely to be in part due to the less stringent probabilistic matching used by ISD as opposed to the exact matching used for AMND retrievals. Probabilistic matching was used to avoid a possible 3% false negative rate for each of the maternal variables required to be an exact match, five variables in this case (Newcombe, 1988).

A higher proportion of deliveries than expected also fell into the AMND only category. Approximately 19% of all the AMND deliveries were unmatched in the SMR2 linkage. However the proportions of matched and unmatched SMR2 records for Aberdeen deliveries did vary considerably over time as predicted *(Figure 4.4)*. Approximately 22% of the Aberdeen deliveries prior to 1976 were only found in the AMND records. There were 28 births recorded in the AMND system that occurred in 1967 and 1968 which could not be part of the SMR2 system as it only began in 1969. For the remaining 471 AMND only

births that occurred prior to 1976 no matches were found among the 946 Aberdeen deliveries in the SMR2 only file for the corresponding time period despite systematic checking. No simple explanation could therefore be found for the lack of matching, in particular the dates of delivery, maternal age, maternal heights, birthweight and gestational age were compared in detail for the two unmatched sets of records without any further common records being found and without simple coding errors being identified. The more likely reason for the high proportion of AMND only records before 1976 was the lack of completeness of the SMR2 data, estimated to be less than 90%, before 1976 (Information and Statistics Division, 1997). However the AMND system should have registered all births in Aberdeen before 1976, given that it claimed complete coverage from the 1950s. This supports the premise that the AMND only deliveries prior to 1976 were probably valid deliveries but were simply not coded or received by SMR2.

For the deliveries which occurred from 1976 onwards the proportion of Aberdeen deliveries in AMND only but not in SMR2 is much reduced in this data to approximately 6.8% of the total in the merged file. This is closer to but slightly greater than the expected proportion of 3% given the 97% coverage that SMR2 claims from approximately 1976 onwards. However, as before after careful systematic checking of the unmatched SMR2 records with those in AMND and not linked to an SMR2 record, using the key variables of year of delivery, maternal age, maternal parity, birthweight and gestational age it was apparent that these were not the result of simple coding errors. Accounting for part of the difference may have been that home deliveries were not recorded in the SMR2 system until 1992 (Information and Statistics Division, 1997) but were in theory collected by AMND from the early 1950s. However this is only likely to explain a small proportion of the unmatched cases given that the prevalence of home deliveries in Scotland was estimated to be less than 1% of all births during this period (Macfarlane and Mugford, 2000).

Hence the differences over time in the proportions of deliveries according to record source seen in *Figure 4.4* are largely understandable in terms of the different development of the independent data recording systems and the different types of matching used to obtain the two linkages. The question that remains was whether there was any systematic bias present in the inclusion or exclusion of the Aberdeen deliveries from the SMR2 records.

iii. Bias in the inclusion of Aberdeen deliveries in SMR2

Of the 8057 second generation deliveries in the *Merged file,* 7133 (88%) were Aberdeen deliveries. Simple tabulations and cross-tabulations did suggest some bias in the type of Aberdeen deliveries that were only detected in the AMND and not detected in the SMR2 system. In particular it seemed that Aberdeen born infants found only in the AMND system appeared overall to be lighter at birth and more likely to be the first born infants of younger mothers (*Table 4.2).* However the deliveries that were found in AMND only were also almost twice as likely to have occurred before 1976 than the deliveries that were also found in the SMR2 system (*Table 4.3*) . Before 1976 the first generation mothers were relatively young and likely to be delivering their first infants given that they were born only 20-25 years earlier. Indeed analyses of key maternal variables by data source, restricted to the Aberdeen deliveries and stratified according to whether the delivery occurred before or after 1976, confirm that the apparent differences in the characteristics of infants excluded from the SMR2 system was largely a period effect (*Table 4.2).* The incompleteness of the SMR2 system prior to 1976 meant that most of the early Aberdeen deliveries were found only in AMND, with the proportion dropping sharply following 1976, which explains the over-representation of younger mothers of lower parity delivering lighter infants in that group.

4.4.2 Data cleaning

Following this general check of the data the validation process required different approaches according to whether the delivery records were found in both SMR2 and AMND systems or came from only one source. This process is described in detail below and summarised in *Figure 4.5.*

i. Matched deliveries (identified in both AMND and SMR2)

The next step in the data checking involved searching for and deleting potentially inappropriately linked records by comparing the two independently coded second generation delivery records that had been assigned to the same first generation woman by both the AMND and the SMR2 matching processes. Deliveries were matched on maternal identity keys and offspring year of delivery in the *Merged file* so these could not be used in the checking process. Thus three other infant and three other maternal key variables were

used to check the quality of the match between the two independently coded delivery records.

The three infant variables and the acceptance limits for the pairs of values were:

- birth weight – allowed to vary by up to 50g
- gestational age – allowed to vary by 1 week
- sex – same

Similarly the requirements for the three maternal variables were:

- Maternal parity – same
- Maternal age at delivery – same
- Maternal height – allowed to vary by up to 5cm.

When these criteria were not met for all of the six matched variables the "matched" pair of records were examined in further detail. If one of the six matching variables failed the criteria then all others needed to be consistent (within the above limits) to retain the record outright. If there was more than one inconsistency then in addition to these key variables the mother's own year of delivery was used along with the consistency of her gravidity, previous abortions (spontaneous and therapeutic) and number of surviving children to reject or accept the match. The linkage score obtained by the ISD probabilistic linkage process was used as an adjunct to this process. The higher the linkage score the more likely a record was to be retained in the face of one or more inconsistent key variable differences and conversely the lower the score the less likely it was to be retained. However it was not used as a stand alone criteria.

The independent linkage to the two delivery record systems had produced highly consistent results for the 3478/8057 (43.2%) of the second generation delivery records that were found in both AMND and SMR2. Birth weight in grams was identical from SMR2 and AMND in 92% of the matched records. In only 1% (35/3478) did the coded measurement differ by more than 50g. Completed weeks of gestation at delivery matched exactly for 80% of the linked records and for 98.5% differed by only plus or minus 1 week. After checking each of the six chosen variables, and the criteria for matching described above, 17 records were dropped because of irresolvable multiple matched variable inconsistencies. A further 11 records had variables recoded because of the apparent miscoding of a measurement in one of the record pairs. This reduced the total number of

second generation delivery records from 8057 to 8040, representing deliveries to 3935 first generation mothers (*Figure 4.5).*

ii. Within woman – "consecutive" deliveries

The next stage of the data cleaning involved considering the set of delivery records that had been matched to each individual first generation woman. An advantage of the SMR2 and AMND linkages is that they were able to provide complete data on all a first generation female's second generation deliveries in Scotland over her entire reproductive life (1967-1999), rather than just being limited to one delivery per woman or to a more limited time period for second generation data collection. Of the 8040 remaining second generation delivery records in the *Merged file*, 7001(87.1%) were one of a "set of deliveries" assigned to the same first generation woman. These sets of presumed sibling delivery records came from any source, and most usefully for checking purposes were a mix of SMR2 only, AMND only and both SMR2 and AMND. First generation maternal information was repeated on each second generation delivery record and this provided a useful check on the validity of the match between a mother and her offspring delivery records. In particular change in parity and age between consecutive births and the consistency of fixed maternal variables such as maternal height were used to confirm the validity of the linkage. Repeated maternal height measures are however subject to considerable variation due to measurement error so agreement on this variable was not used as a stand-alone criterion. To check the consistency in key maternal variables for the same woman in consecutive deliveries difference variables were created which calculated change in each measure over time. The key checks used and the requirements for consistency (shown in brackets) were:

- Change in maternal parity between deliveries (always increasing)
- Change in maternal age (consistent with change in year of delivery)
- Maternal height (consistent within 5cm due to possible measurement error)
- Interpregnancy interval (greater than 9 months and consistent with parity change)

An important check at this stage involved checking that only one "set of deliveries" (defined by parity always increasing and not being either repeated or decreasing over time) was assigned to each woman. Using the above checks it was often clear which were the appropriate deliveries however where doubt remained then the deciding variable to include

or exclude deliveries was the linkage score (for records found in SMR2). For consistency the records with the lowest linkage score were dropped when more than one potentially appropriate "set of deliveries" had been matched to a single woman. In virtually every case this corrected the problems with inconsistencies in maternal height and parity between consecutive deliveries to the same woman. Where only one variable differed between consecutive records, particularly height being more than 3 cm different, the records were retained if there was no evidence to suggest that the records could not otherwise belong to the same woman.

These checks eliminated 112 records and reduced the total second generation deliveries from 8040 to 7928, belonging to 3932 first generation mothers *(Figure 4.5).*

iii. Consistency check for single source data

The delivery records for which the least consistency checks were possible was where only one second generation delivery was assigned to a first generation woman and further that it had only been found in either SMR2 or AMND but not in both. These deliveries represented 1039 (12.9%) of the total second generation records. Other than basic consistency checks on the likelihood of birth weight and gestational age combinations the only other possible check involved ensuring that maternal age at delivery was consistent with the difference between the first generation mother's own year of birth and her offspring's recorded year of birth. This was true for all 1039 single source records so no further records were eliminated *(Figure 4.5).*

4.4.3 Creation of the final second generation data

After these checking and cleaning procedures simple tabulations of key perinatal variables (birthweight, gestational age, maternal age, parity and height), suggested that the 7928 second generation delivery records that remained were all within appropriate limits and that none further could be eliminated for obvious inconsistencies.

Therefore in order to create one file of second generation deliveries with consistent variable names, the following three steps were taken:

- For deliveries only in SMR2 these were retained with the variable names previously assigned.

- For deliveries only in AMND these too were retained but the variable names were matched to those in SMR2 so that where a delivery occurred in Aberdeen but was not recorded by SMR2 the AMND values were assigned to the SMR2 record.
- For deliveries in both, which had been previously checked for consistency the SMR2 values were retained unless they were unknown in which case the AMND values were substituted as long as the values were appropriate.

Hence the checked and cleaned second generation file consisted of 7928 viable, singleton deliveries to 3932 first generation women.

4.5 Validation of the SMR2 and AMND record linkages using self-reported questionnaire responses

In May 2001 a postal questionnaire was sent by ISD to all the original Aberdeen Child Development Survey members who had been traced through GRO and for whom a presumed current addresses had been identified. The postal questionnaire requested information about general health in addition to historical and current social circumstances for the original study members who were aged between 46 and 51 years of age in 2001. In particular the questionnaire requested information about a female's reproductive history including the number and sex of the children she had delivered and their year and place of delivery.

By January 2002 there had been 3197 responses from the 4681 questionnaires sent to the traced first generation females, a response rate of 68.3%. As for the record linkage information, the questionnaire data was also returned anonymised with a numerical identifier, different from that on the record linkage file. However for women who gave their consent on the returned questionnaire it was possible for ISD to link the anonymised questionnaire identifier with the identity key in the second generation delivery file. This enabled a validation of the reproductive histories obtained for a subset of the first generation females via the SMR2 and AMND linkages.

4.5.1 The validation process using the questionnaire data

A random sample of 200 numerical identifiers of first generation women, who claimed to have reproduced according to their questionnaire responses and who had given their

permission for linkage to their delivery records, were sent to ISD so that their equivalent identifier could be located in the SMR2 and AMND linkage file. This allowed two sets of independently obtained (still anonymised) reproductive histories to be compared, one set from the self-reported questionnaire and one from the SMR2 and AMND linkage. Validation was only possible for woman who had said they had reproduced because of the necessity for them to give consent for linking the questionnaire information to their delivery records.

4.5.2 Validation results

For the 200 women who reported that they had reproduced in the postal questionnaire, 181 (90.5%) had been linked to deliveries in the SMR2 and AMND linkage.

Of these 181:

150 were exact matches in terms of number of children, sex and years of delivery

18 were missing one Scottish delivery in the SMR2 and AMND linkage

9 were missing one delivery from outside of Scotland

4 had 1 extra SMR2 birth appended to their self-reported deliveries

19 of the 200 women who reported that they had delivered offspring in the questionnaire had not been linked to any deliveries in the SMR2 and AMND linkage.

For these 19 women:

14 delivered 24 children in Scotland and 1 outside Scotland

5 delivered all their 13 children outside Scotland

In terms of the second generation deliveries, the 200 women in the questionnaire reported a total of 384 second generation deliveries, (a rate of 1.92 live births per woman).

Of these 384 second generation infants:

319 were correctly identified by the SMR2 and AMND linkage

42 Scottish deliveries were missing from the SMR2 and AMND linkage

23 deliveries occurred outside Scotland

Of the 42 Scottish deliveries recorded in the questionnaire responses but not found in the SMR2 or AMND linkage, additional information from the questionnaire shows that 26

occurred in Aberdeen and 14 occurred in Scotland but outside Aberdeen. The remaining 2 of the missed Scottish deliveries were twins who were excluded from the record linkage.

For the 14 missed Scottish, but not Aberdeen deliveries, 10 occurred prior to 1976 when the SMR2 system was acknowledged to be much less complete, as discussed earlier. For the 26 singleton Aberdeen deliveries, 20 occurred prior to 1976, when the AMND system was operational but given the exact matching requirements for identifying females did not capture all the Aberdeen deliveries (*Figure 4.4*). They may also have been missed by the SMR2 system as for the non-Aberdeen deliveries. Therefore 10 of the 40 singleton deliveries occurred after 1975 and appear to have been missed by both the SMR2 and AMND linkages.

In addition there were 4 deliveries found in the SMR2 linkage that were not reported by the women in the questionnaire.

4.5.3 Summary of the validation exercise

The linkage to SMR2 and AMND was not able to trace delivery records of infants born outside of Scotland, therefore for this random sample of 200 women from the first generation, the linkage correctly identified 319 (88.4%) of the 361 self-reported Scottish deliveries. This is equivalent to an 11.6% failure to capture Scottish deliveries, which is in excess of the 3% rate quoted by ISD. However 30/40 (75%) of the missed Scottish deliveries occurred prior to 1976 when the SMR2 system was acknowledged to be incomplete.

The 4 extra deliveries found in SMR2 and not self-reported suggests a false positive rate of just over 1% which is in accordance with the rate that ISD quote when using probabilistic methods of linkage.

Overall this validation using a small subset of 200 first generation women chosen at random was reassuring in terms of the validity of the anonymised record linkage to SMR2. In particular the 83% (150/181 women) rate of agreement for complete reproductive histories for first generation women and the over 88% correct linkage to second generation infants with an apparent low rate of false positives suggests that the methods used to obtain the intergenerational data have been largely successful, acknowledging the limitations of

the record systems themselves, especially the incomplete records of SMR2 prior to 1976 and the exact matching used to capture AMND second generation deliveries.

4.6 Summary

This chapter has described the process used to define the second generation for this intergenerational study. Two separate linkages were used to locate deliveries to the first generation women that occurred in Scotland and where there was duplication this was utilised for validation purposes of the final data. In addition data recently obtained from self-reported questionnaires sent to the first generation was reassuringly similar to the data obtained from the anonymised, probabilistic linkage.

Therefore the final second generation data consists of 7928 deliveries linked to 3932 first generation females. In Chapter 6 the characteristics of the first generation females who were linked to deliveries will be considered and in Chapter 7 the perinatal characteristics of the second generation infants will be considered in more detail. The next chapter formally defines the intergenerational dataset and the methods to be used in the intergenerational analyses.

Figure 4.1 : **Summary of steps involved in obtaining the anonymised second generation SMR2 records**

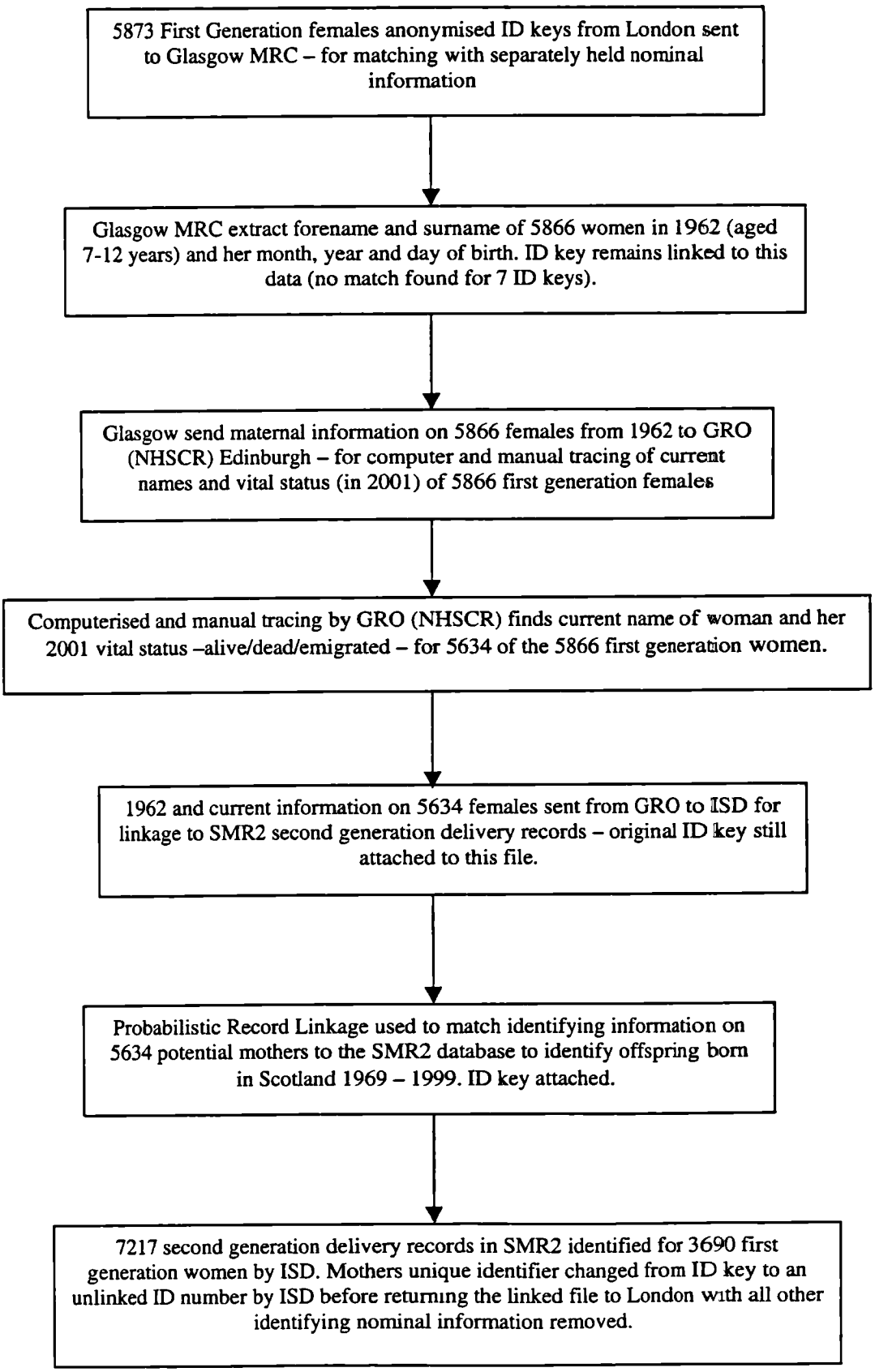


Figure 4.2 : **General schema for the distribution of weights (linkage scores) in probabilistic record linkage**

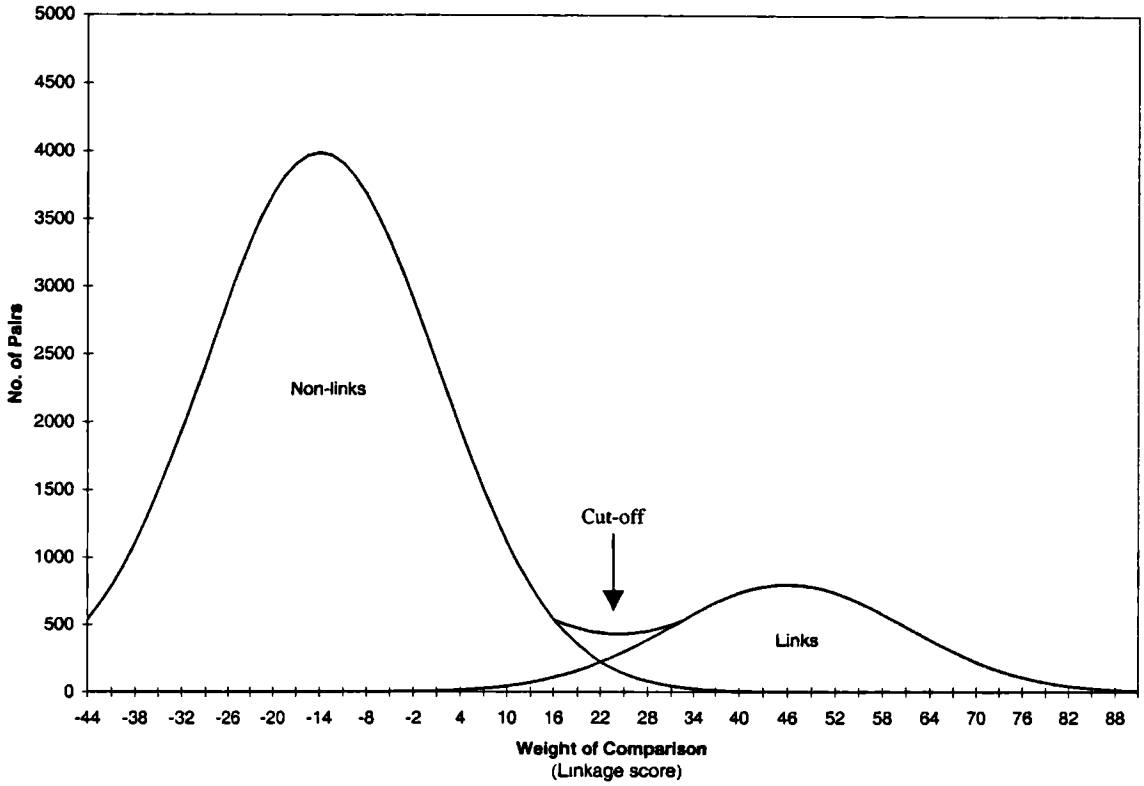


Figure 4.3 : **Actual distribution of linkage scores (weights) for the probabilistic linkage of Aberdeen first generation maternal data to all SMR2 records 1969-1999**

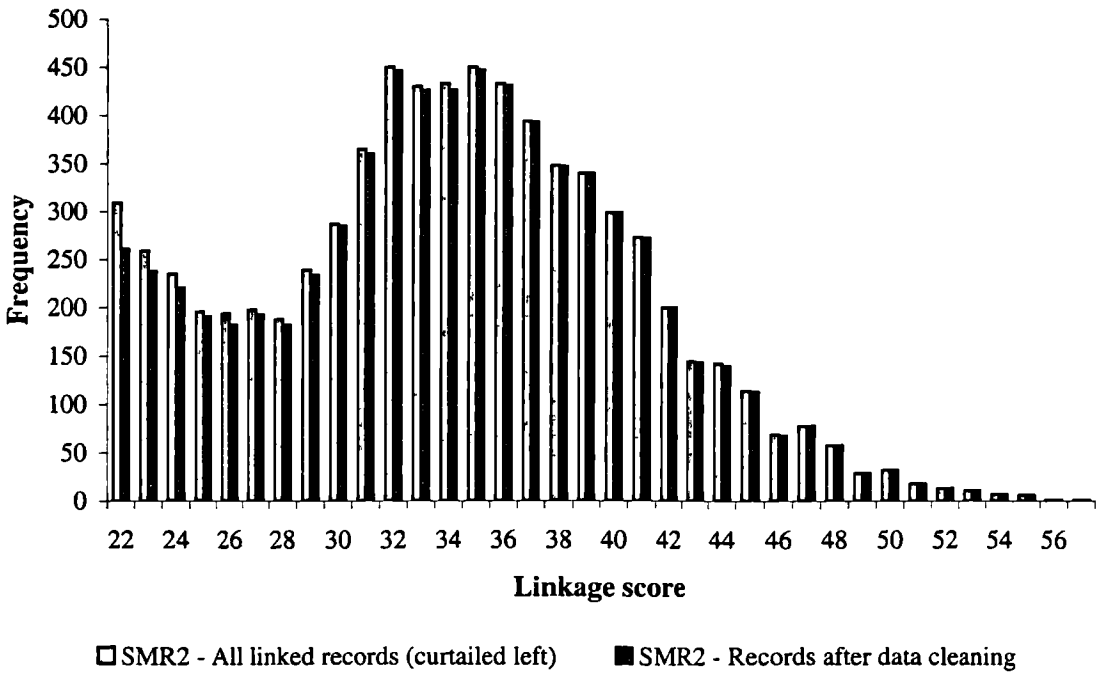


Table 4.1 : **Perinatal variables requested from each of the three SMR2 standard coding forms used between 1969 and 1999 in the probabilistic linkage**

Description of requested variable	**Variable name on SMR2 form**		
	<1975	**1975 – March 1997**	**April 1997 - 1999**
General			
Adult height	Height (cm)	Height (cm)	Height (cm)
Marital status	Marital status	Marital status	Marital status
Age at marriage	Date of marriage	Date of marriage	-
Woman's social class (Occupational classification)	Usual occupation of Mother	Occupation - Mother	-
Partner's social class (Occupational classification)	Husband's occupation	Occupation – Husband or Partner	-
Social Class	-	* Social Class	-
Pregnancy Specific Details			
Maternal age at pregnancy/delivery	Age (years)	Age (years)	Age on admission *
Maternal gravidity	Total number previous pregnancies	Total number previous pregnancies	Previous pregnancies Total number
Previous Spontaneous Abortions	Abortions	Spontaneous Abortions	Spontaneous Abortions
Previous Therapeutic Abortions	-	Therapeutic Abortions	Therapeutic Abortions
Perinatal Deaths	Stillbirths + Deaths in first month	Perinatal Deaths	Stillbirths + neonatal deaths
Children living	Surviving children	Children now living	-
Parity	-	Parity*	Parity*
Time of Booking	Date of Booking	Gestation at Booking*	Gestation at Booking*
Gestation at Delivery	Date of delivery	Estimated gestation at delivery or abortion	Estimated gestation at delivery or abortion
Certainty of gestation	LMP – date certainty	Certainty of gestation based on LMP	Certainty of gestation based on LMP
Smoking History	-	Booking smoking history	Booking smoking history
Smoking in this pregnancy	-	Smoker during pregnancy	Smoker during pregnancy
Perinatal details			
Date of delivery	Year of delivery	Year of delivery	Year of delivery
Duration of Pregnancy	-	Calculated gestation*	Estimated gestation
Multiple Birth?	Number of births this admission	Number of births this pregnancy	Number of births this pregnancy

BABY1			
Sex	Sex	Sex	Sex
Birthweight	Birthweight (g)	Birthweight (g)	Birthweight (g)
Condition at birth	Outcome of pregnancy	Outcome of pregnancy	Outcome of pregnancy
Type of Delivery		Mode of delivery	Mode of Delivery
Resuscitation	-	-	Resuscitation
Further condition at birth	-	Apgar score 5 mins	Apgar score 5 mins
BABY 2			
Sex	Sex	Sex	Sex
Birthweight	Birthweight (g)	Birthweight (g)	Birthweight (g)
Condition at birth	Outcome of pregnancy	Outcome of pregnancy	Outcome of pregnancy
Resuscitation		Resuscitation	Resuscitation
Further condition at birth	-	Apgar score 5 mins	Apgar score 5 mins
BABY 3			
Sex	-	-	Sex
Birthweight	-	-	Birthweight (g)
Condition at birth	-	-	Outcome of pregnancy
Type of Delivery	-	-	Mode of delivery
Resuscitation	-	-	Resuscitation
Maternal Conditions			
Pre-eclampsia, APH, Delivery complications e.g. PPH, Maternal death	ICD8 discharge codes	ICD8 and ICD9 discharge codes	ICD10 discharge codes

Notes:

All these variable names above match the variable name on the appropriate SMR2 form

- Indicates variable not available on this form

* These are derived data items (1975 onwards) – automatically derived from the SMR2 form or specifically requested for this linkage

Figure 4.4 : **Percentage of second generation deliveries for each year of delivery according to data source (SMR2 only, AMND only or Both).**

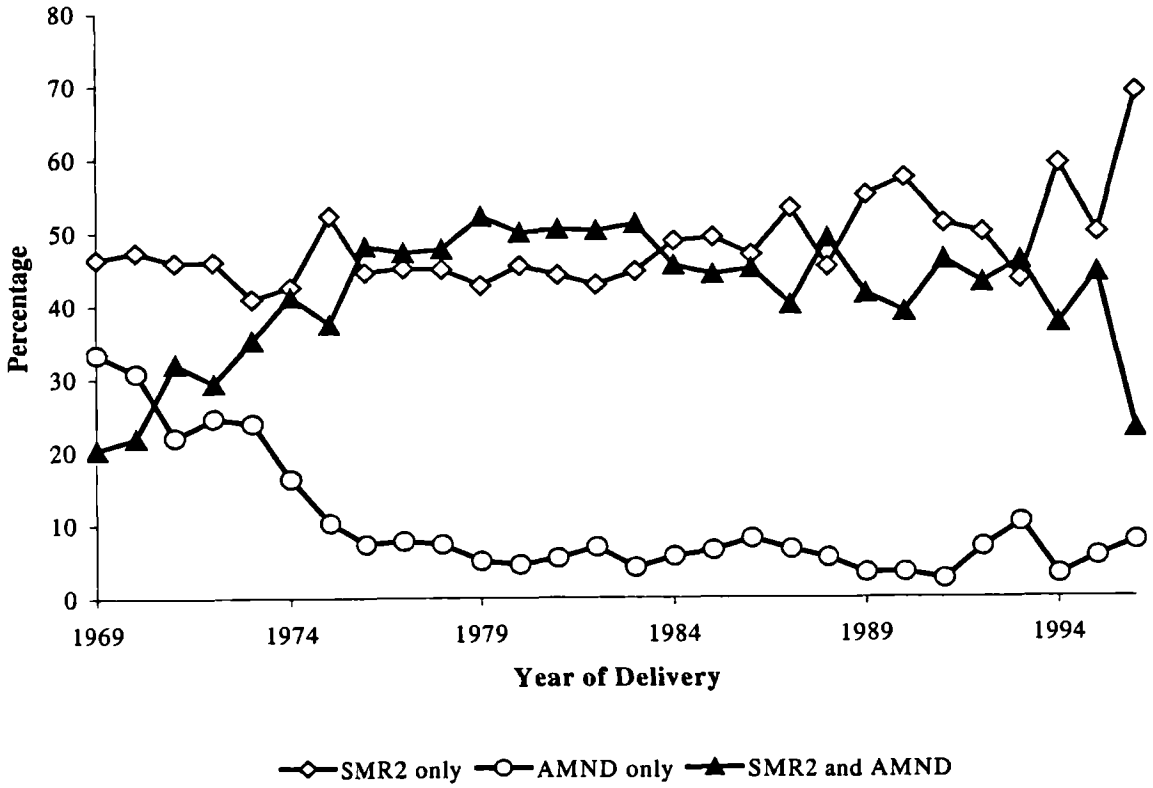


Figure 4.5 : **Summary of the derivation of the Amalgamated SMR2 and the Merged files and the steps in the data cleaning to create the second generation dataset**

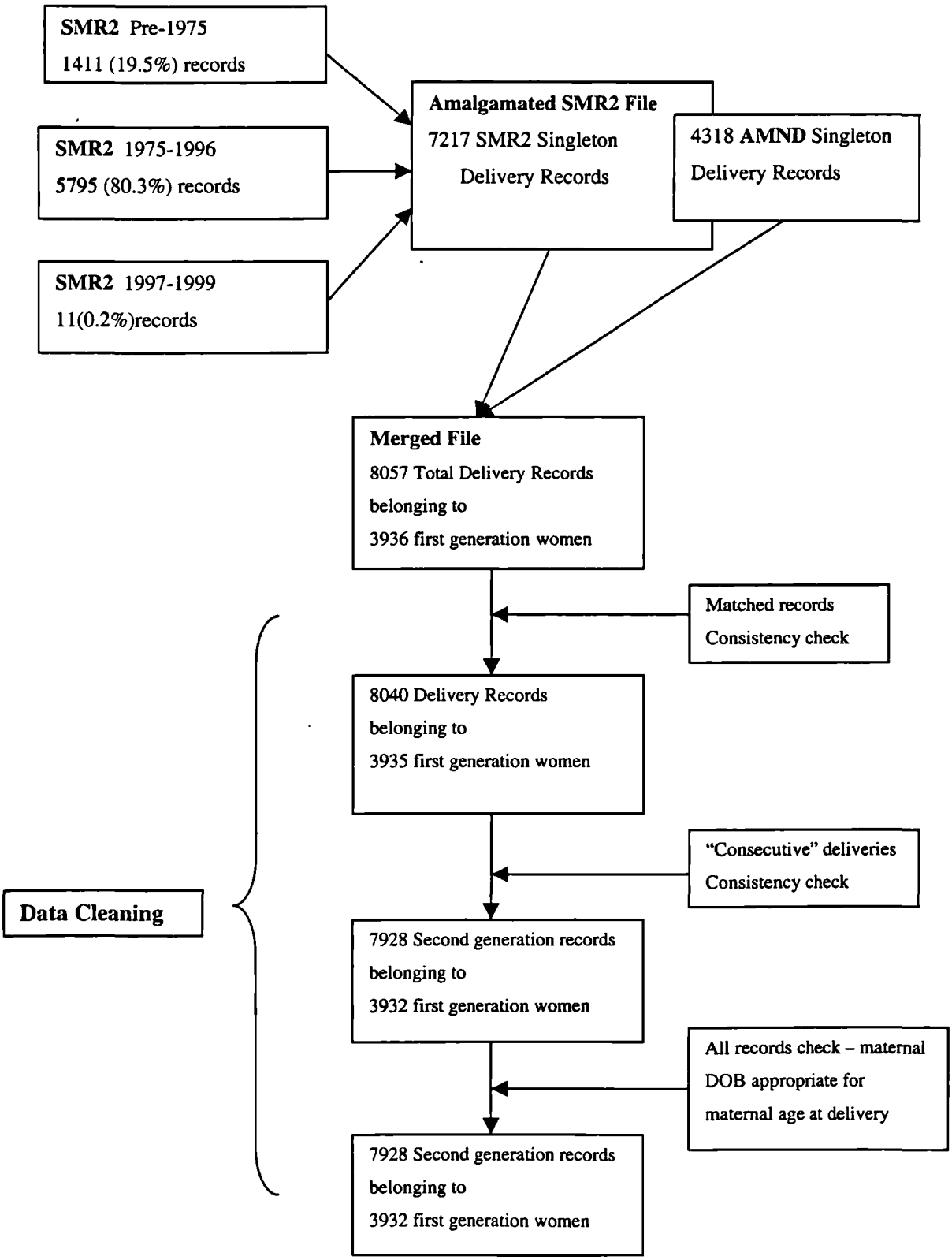


Table 4.2 : **Perinatal characteristics according to delivery period and data source for Aberdeen deliveries (n=7133)**

Perinatal characteristic	Delivery Period	Data Source			p-value**
		AMND only	SMR2 only	AMND and SMR2	
Birthweight (g)	**ALL**	3232 (566)	3269 (540)	3315 (550)	p<0.001
Mean (SD)	**Pre 1976**	3220 (552)	3224 (545)	3238 (556)	p=0.44
	1976-1999	3283 (572)	3333 (540)	3339 (547)	p=0.002
Maternal Age (Yr)	**ALL**	22.4 (4.9)	25.2 (5.2)	25.8 (4.9)	p<0.001
Mean (SD)	**Pre 1976**	19.2 (1.9)	20.3 (1.9)	20.2 (1.8)	p=0.45
	1976-1999	26.9 (4.2)	28.0 (4.5)	27.5 (4.2)	p=0.21
Maternal Parity*					
Frequency (%)	**All**				
0		457 (54.6)	1238 (44.3)	1500 (43.3)	
1		260 (31.1)	1067 (38.3)	1355 (39.1)	X^2=35.7 (4d.f.)
2+		120 (14.3)	487 (17.4)	608 (17.6)	p<0.001
Maternal Parity*					
Frequency (%)	**Pre 1976**				
0		359 (71.9)	626 (66.4)	549 (68.0)	
1		118 (23.7)	273 (29.0)	219 (27.1)	X^2=5.1(4d.f.)
2+		22 (4.4)	44 (4.6)	40 (4.9)	p=0.28
Maternal Parity*					
Frequency (%)	**1976-1999**				
0		98 (29.0)	612 (33.1)	951 (35.8)	
1		142 (42.0)	794 (42.9)	1136 (42.8)	X^2=14.4 (4d.f.)
2+		98 (29.0)	443 (24.0)	568 (21.4)	p=0.01

***Maternal parity** only available for n=7092 infants born in Aberdeen

**** *p-values*** from partial F-test for continuous variables and Chi-squared tests for categorical variables

Table 4.3: **Source of Data and Period of Delivery for Aberdeen deliveries (n=7133)**

Delivery Period	Data Source			TOTAL
	AMND only	SMR2 only	Both	
Before 1976	499 (59.6)	946 (33.4)	808 (23.3)	2253 (31.6)
1976-1999	338 (40.4)	1887 (66.6)	2655 (76.7)	4880 (68.4)
TOTAL	837 (100.0)	2833 (100.0)	3463 (100.0)	7133 (100.0)

isd | Information & Statistics Division
National Health Service in Scotland

Medical In Confidence
Maternity Record

Patient Identification

Hospital

Health Records System ID | Patient Identifier | Copprsh SMR Episode Record Key

Surname | Patient's Address

First Forename

Second Forename

Previous Surname

Date of Birth

Sex (Gender) 2

Marital Status

Postcode

Central Index (CI)/CHI Number | Ethnic Group

NHS Number | GP Practice Code

Alternative Case Ref. Number | GMCNo of Referring GP/GDP/Consultant

Episode Management

Spell/ Care Package ID | Location/ Hospital | Admission Date

Specialty/ Discipline | Admission Type 4 2

Significant Facility 1 1 | Admission Reason

Clinical Facility Start | Admission /Transfer From

Consultant/HCP Responsible for Care | Admission /Transfer From — Location

Management of Patient | GP Referral Letter Number

Patient Category

Provider | Purchaser | Contract Serial Number | Contract Service Number | Iso Resource Group | Invoice Number | Invoice Line

Contract Identifier

Contract Charge

Previous Pregnancies

Total Number | Spontaneous Abortions (Miscarriages) | Therapeutic Abortions

Caesarean Sections | Stillbirths | Neonatal deaths

Maternal Discharge Data

Ready for Discharge Date

Date of Discharge

Clinical Facility End

Condition on Discharge

Discharge Type

Discharge/Transfer To

Discharge/Transfer To - Location

Booking Smoking History

Smoker during Pregnancy

General Clinical - Maternal Condition

Main Condition/ Principal Diagnosis/ Problem Managed - ICD 10

Other Condition/ Comorbidity/ Complication - ICD 10 - 2

Other Condition/ Comorbidity/ Complication - ICD 10 - 3

Other Condition/ Comorbidity/ Complication - ICD 10 - 4

Other Condition/ Comorbidity/ Complication - ICD 10 - 5

Other Condition/ Comorbidity/ Complication - ICD 10 - 6

Operation/Procedure

Main Operation/Procedure | Date Main Operation

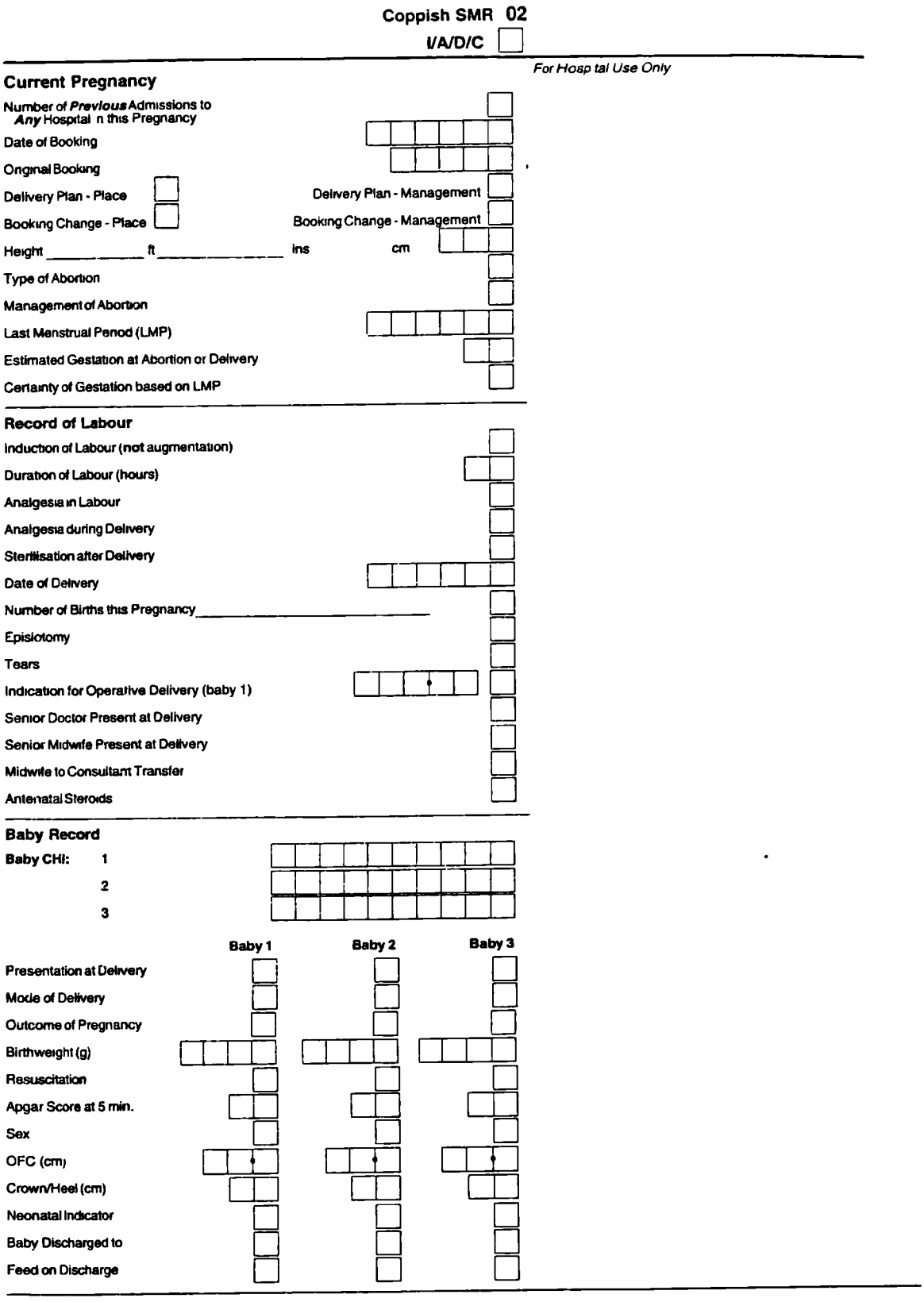
Clinician Responsible

Other Operation/Procedure (OPP2) | Date (OPP2)

Clinician Responsible (2)

1/96

Appendix 1: Facsimiles of SMR2 forms used for routine collection of maternity discharge data (1969-1999)


Coppish SMR 02

I/A/D/C

For Hosp tal Use Only

Current Pregnancy

Number of *Previous* Admissions to *Any* Hospital n this Pregnancy

Date of Booking

Original Booking

Delivery Plan - Place

Booking Change - Place

Delivery Plan - Management

Booking Change - Management

Height _____ ft _____ ins cm

Type of Abortion

Management of Abortion

Last Menstrual Period (LMP)

Estimated Gestation at Abortion or Delivery

Certainty of Gestation based on LMP

Record of Labour

Induction of Labour (not augmentation)

Duration of Labour (hours)

Analgesia in Labour

Analgesia during Delivery

Sterilisation after Delivery

Date of Delivery

Number of Births this Pregnancy _____

Episiotomy

Tears

Indication for Operative Delivery (baby 1)

Senior Doctor Present at Delivery

Senior Midwife Present at Delivery

Midwife to Consultant Transfer

Antenatal Steroids

Baby Record

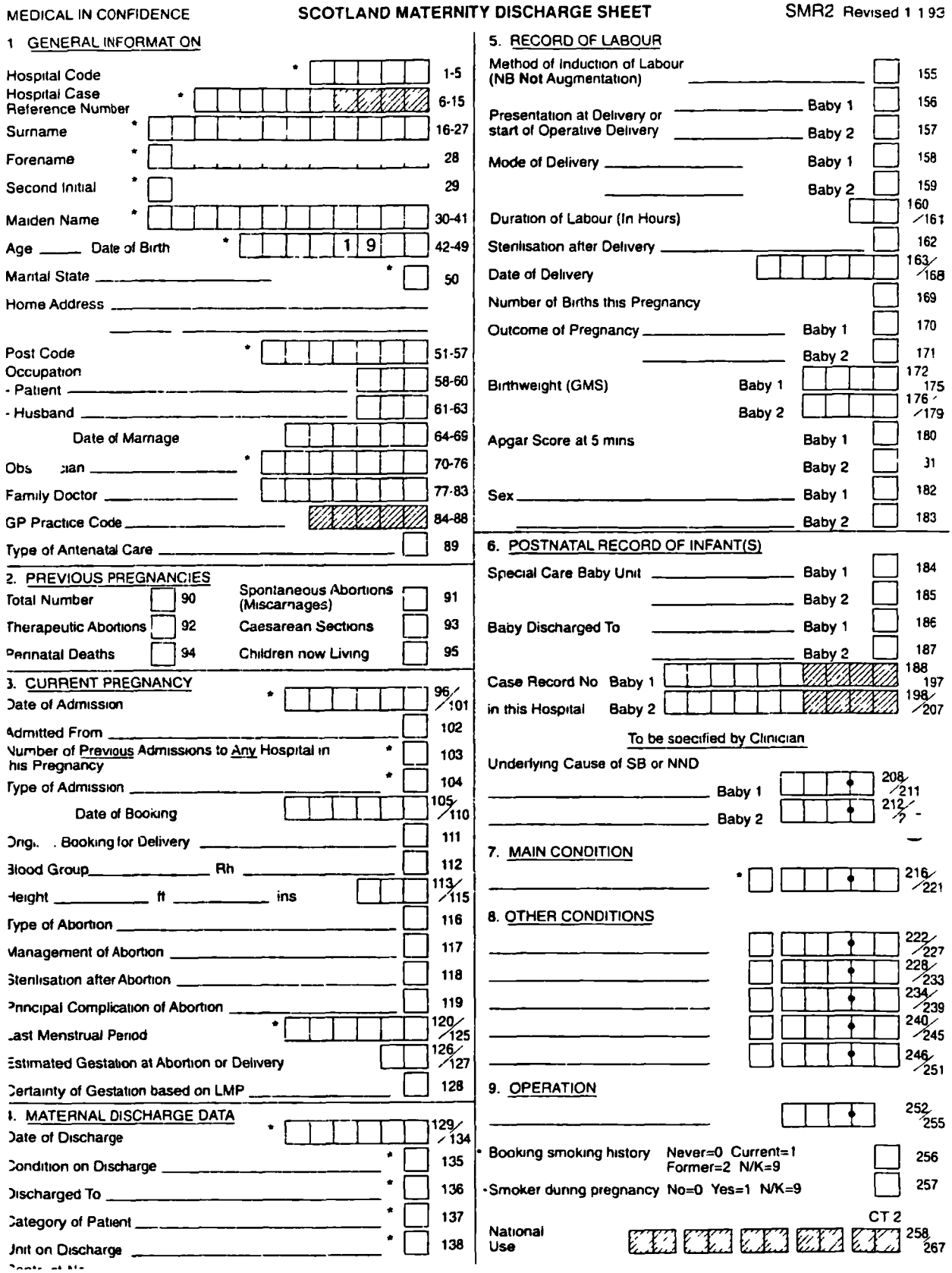
Baby CHI: 1

2

3

	Baby 1	Baby 2	Baby 3
Presentation at Delivery			
Mode of Delivery			
Outcome of Pregnancy			
Birthweight (g)			
Resuscitation			
Apgar Score at 5 min.			
Sex			
OFC (cm)			
Crown/Heel (cm)			
Neonatal Indicator			
Baby Discharged to			
Feed on Discharge			

Appendix 1: Facsimiles of SMR2 forms used for routine collection of maternity discharge data (1969-1999)


MEDICAL IN CONFIDENCE

SCOTLAND MATERNITY DISCHARGE SHEET

SMR2 Revised 1 1 93

1 GENERAL INFORMAT ON

Hospital Code * 1-5

Hospital Case Reference Number * 6-15

Surname * 16-27

Forename * 28

Second Initial * 29

Maiden Name * 30-41

Age ____ Date of Birth * 1 9 42-49

Marital State ____ * 50

Home Address ____

Post Code * 51-57

Occupation

- Patient ____ 58-60

- Husband ____ 61-63

Date of Marriage 64-69

Obs ician ____ * 70-76

Family Doctor ____ 77-83

GP Practice Code ____ 84-88

Type of Antenatal Care ____ 89

2. PREVIOUS PREGNANCIES

Total Number 90

Spontaneous Abortions (Miscarriages) 91

Therapeutic Abortions 92

Caesarean Sections 93

Perinatal Deaths 94

Children now Living 95

3. CURRENT PREGNANCY

Date of Admission * 96/101

Admitted From ____ 102

Number of Previous Admissions to Any Hospital in his Pregnancy * 103

Type of Admission ____ * 104

Date of Booking 105/110

Origin . Booking for Delivery ____ 111

Blood Group____ Rh ____ 112

Height ____ ft ____ ins 113/115

Type of Abortion ____ 116

Management of Abortion ____ 117

Sterilisation after Abortion ____ 118

Principal Complication of Abortion ____ 119

Last Menstrual Period * 120/125

Estimated Gestation at Abortion or Delivery 126/127

Certainty of Gestation based on LMP ____ 128

4. MATERNAL DISCHARGE DATA

Date of Discharge * 129/134

Condition on Discharge ____ * 135

Discharged To ____ * 136

Category of Patient ____ * 137

Unit on Discharge ____ * 138

5. RECORD OF LABOUR

Method of Induction of Labour (NB Not Augmentation) ____ 155

Presentation at Delivery or start of Operative Delivery ____ Baby 1 156

____ Baby 2 157

Mode of Delivery ____ Baby 1 158

____ Baby 2 159

Duration of Labour (In Hours) 160/161

Sterilisation after Delivery ____ 162

Date of Delivery 163/168

Number of Births this Pregnancy 169

Outcome of Pregnancy ____ Baby 1 170

____ Baby 2 171

Birthweight (GMS) Baby 1 172/175

Baby 2 176/179

Apgar Score at 5 mins Baby 1 180

Baby 2 31

Sex ____ Baby 1 182

____ Baby 2 183

6. POSTNATAL RECORD OF INFANT(S)

Special Care Baby Unit ____ Baby 1 184

____ Baby 2 185

Baby Discharged To ____ Baby 1 186

____ Baby 2 187

Case Record No Baby 1 188/197

in this Hospital Baby 2 198/207

To be specified by Clinician

Underlying Cause of SB or NND

____ Baby 1 208/211

____ Baby 2 212/?

7. MAIN CONDITION

____ * 216/221

8. OTHER CONDITIONS

____ 222/227

____ 228/233

____ 234/239

____ 240/245

____ 246/251

9. OPERATION

____ 252/255

* Booking smoking history Never=0 Current=1 Former=2 N/K=9 256

* Smoker during pregnancy No=0 Yes=1 N/K=9 257

CT 2

National Use 258/267

Appendix 1: Facsimiles of SMR2 forms used for routine collection of maternity discharge data (1969-1999)

KEY TO CODED ITEMS

Marital State [50]
1 = Never married (Single)
2 = Married
3 = Widowed
4 = Divorced
5 = Separated
8 = Other
9 = Not Known

Type of Antenatal Care [89]
0 = None
1 = GP/Midwife
2 = GP care with specialist consultation
3 = Hospital Only
4 = GP and Hospital Shared
5 = Midwife Only
6 = Other
9 = Not Known

Admitted from [102]
0 = Not admitted
1 = Home
2 = Other Hospital
3 = GP unit outwith this hospital
4 = Other specialty in this hospital

Type of Admission [104]
0 = Domiciliary (Not Admitted)
1 = Abortion (includes threatened abortion and ectopic pregnancy)
2 = Pregnant but not in labour
3 = In Labour
4= Born before arrival
5 = Admitted after delivery at home
6 = Admitted after delivery in any hospital
8 = Other (e.g. doubtfully pregnant)

nal Booking for Delivery [111]
.Not booked prior to this admission
1 = Booked for Home delivery
2 = This Hospital (Consultant Unit)
3 = This Hospital (GP Unit)
4 = Other Hospital (Consultant Unit)
5 = Other Hospital (GP Unit)
6 = Midwife Unit - This Hospital
7 = Midwife Unit - Other Hospital
9 = Not Known

Blood Group [112]
1 = O Rh -ve
2 = O Rh +ve
3 = A Rh -ve
4 = A Rh +ve
5 = B Rh -ve
6 = B Rh +ve
7 = AB Rh -ve
8 = AB Rh +ve
9 = Not Known

Type of Abortion [116]
0 = Threatened Abortion (still pregnant on discharge)
1 = Spontaneous or incomplete abortion
2 = Missed abortion
3 = Hydatidiform mole
4 = Therapeutic Abortion
5 = Suspected illegal abortion
6 = Failed therapeutic abortion
Ectopic Pregnancy
Unspecified abortion

Management of Abortion [117]
0 = Not operative (i e. management of threatened or spontaneous complete abortion)
1 = D + C
2 = Vacuum aspiration
3 = Hysterotomy
4 = Prostaglandin (all forms)
5 = Amniotic infusion (other than Prostaglandin)
8 = Other (including ectopic pregnancy)
9 = Not stated

Sterilisation after Abortion [118]
0 = None
1 = Laparoscopy
2 = Laparotomy
3 = Laparascopy Other hospital
4 = Laparatomy Other hospital
8 = Other
9 = Not stated

Principal Complication of Abortion [119]
0 = None
1 = Haemorrhage
2 = Sepsis
3 = Trauma to Cervix or uterus
4 = Damage to bowel
5 = Retained products requiring re-evacuation
8 = Other
9 = Not stated

Certainty of Gestation [128]
0 = Not applicable
1 = Certain
2 = Uncertain

Condition on Discharge [135]
0 = Domiciliary Delivery
1 = Still pregnant
2 = Aborted (all types of completed abortion)
3 = Delivered
4 = Post natal care only
5 = Pregnancy not confirmed
8 = Other (e.g. known missed abortion)

Discharged to [136]
0 = Domiciliary Delivery
1 = Home Care
2 = Other hospital - GP maternity unit
3 - Other hospital - specialist maternity unit
4 = Other hospital or institution
5 = Other unit in this hospital
6 = Died (PM)
7 = Died (No PM)
8 = Other

Category of Patient [137]
1 = Amenity
2 = Paying
3 = NHS
7 = Special arrangement (see manual)

Unit on Discharge [138]
1 = Obstetric (Consultant) In-Patient
2 = Obstetric (General Practitioner) In-Patient
3 = Home or Other confinement not admitted to hospital
4 = Day Case (Consultant or GP Hospital) (for definition see manual)
5 = Midwife Only Unit
6 = Midwife to Consultant transfer this episode in labour ward
7 = Midwife to Consultant transfer this episode in post-natal ward
9 = Other or Not Known

Method of Induction of Labour [155]
0 = None
1 = ARM
2 = Oxytocics
3 = ARM + Oxytocics
4 = Prostaglandins (includes Cervical Priming)
5 = ARM + Prostaglandins
6 = Prostaglandins + Oxytocics
7 = Prostaglandins + ARM + Oxytocics
8 = Other
9 = Not Known

Presentation at Delivery or start of Operative Delivery (Baby 1 and Baby 2) [156], [157]
1 = Occipito - anterior
2 = Occipito - posterior
3 = Occipito - lateral
4 = Breech
5 = Face/brow
6 = Shoulder
7 = Cord
8 = Other
9 = Not Known

Mode of Delivery (Baby 1 and Baby 2) [158], [159]
0 = Normal, spontaneous vertex, vaginal delivery, occipito - anterior.
1 = Cephalic vaginal delivery with abnormal presentation of head at delivery, without instruments, with or without manipulation.
2 = Forceps, low application, without manipulation, forceps delivery NOS
3 = Other forceps delivery. Forceps with manipulation. High forceps. Mid forceps
4 = Vacuum extraction ventouse.
5 = Breech delivery, spontaneous assisted or unspecified partial breech extraction
6 = Breech extraction. Breech extraction: NOS or Total or Version with breech extraction
7 = Elective (planned) Caesarean Section
8 = Emergency, other and unspecified Caesarean Section
9 = Other and unspecified method of delivery.

Sterilisation after Delivery [162]
0 = None
1 = Laparoscopy
2 = Laparotomy
3 = Laparoscopy other hospital
4 = Laparotomy other hospital
8 = Other
9 = Method Not Stated

Outcome of Pregnancy (Baby 1 and Baby 2) [170], [171]
1 = Live birth
2 = Still birth
3 = Live birth died < 7 days
4 = Live birth died 7-28 days
5 = Live birth died after 28 days
8 = Dead born infant (one of multiple) at less than 24 weeks

Sex (Baby 1 and Baby 2) [182], [183]
1 = Male
2 = Female
8 = Other or Not Known

Special Care Baby Unit (Baby 1 and Baby 2) [184], [185]
0 = Not Admitted
1 = Admitted for up to 48 hours
2 = Admitted for more than 48 hours
9 = Not known

Baby Discharged to (Baby 1 and Baby 2) [186], [187]
1 = Home
2= Remaining in Special Care Baby Unit
3 = Special Care Baby Unit but home with mother
4 = Transfer to Other Hospital

Appendix 1: Facsimiles of SMR2 forms used for routine collection of maternity discharge data (1969-1999)

SCOTTISH HOSPITAL IN-PATIENT RECORDS

Maternity Discharge Record SMRM (Part I)

Notes for completion of sheet

General 1 This form should be completed for every maternity patient discharged or transferred and the top copy sent to the Scottish Home & Health Department, Statistics Branch, 113/115 George Street, Edinburgh EH2 4YT The bottom copy should be kept for inclusion in the case record as a patient identification and summary sheet or for other hospital use, and the second copy may be sent to General Practitioners.

Items in italic are included for the convenience of hospitals and need not be completed where the bottom sheet is not to be retained.

2. Use legible block capitals throughout. A ball-point pen should be used.
3. In those instances where the key to the code used is not given on the front of the form you may specify in the space provided in addition to coding.
4. Complete dates are required where applicable: the year must be given but leave blanks for day and month if not known.
5. Code numbers must be given in addition to specifications.

Hospital Case Reference Number: If this number is less than six digits the remaining boxes should be completed by inserting preceding zeros, e.g. 001234. Alphabetical characters must not be used

Current Surname/Maiden Surname: Start with left-hand box.
Names containing more than twelve letters should be entered as follows: | D | U | R | H | A | M | - | R | O | B | E | R | T S O N |
An apostrophe or a hyphen occurring in a name should be allocated a separate box. Where current surname and maiden surname are the same, both should be entered.

Names: Insert the first two initials in the appropriate box. If one initial only, enter in right-hand box, leaving the other blank.

Family Doctor: Specify in space provided and enter the number allocated by the Scottish Home and Health Department.

Previous Pregnancies: Enter the number from 0-9 (9=9 or more) in appropriate boxes. If zero is entered in box 68, boxes 69-80 should be left blank.

Obstetrician: Record the name of the consultant obstetrician or general practitioner in clinical charge of the patient in hospital. Where the department is sub-divided into more than one unit, the unit number allotted by the hospital should be entered in box 11.

Original Booking: Specify and code as follows:—
1 = Not booked prior to this admission
2 = Booked for home delivery
3 = This hospital (Consultant Unit)
4 = This hospital (G.P. Unit)
5 = Other hospital (Consultant Unit)
6 = Other hospital (G.P. Unit)
9 = Other or not known

Blood Group: Specify and code as follows:—
= O Rh.—ve
_ = O Rh.+ve
3 = A Rh.—ve
4 = A Rh.+ve
5 = B Rh.—ve
6 = B Rh.+ve
7 = AB Rh.—ve
8 = AB Rh.+ve
9 = Not known

Type of Admission: Specify and code as follows:—
‡0 = Not Admitted to Hospital
1 = From home*—admitted in labour and delivered
2 = From home*—admitted NOT in labour and delivered
3 = From home*—admitted NOT in labour and NOT delivered
4 = From home*—admitted after delivery
5 = From home*—admitted in labour and transferred to other hospital
6 = Transferred from other hospital—admitted in labour and delivered
7 = Transferred from other hospital—admitted NOT in labour and delivered
8 = Transferred from other hospital—admitted NOT in labour and NOT delivered
9 = Transferred from other hospital—admitted after delivery

Discharged to: Specify and code as follows.—
1 = Home
2 = Convalescent Hospital
3 = Other hospital
4 = Transfer to other speciality in this hospital
5 = Died (P.M.)
6 = Died (no P.M.)
9 = Other or not known

Unit on Discharge: Specify and code as follows:—
1 = Obstetric (Consultant)
2 = Obstetric (General Practitioner)
‡3 = Home or other confinement not admitted to hospital
9 = Other or not known

Operation not connected with delivery: Specify and code as follows:—
0 = None
1 = Artificial Termination with Sterilisation
2 = Artificial Termination without Sterilisation
3 = Post Partum Sterilisation
4 = Sterilisation at Caesarean Section
5 = Hysterectomy
6 = Removal of Ovarian Cyst or other Abdominal Operation
7 = Shirodkar
8 = Cone Biopsy
9 = Other

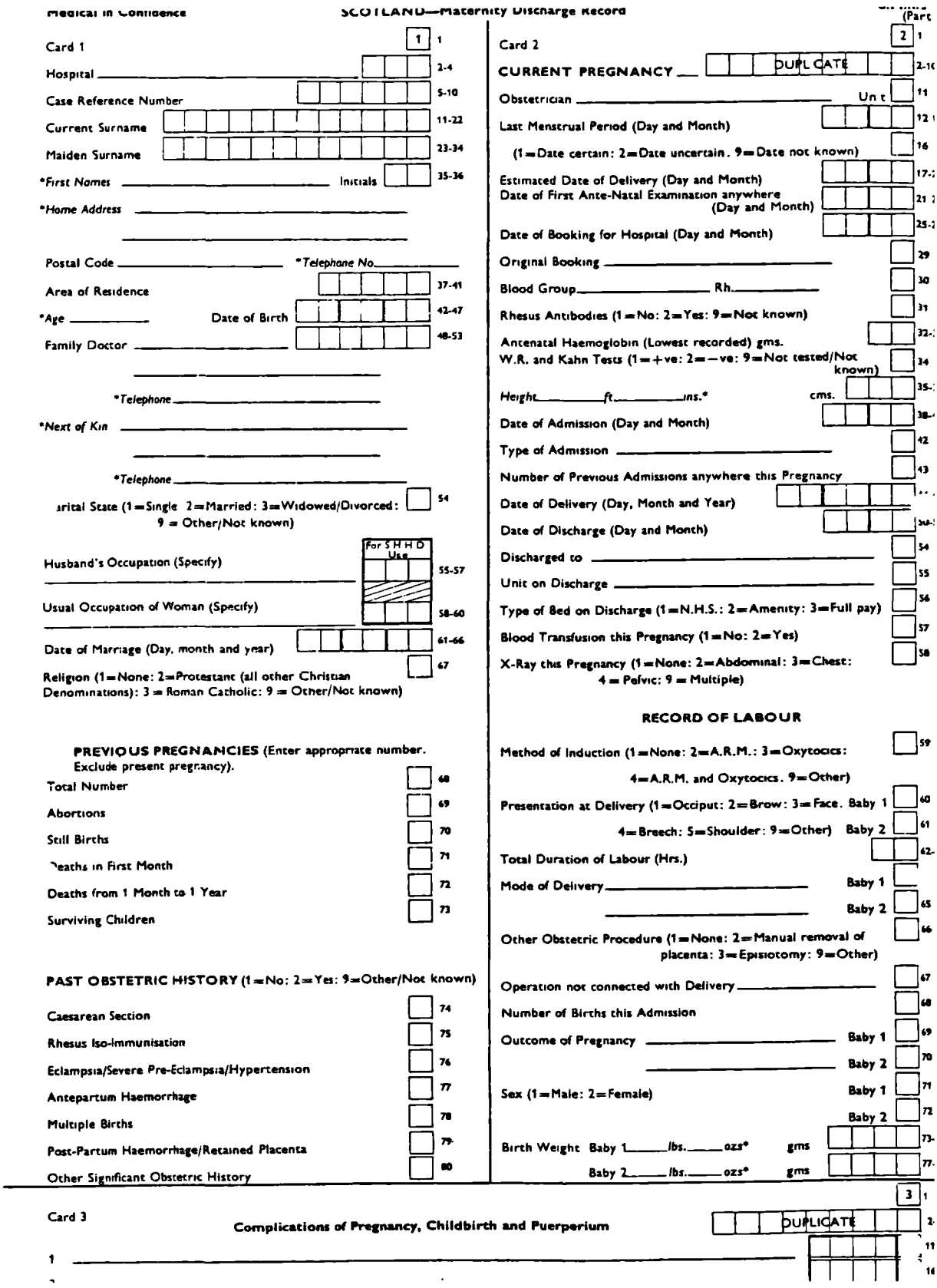
Mode of Delivery: Specify and code as follows:—
0 = Spontaneous
1 = Manipulation without instruments
2 = Forceps, mid and high
3 = Forceps, low
4 = Forceps, unspecified
5 = Vacuum extractor
6 = Caesarean section
8 = Other surgical or instrumental
9 = Unspecified type of delivery

If more than one baby enter particulars of first two babies born.

Outcome of Pregnancy: Specify and code as follows:—
0 = *Stillbirth*
1 = Baby discharged alive to care of parent
2 = Baby transferred from maternity nursery to care elsewhere in same hospital.
3 = Baby transferred from maternity nursery to care in other hospital
4 = Baby discharged to other non-hospital care
5 = Baby died before discharge or transfer within 24 hrs. of birth
6 = Baby died before discharge or transfer within 1–6 days of birth
7 = Baby died before discharge or transfer in 7 days and over after birth
8 = Baby temporarily detained in hospital

Complications of Pregnancy, Childbirth and Puerperium:
Specify and code according to the 8th revision of the International Classification of Diseases. Enter principal complication first.

Appendix 1: Facsimiles of SMR2 forms used for routine collection of maternity discharge data (1969-1999)



Medical in Confidence

SCOTLAND—Maternity Discharge Record

(Part

Card 1 [1] 1

Hospital 2-4

Case Reference Number 5-10

Current Surname 11-22

Maiden Surname 23-34

*First Names Initials 35-36

*Home Address

Postal Code *Telephone No.

Area of Residence 37-41

*Age Date of Birth 42-47

Family Doctor 48-53

*Telephone

*Next of Kin

*Telephone

arital State (1=Single 2=Married: 3=Widowed/Divorced: 9 = Other/Not known) 54

For S H H D Use

Husband's Occupation (Specify) 55-57

Usual Occupation of Woman (Specify) 58-60

Date of Marriage (Day, month and year) 61-66

Religion (1=None: 2=Protestant (all other Christian Denominations): 3 = Roman Catholic: 9 = Other/Not known) 67

PREVIOUS PREGNANCIES (Enter appropriate number. Exclude present pregnancy).

Total Number 68

Abortions 69

Still Births 70

Deaths in First Month 71

Deaths from 1 Month to 1 Year 72

Surviving Children 73

PAST OBSTETRIC HISTORY (1=No: 2=Yes: 9=Other/Not known)

Caesarean Section 74

Rhesus Iso-Immunisation 75

Eclampsia/Severe Pre-Eclampsia/Hypertension 76

Antepartum Haemorrhage 77

Multiple Births 78

Post-Partum Haemorrhage/Retained Placenta 79

Other Significant Obstetric History 80

Card 2 [2] 1

CURRENT PREGNANCY DUPLICATE 2-10

Obstetrician Unit 11

Last Menstrual Period (Day and Month) 12

(1=Date certain: 2=Date uncertain. 9=Date not known) 16

Estimated Date of Delivery (Day and Month) 17-20

Date of First Ante-Natal Examination anywhere (Day and Month) 21-24

Date of Booking for Hospital (Day and Month) 25-28

Original Booking 29

Blood Group Rh. 30

Rhesus Antibodies (1=No: 2=Yes: 9=Not known) 31

Antenatal Haemoglobin (Lowest recorded) gms. 32-33

W.R. and Kahn Tests (1=+ve: 2=−ve: 9=Not tested/Not known) 34

Height ft. ins. cms. 35-37

Date of Admission (Day and Month) 38-41

Type of Admission 42

Number of Previous Admissions anywhere this Pregnancy 43

Date of Delivery (Day, Month and Year)

Date of Discharge (Day and Month)

Discharged to 54

Unit on Discharge 55

Type of Bed on Discharge (1=N.H.S.: 2=Amenity: 3=Full pay) 56

Blood Transfusion this Pregnancy (1=No: 2=Yes) 57

X-Ray this Pregnancy (1=None: 2=Abdominal: 3=Chest: 4 = Pelvic: 9 = Multiple) 58

RECORD OF LABOUR

Method of Induction (1=None: 2=A.R.M.: 3=Oxytocics: 4=A.R.M. and Oxytocics. 9=Other) 59

Presentation at Delivery (1=Occiput: 2=Brow: 3=Face. 4=Breech: 5=Shoulder: 9=Other) Baby 1 60 Baby 2 61

Total Duration of Labour (Hrs.) 62-64

Mode of Delivery Baby 1 65 Baby 2

Other Obstetric Procedure (1=None: 2=Manual removal of placenta: 3=Episiotomy: 9=Other) 66

Operation not connected with Delivery 67

Number of Births this Admission 68

Outcome of Pregnancy Baby 1 69 Baby 2 70

Sex (1=Male: 2=Female) Baby 1 71 Baby 2 72

Birth Weight Baby 1 lbs. ozs* gms 73-76

Baby 2 lbs. ozs* gms 77-80

Card 3 [3] 1

Complications of Pregnancy, Childbirth and Puerperium DUPLICATE 2-10

1 11-16

Appendix 1: Facsimiles of SMR2 forms used for routine collection of maternity discharge data (1969-1999)

Chapter 5:
Definitions and Statistical Methods

This chapter is concerned with the definition of the intergenerational data sets and the methods to be used in the descriptive, intergenerational and lifecourse analyses.

5.1 Definitions

This study is complex in its use of data on several generations, therefore the following nomenclature is used for clarity. There are three generations with data available. These three **generations** are referred to throughout the analyses and discussion as:

- **G0 (Grandparental) Generation:** refers to the parents of the first generation for whom we have information on biological and social status in adulthood from the original Child Development Study including the mother's obstetric records relating to the birth of the first generation infant.
- **G1 (First) Generation:** refers to the original Child Development Study members born between 1950 and 1955 in Aberdeen, Scotland, and attending Primary School in Aberdeen in 1962. This study was described in Chapter 3. Adult characteristics for the females of this generation were obtained if linkage was made to their offspring's obstetric records.
- **G2 (Offspring) Generation:** refers to the second generation infants identified via linkage of the first generation women to their delivery records. Perinatal data for these infants was abstracted either from the Aberdeen Maternity and Neonatal Databank (AMND) or the Scottish Maternity Records (SMR2) or both. The data sources and linkage process used to obtain this data was described in Chapter 4.

5.2 Defining the intergenerational dataset

Chapters 3 and 4 separately outlined the origins of the first (G1) and second (G2) generations, albeit with the second being dependent for its existence on the reproductive status of the first. Chapter 3 described the 5210 core first generation women (G1) who formed the group of potential mothers of the second generation (G2). These females were a subset of the 5873 females in the original Child Development Study who were born in Aberdeen between 1950 and 1955 and for whom complete information on size at birth was available. For 5634 of the 5873 first generation females, the General Registrars Office (GRO) in Scotland provided an updated vital status in 2001, which was used to facilitate the linkage of these women to their obstetric records in the SMR2

record systems. This process of determining the second generation was described in Chapter 4. These processes of defining the core first generation and undertaking the second generation linkage were carried out independently. The reconciliation of the two is summarised in Figure 5.1. The following steps were then followed to define the intergenerational datasets.

1. The first generation (G1) was restricted to 4997 females who were both core first generation females (with complete perinatal information) and successfully traced by GRO in 2001. Of these 4997 females 3485 were linked to valid second generation (G2) delivery records, either in the AMND, SMR2 systems or in both. The 7080 singleton viable offspring delivered to these 3485 first generation females formed the basis for the second generation. The remaining 1512 of the 4997 G1 females were not identified as having reproduced within Scotland. In Chapter 6 the characteristics of the 3485 first generation women who were linked to second generation deliveries are compared to the 1512 who were not linked.
2. In Chapter 7 the 7080 second generation infants who were the offspring of the 3485 G1 women are described in terms of their own size at birth. These analyses are initially restricted to the 7014 liveborn singleton G2 infants with complete birthweight information and finally to the 6954 G2 infants with complete information on duration of gestational in addition to birthweight.
3. In Chapter 8 and in the intergenerational analyses in Chapters 9 and 10 the dataset is restricted to intergenerational pairs of mothers and liveborn infants for whom we have complete perinatal and parental data* on both generations. This restricts the ***intergenerational dataset*** to 3231 first generation singleton mothers (G1) and their 6539 liveborn singleton offspring (G2).
4. The ***intergenerational and lifecourse dataset*** used in Chapters 11 and 12 is restricted to the 3090 G1 mothers and their 6369 G2 offspring with complete maternal childhood growth information in addition to complete perinatal and parental data.

The derivation of these intergenerational datasets is outlined in *Figure 5.2.* Importantly there is no evidence of any significant statistical difference between the excluded and included G1 mothers and G2 infants in terms of measures of size at birth, which are the outcomes of interest for the thesis (*Tables 5.1 and 5.2*).

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* The variables required to be complete are birthweight and gestational age for mother and infant, together with maternal height, age at delivery and parity and paternal socioeconomic status at the time of delivery.

5.3 Statistical methodology

The statistical methods used for the descriptive, comparative, intergenerational and lifecourse analyses are presented here according to the specific objectives described in Chapter 2. All statistical analyses were carried out using STATA version 6.0. The outcome of interest throughout these analyses is offspring size at birth. This is measured by three variables: absolute birthweight, gestational age at delivery and fetal growth (birthweight adjusted for gestational age SD score) as outlined in Chapter 2. In Chapters 6 to 9 all three outcome variables are considered but in Chapters 10 to 12 the emphasis is largely on fetal growth (SD score) alone, as this measure incorporates aspects of both absolute size and maturity.

A. Description of study population

i. To check that the G1 and G2 generations are representative of their contemporary Aberdeen and Scottish populations respectively in terms of measures of size at birth.

This was undertaken in **Chapter 3** for G1. Graphical comparisons were made between the distribution of mean and standard deviation of G1 birthweight for each week of gestational age and the distribution of mean and standard deviation of birthweight for each week of gestational age of all the female, singleton live births registered in Aberdeen between 1950 and 1955. This latter data was abstracted from the AMND record system. G1 females were born in Aberdeen over the same time period but had additionally remained in Aberdeen until at least 1962 and had entered primary school.

The G2 births occurred between 1967 and 1999. In **Chapter 7** the distribution of G2 mean and standard deviation of birthweight for each week of gestational age is compared to the mean and standard deviation of birthweight for each week of gestational age for all singleton female live births in Scotland born over approximately the same time period between 1975 and 1990. This data was available from ISD and was the most complete comparison data available. Less than 23% of all G2 births occurred before this time period, and importantly only 2% occurred after 1990 when neonatal care was undergoing rapid change, which may have altered survival particularly at lower gestational ages. The comparison of measures of size at birth in Chapter 7 is largely graphical, as it is for the G1 births.

ii. To establish that both generations size at birth measures (G1 and G2) are patterned in ways that are consistent with perinatal trends described in the relevant epidemiological literature.

Size at birth is assessed using the three measures previously defined in Chapter 2, namely absolute birthweight, gestational age at delivery and fetal growth (SD score). In **Chapter 8** mean and standard deviation of size at birth measures are tabulated for parental categorical variables and linear regression is used to assess the linear trend in these crude associations with parental variables within each generation. The maternal variables considered are maternal height, maternal age at delivery, parity and pregnancy specific hypertension in both G0 and G1 females and smoking status for G1 adults. Paternal social class is used as a measure of social status, being the most complete social indicator available. It is defined according to the Registrar General occupational classification relevant to the time of offspring delivery, with grades of I, II, IIINM, IIIM, IV, V and "other" for both generations. Maternal pre-marital occupation and completed education are available for a subset of the G0 and G1 mothers. Linear regression is used to quantify the effects of and examine the joint effects of the parental variables on offspring size at birth within each generation. The linearity of the relationships between maternal explanatory variables and mean size at birth and possible statistical interactions between plausible explanatory variables are assessed using likelihood ratio tests (Clayton and Hills, 1993).

B. Data quality assessment

i. To describe and evaluate the methods used in the linkage of the first generation females to their second generation deliveries.

The methods used to link the first generation females to their second generation deliveries were described in detail in **Chapter 4**. The strategies used to amalgamate the data obtained from both AMND and SMR2 record systems were outlined and the procedures used to clean the intergenerational data were described. A systematic approach was taken that utilised the repeated perinatal information obtained from records in both AMND and SMR2 for approximately 40% of the deliveries. All information was anonymised but range checks were carried out on each perinatal and parental measure and consistency checks were performed for maternal and infant variables using matched records and consecutive deliveries to the same first generation mother. Where there were neither matches from two record sources nor sibling records, checks were based on the consistency of delivery dates and maternal dates of birth and

recorded age. The linkage score obtained for each SMR2 record was used as an additional determinant of appropriate linkage in equivocal cases.

ii. **To evaluate the completeness of the linkage of the first generation females to their second generation deliveries and to determine if there is any selection bias in the first generation females who were linked to second generation deliveries.**

This is evaluated in **Chapter 6** by comparing the rate of linkage for the G1 females with the age-specific fertility rates for Scotland for all women born between 1950 and 1955. Linkage is used as a proxy for reproduction, defined as the successful delivery of at least one singleton, liveborn infant. Possible reasons for the underestimation of the rate of reproduction by the rate of linkage are discussed. Mean G0 parental characteristics and G1 size at birth and size and educational childhood measures are tabulated separately according to adult trace status (2001 GRO vital trace of G1 adult females) and linkage status and also for linkage after stratifying the data according to trace status. Tests for heterogeneity are used to assess whether significant differences exist between mean values of continuous variables and Chi-squared tests (Altman, 1991) are used to assess differences in the frequency distribution of categorical variables in each of these tabulations.

Logistic regression is used to estimate the odds of a G1 female having been linked to G2 deliveries according to her G0 parental characteristics and her own birth and childhood size. Crude odds ratios and odds ratios adjusted for G1 adult trace status are estimated for each categorical explanatory variable, after assessing the evidence for effect modification between the explanatory variables and adult trace status. Crude and adjusted odds ratios are presented to firstly assess the extent of any bias due to trace status and secondly to estimate the odds of reproduction, rather than just linkage.

Two methods are used to evaluate whether the results are biased due to non-random migration of G1 females out of Scotland before reproductive age. The first method limits the analyses to the subgroup of women who were traced to Scotland in 2001, implicitly assuming that they had spent all their childhood and reproductive lives there. Comparing the results restricted to this subgroup of women to those obtained in the logistic regression adjusted for status, using all women, indicates whether bias is present. The second method uses sensitivity analyses to reclassify varying proportions of the unlinked women who had moved out of Scotland prior to 2001 to the linked group. Comparisons of the odds ratios estimated under different reclassifications allows a further assessment of whether bias is present and if so what the consequences of this bias might be. Further details are given in Section 6.6.2.

C. Cross-sectional and intergenerational comparisons

Before considering the intergenerational associations in size at birth measures and its determinants across generations a cross-sectional comparison of size at birth measures for the two generations (G1 and G2) is undertaken. This is to compare the absolute distributions of size at birth measures over two generations and over two time periods when obstetric and neonatal practise was undergoing rapid change, before considering the intergenerational associations.

i. To compare the distribution of size at birth measures in first and second generation infants in a cross-sectional manner to consider any changes over time, particularly in the light of changing obstetric and neonatal practises.

In **Chapter 7** the distributions of G1 absolute birthweight, gestational age at delivery and fetal growth (SD score) are compared in a cross-sectional manner, to determine any change in the distributions over time and over generations. This is largely descriptive and consists of comparisons of measures of central tendency and range followed by comparisons of the proportions of infants classified into the usual "clinically at risk" categories of absolute birthweight, gestational age and birthweight for gestational age. In addition the distributions are superimposed graphically using absolute frequency, rather than percent frequency, to facilitate the comparisons. For this cross-sectional comparison the first generation is not simply restricted to the group of G1 females who were linked to viable deliveries, but also includes males and all females who were part of the original Child Development Study. This allows the comparison of male and female measures of size at birth for the two generations. In particular the G1 and G2 distributions of gestational age are compared in the light of changes in obstetric and perinatal medicine and practise over the last 50 years. Fetal growth scores cannot be meaningfully directly compared because they are standardised according to different reference populations (Chapter 2), however mean birthweight in grams for each week of gestational age is directly comparable across generations and is compared graphically.

ii. To describe the intergenerational continuities in size at birth measures for first and second generation infants and in particular to examine the continuity in the intergenerational risks of adverse birth outcome (LBW, pre-term delivery and SGA).

In **Chapter 9** the intergenerational continuities in absolute birthweight, gestational age at delivery and fetal growth (birthweight for gestational age) are examined firstly by cross-tabulations of the distribution of G2 measures according to categories of the

corresponding G1 measures, with Chi-squared tests used to assess heterogeneity. The mean G2 size at birth measures are estimated according to categories of G1 size at birth measures and the complete distributions of G2 offspring size at birth measures for each category of corresponding G1 maternal size measure are compared by graphical means, using frequency percentages. This allows a consideration of both the differences in the mean values and the shape and range of all G2 values according to the distribution of G1 values. Linear regression is used to quantify the crude intergenerational associations in size at birth measures and to adjust the estimates for all other available G1 parental adult influences.

Clinically infants are at increased risk of perinatal death and later adverse sequelae if they meet the criteria for low birth weight, preterm or small for gestational age classifications. Therefore in Chapter 9 logistic regression is used to estimate the risks of adverse birth outcome in the G2 infants if the G1 mother was similarly classified at birth. The crude odds ratios and those adjusted for other known G1 parental determinants of reduced fetal size or maturity are estimated. The intergenerational mother-offspring pairs are not only one-to-one but may be one-to-many, as G1 mothers may be linked to more than one G2 delivery. Hence robust standard errors are used (with G1 mothers unique identifier as the cluster variable) to compensate for this (Huber, 1967).

Because the intergenerational dataset has attempted to capture all G2 deliveries for each G1 woman it is possible to estimate the risk of repeating adverse birth outcomes in consecutive pregnancies to the same mother, if she had a previous adverse outcome. Logistic regression is used to obtain crude and adjusted estimates after controlling for other G1 maternal factors known to influence adverse birth outcomes using robust standard errors to control for any repeated maternal information.

iii. **To further describe intergenerational continuities in the adult determinants of size at birth measures and to consider if the continuities in size at birth may be partly explained by the intergenerational continuity in parental biological and social characteristics.**

In **Chapter 10** intergenerational continuities in the adult determinants of offspring size at birth are considered. Continuities in maternal adult height, age at first pregnancy, total family size, hypertension in pregnancy and paternal social class are considered for all intergenerational pairs using cross–tabulations of the distribution of categorical variables and Chi-squared tests to assess heterogeneity. Linear regression is used to estimate the mean influence of G0 maternal adult height and parental age at first

pregnancy on the corresponding G1 adult characteristic. Both G0 maternal and paternal age are available for each G1 mother so the influence of each, separately and jointly, are evaluated. Parity and gravidity are available in both AMND and SMR2 record systems and these variables are used to compare family size across generations for the subset of G0 mothers in whom this information is most complete.

Gestational hypertension is the most common pregnancy-specific maternal complication, affecting at least 10% of all pregnancies in Scotland (Wilson et al., 2000). It is examined in Chapter 10 in an intergenerational context to assess the extent of continuity in the condition and to determine if that continuity acts via influences on fetal growth. Incidence rates of gestational hypertension are compared for the two generations and logistic regression is used to estimate the crude odds of a G1 pregnancy (carrying a G2 infant) being affected by hypertension if her own G0 pregnancy had been similarly affected. Logistic regression is also used to adjust the odds for maternal fetal development to consider how far her own fetal growth mediates the association.

Continuity in paternal social class is examined using frequency cross-tabulations of occupational social class and heterogeneity is assessed by the Chi-squared test. G0 paternal social class is also broadly grouped as either non-manual or manual and the odds of a G1 partner being in the same broad group as the father of the G1 female are examined using logistic regression.

Restricting the outcome to fetal growth, multivariate regression is used in the same chapter to assess the importance of intergenerational continuity in within generation adult determinants of size at birth for explaining intergenerational continuities in fetal growth. Likelihood ratio tests are used to assess the linearity of explanatory variables and to assess evidence of statistical interaction between related measures. G0 and G1 adult parental determinants of size at birth are then added to the multivariate model to assess their influence on the outcome of G2 fetal growth conditional on G1 fetal growth. Robust standard errors are used throughout to take account of the repeated G1 parental information. Multiple statistical testing is carried out in this process therefore p-values are interpreted with caution.

Finally change in socioeconomic status between G1 childhood and adult reproductive life is considered in terms of its effect on G1 adult determinants of G2 offspring size at birth and on G2 fetal growth itself. The distribution of G2 size at birth according to four maternal categories of social class stability or change between childhood and adulthood (temporally ordered) are compared graphically using percentage frequencies.

D. Adding the temporal dimension

i. To consider how far G2 size at birth might be influenced by the development of the G1 mother over her life course, using the example of differential maternal growth.

This is addressed in **Chapter 11** by considering firstly the biological and social patterning of G1 childhood size. Measurements of childhood height and weight are available for most G1 females at school entry, when they were usually aged between 4 and 6 years of age. The means of these G1 childhood weights, heights, Body Mass Indices (BMI), and standardised weight and height adjusted for age scores are initially tabulated for categorical G0 adult parental characteristics. Linear regression is used to examine the associations and likelihood ratio tests are used either for evidence of linear trend or heterogeneity, if there was no evidence of a graded effect in mean size for each of the childhood size outcomes. Restricting the outcome to standardised weight and height adjusted for age measures linear regression is used to determine the crude and mutually adjusted estimates of effect of each G0 maternal characteristic, treated as continuous variables, and paternal social class and pregnancy-specific hypertension treated as categorical variables.

In a second stage cross-tabulations and Chi-squared tests for heterogeneity are used to consider the frequency distribution of G1 childhood size at school entry (using weight for age) according to quintile of G1 fetal growth (birthweight for gestational age).

To add a lifecourse perspective to these measures the focus of interest is shifted from absolute size to postnatal change in size, between birth and school entry. The two size measures used to determine change are birthweight adjusted for gestational age and weight at 4 to 6 years adjusted for age at measurement. A graphical approach is initially used to illustrate the average trajectory of change in G1 size between birth and school entry according to each category of G0 parental social and biological characteristic. The slope of each trajectory is considered as a proxy indication of either "catch-up" (positive slope) or "catch-down" (negative slope) over time relative to the mean change in size for all G1 infants. A measure of postnatal change in childhood size, called "childhood growth", is calculated which is independent of fetal growth and is used as the outcome for the regression analyses that follow (see section ii below). Linear regression is used to determine the mutual effect of the G0 parental characteristics on change in G1 size in childhood (G1 childhood growth). Likelihood ratio tests are used to assess the linear

trend or significance of each variable in predicting childhood growth. To assess the influence of differential G1 childhood growth on G2 fetal growth, mean G2 fetal growth is tabulated according to the quintiles of G1 childhood growth and linear regression is used to assess the trend in mean G2 size at birth. The complete distributions of G2 fetal growth according to each quintile of G1 childhood growth are compared graphically, using percentage frequencies.

ii. To estimate statistically independent measures of change in maternal size over time to facilitate the determination of the independent effects of different time periods of development on G2 size at birth.

One of the major problems in analysing lifecourse data is that the variables measured over time are highly correlated and so unravelling their independent effects using multivariate analysis is difficult. It would be preferable if measures were statistically independent, rather than being highly correlated. Repeated maternal absolute size measures are particularly strongly correlated. In an attempt to capture change over time two sets of residuals are created to define two new variables. In **Chapter 11** "childhood growth" was defined as the change in childhood size between birth and school entry (as above). G1 childhood growth is defined as the residual value after standardised G1 childhood weight for age is regressed on standardised G1 fetal growth. That is childhood growth for each G1 female is the vertical deviation from the mean population growth for all G1 infants with the same initial fetal growth. This continuous variable is statistically independent of fetal growth. The same method was used to calculate a measure of G1 maternal height change between school entry (4 to 6 years of age) and adult reproductive life in **Chapter 12.** In this case G1 adult height, internally standardised as a standard deviation score, was regressed on the standardised G1 height for age score measured at 4 to 6 years of age. The residuals created the "height change", a continuous variable independent of height in childhood and largely independent of fetal and childhood growth. These measures of temporal change are used in the intergenerational and lifecourse analyses in Chapter 12.

E. Towards a lifecourse and intergenerational approach to the data.

i. To consider if social inequalities in G2 size at birth may be partly explained by continuity of socioeconomic environment or social patterning of maternal lifecourse variables.

Before considering the mutually adjusted effects of all the intergenerational and lifecourse variables on G2 fetal growth, the specific issue of socioeconomic inequalities

in offspring size at birth is revisited in **Chapter 12.** Linear regression is used to consider the crude association between G2 fetal growth and each of G1 early and adult social class measures, treated categorically. Multivariate regression is then used to consider the mutually adjusted effect of both social class measures. This is to determine whether differences in G2 size at birth are either due to the effect of one social class measure or to the effects of different social class environments acting at different times in G1 females' lifecourse development.

ii. **To consider the joint effects of all the biological and social, lifecourse and intergenerational determinants of G2 size at birth using an approach that incorporates the temporal dimension of the data.**

In all the multivariate analyses in **Chapter 12** the outcome measure is G2 fetal growth. Firstly the multivariate analyses are limited to considering measures of social class and maternal growth. Having established the social patterning of measures of temporal change in maternal growth they are entered into the multivariate analysis in an attempt to understand whether differential childhood growth might mediate the socioeconomic influences on G2 offspring size at birth.

In the final set of multivariate analyses all the intergenerational and derived lifecourse variables which had previously been shown to influence G2 size at birth are entered into a multivariate regression model in an attempt to understand better the determinants of G2 offspring size at birth. Variables are entered into the multivariate regression model in a stepwise way, reflecting the temporal order in which they naturally occur and are assumed to exert their influence. Entering the variables in this way attempts to consider whether each has a direct effect on G2 size at birth or whether their effect is mediated or moderated by later maternal development or status. Paternal social class and G1 maternal smoking are treated as categorical explanatory variables, maternal pre-eclampsia as a binary variable (yes or no) but all other explanatory variables are treated as continuous. All G1 maternal size measures are included as standardised variables (normalised SD scores). Likelihood ratio tests are used to check there is no evidence of departure from linearity for these continuous variables and no evidence of statistical interaction. Robust standard errors are calculated to account for the repeated G0 and G1 information in consecutive G2 deliveries to the same G1 mother. Multiple statistical testing is used so results are interpreted with caution. Therefore the influence of each variable is assessed according both to earlier results and biological plausibility, in addition to the level of statistical significance. At the conclusion of Chapter 12 a "temporal map" is provided to illustrate the way in which all

the intergenerational and lifecourse variables influence each other and G2 size at birth over time.

5.4 Summary

The intention is to address the determinants of G2 offspring size at birth using an intergenerational and a lifecourse approach, rather than just focusing on the immediate G1 adult parental environment during pregnancy.

The approach is piecewise, looking firstly at the intergenerational continuities in size at birth and its determinants (*Chapters 9 and 10*), then considering how other time-points in the life course of a woman might also influence her reproductive outcomes, specifically looking at growth in childhood (*Chapter 11*). Finally these aspects are considered together in an intergenerational and lifecourse analysis looking at determinants of offspring (G2) size at birth (*Chapter 12*). *Figure 5.3* summarises the process diagrammatically. This is a simplified view that suggests the temporal relationships between the lifecourse and intergenerational data but not necessarily the direct and indirect pathways of association. It will be used at the beginning of chapters 7 to 12 to highlight the focus area of analysis for each chapter.

A lifecourse approach requires not only lifecourse data but also analyses that take account of the temporal dimension of the data. Therefore where possible analyses include explanatory variables that capture change over time, rather than just cross-sectional measurements made at discrete time-points. These measures have the advantage of being statistically independent so that in a multivariate model it is easier to recognise which time period and measure is of greatest importance in determining the outcome.

Multivariate regression methods are used throughout rather than other complex statistical methods in an attempt to keep the analyses understandable rather than the "black-box" approach that may occur if more complex models such as multilevel or structural equation methods are used. Although these complex methods may be useful for unravelling the complex effects of correlated variables, biologically appropriate *a priori* assumptions need to be available to make the results of these methods meaningful.

Using the example of socioeconomic inequalities in offspring size at birth it is intended to show that such an intergenerational and lifecourse approach begins to clarify

how these gradients are generated over time and therefore where interventions to improve pregnancy outcome, and therefore later health, might be of the greatest benefit.

Figure 5.1 : **Defining the G1 mothers: A reconciliation of the results of the independent GRO tracing of the 5866 first generation women with the 5210 core females identified in Chapter 3.**

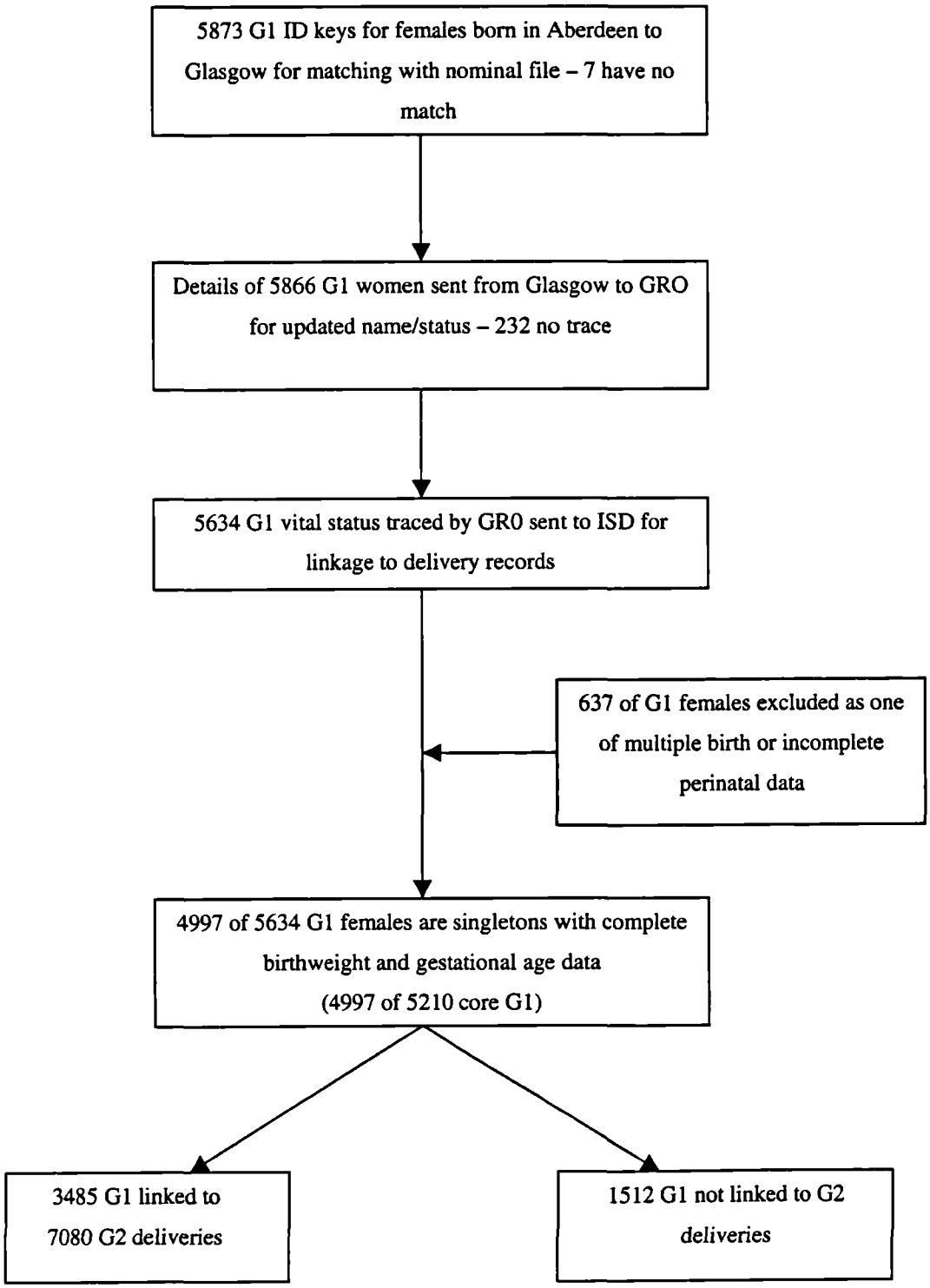


Figure 5.2 : **Summary of the derivation of the *Intergenerational* and the *Intergenerational and Lifecourse* datasets**

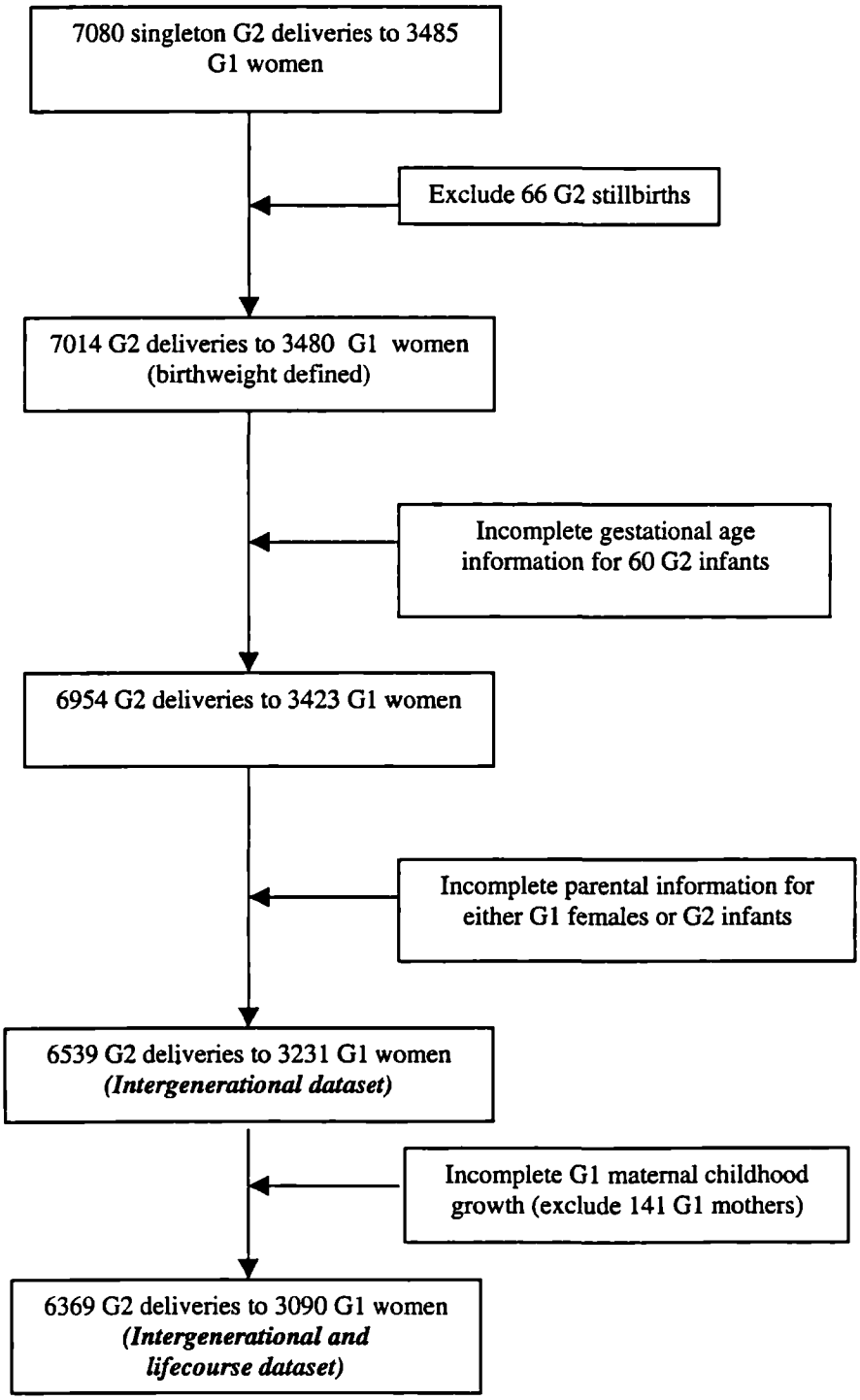


Table 5.1 : **Comparison of mean measures of size at birth of included and excluded G1 mothers in the *Intergenerational* and *Intergenerational and Lifecourse* datasets (n=3485)**

Measurement at birth	Intergenerational			Intergenerational and lifecourse		
	Included n=3231	Excluded n=254	p-value*	Included n=3090	Excluded n=395	p-value*
Mean Birthweight (SD)	3259 (473)	3259 (478)	0.99	3257 (477)	3262 (477)	0.65
Mean gestational age (SD)	39.4 (1.7)	39.4 (1.5)	0.71	39.4 (1.8)	39.4 (1.7)	0.57
Mean fetal growth (SD)	-0.01 (1.0)	-0.01 (1.0)	0.96	-0.01(1.0)	-0.03 (1.0)	0.34

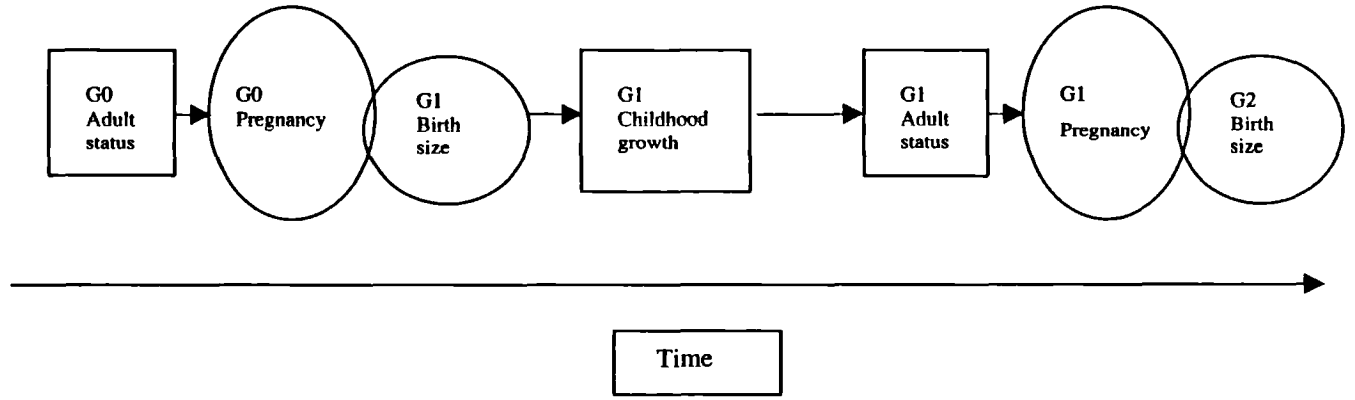
*p-value for test of difference of means

Table 5.2 : **Comparison of mean measures of size at birth of included and excluded G2 infants in the *Intergenerational* and *Intergenerational and Lifecourse* datasets (n=6954)**

Measurement at birth	Intergenerational			Intergenerational and lifecourse		
	Included n=6539	Excluded n=415	p-value*	Included n=6369	Excluded n=585	p-value*
Mean Birthweight (SD)	3310 (531)	3338 (556)	0.28	3309 (531)	3340 (546)	0.16
Mean gestational age (SD)	39.5 (1.8)	39.6 (1.9)	0.38	39.5 (1.8)	39.6 (1.8)	0.36
Mean fetal growth (SD)	-0.06 (1.0)	0.01 (1.1)	0.19	-0.06 (1.0)	0.01 (1.1)	0.14

*p-value for test of difference of means

Figure 5.3 : **Summary diagram of the temporal associations in intergenerational and lifecourse determinants of G2 size at birth**



Chapter 6:

The Aberdeen Intergenerational Dataset : Characteristics of the G1 "Reproducers"

This chapter formally considers the completeness of the intergenerational dataset defined in Chapter 5. It considers the potential reasons for any underestimation of the true rate of reproduction for the first generation females and any potential bias that this may introduce into the intergenerational analyses.

A further major aim of this chapter is to determine whether there are differences in the early life characteristics of G1 women who "reproduce" in adulthood and those who do not. Early life characteristics considered include features of their childhood environment (assumed from their G0 parental biological and social characteristics) and measures of their own early growth and development. Reproduction in this context is defined by the delivery of at least one viable singleton infant and a successful linkage to at least one second generation delivery record is used as a proxy indicator for this.

In most intergenerational datasets there is loss to follow up between generations which has the potential to limit the generalisability of obtained results and may lead to bias in estimates of effect. Often the nature of the deficit in follow up is described but the effect this deficit may have at the analysis stage is overlooked. For this intergenerational cohort sensitivity analyses are used to check the robustness of estimates obtained, using linkage status as a proxy for reproductive status, in the face of potential selective loss to follow-up of G1 females over time.

6.1 Assessing the completeness of the intergenerational linkage

As outlined in Chapter 5, 3485 (70%) of the 4997 core first generation women had second generation deliveries identified in either AMND or SMR2 or in both. Therefore 1512 (30%) of the core first generation women who were traced by GRO in 2001 had no deliveries identified by the linkage processes described in Chapter 4. Using age-specific fertility rates for Scotland between 1967 and 1999 it is estimated that 4997 women born between 1950 and 1955 would be expected to deliver approximately 8750 live born infants over this period if all the women survived to reproductive age (Macfarlane and Mugford, 2000). The linkage outlined in Chapter 4 identified 7080 viable singleton deliveries to 3485 of these women, an average birth rate of just greater than 2.0 singletons per woman who reproduced. At this rate it would be expected that a further 1670 deliveries to approximately 835 women occurred but were not identified by

the linkage. This translates to an estimated rate of non-reproduction for the first generation females of between 13-15%, representing approximately 750 women who did not reproduce, rather than the 1512 or 30% who were not linked.

6.1.1 Possible reasons for the underestimation of the true rate of reproduction using record linkage as a proxy indicator

There are several possible reasons why the non-linkage rate appears to be almost double the expected rate of non-reproduction given the age-specific Scottish fertility rate calculations:

- The actual reproduction rate in the cohort of Aberdeen women over the 1967-1999 period may have been lower than for all Scottish women of the same age.
- There may have been incomplete identification of all Scottish births using the linkage described in Chapter 4.
- A proportion of the G1 females may have delivered outside Scotland where their birth records could not be traced.
- Some G1 females may have died before reaching reproductive age.

The plausibility of each of these reasons will be assessed as much as is possible with the information available.

Firstly, it is theoretically possible that the age-specific fertility rates for the whole of Scotland differ from those for Aberdeen itself where many of the first generation women are likely to have reproduced. However self-reported data obtained independently from the postal questionnaire, described in Chapter 4, estimates that for those 3197 women who had completed and returned questionnaires by January 2002, 13.3% of the respondents remained childless. Applying this figure to the 4997 core first generation women approximately 700 women would have been expected to remain childless had they all survived to reproductive age, which is similar to the figure calculated using the age-specific fertility rates for Scotland. Therefore it seems unlikely that differences between age-specific fertility rates will be an important reason for the higher than expected rate of non-linkage.

Secondly, for the linkage to have captured deliveries that occurred to first generation women in Scotland the records must firstly have been transferred to the SMR2 or AMND record systems and secondly the probabilistic linkage to SMR2 or the exact linkage to AMND must have retrieved them. In particular for the SMR2 records, ISD claim that 3-5% of all Scottish deliveries are missed by this system and, as discussed in

Chapter 4, this figure was likely to have been higher before 1976 when at least 23% of the deliveries occurred (*Table 4.3*). In addition the cut-off linkage score used for inclusion of records from the probabilistic linkage is likely to have removed a small percentage, estimated at approximately 1%, of false negative links as well as false positives. If we assume a conservative 5% rate of missed SMR2 deliveries and a 1% rate of false negative links this would account for approximately 525 of the expected deliveries, or 31% of the estimated deficit in the expected number of births. Hence failure of the SMR2 linkage to identify all Scottish births is estimated to explain almost a third of the calculated deficit in linkage for first generation women. The potential deficit due to the failure to identify second generation Aberdeen deliveries in the AMND system is more difficult to quantify. However given that the matching on first generation maternal variables needed to be exact and further that capturing second generation perinatal data relied on the previous accurate establishment of internal linkages within the AMND system it is likely to have been of some significance.

The importance of the last two potential reasons is assessed in section 6.1.2 using further information about the first generation women obtained in the tracing exercise completed by the General Registrars Office (GRO), Scotland in 2001.

6.1.2 Vital trace status of the first generation in 2001

The GRO tracing process for the 5866 G1 females in the original Aberdeen Child Development Study (of whom the 4997 were a subset) yielded an updated vital status, current in 2001, in addition to the updated nominal information which was used in the linkage to SMR2 obstetric records. This trace status identified whether the G1 females were alive and still resident in the United Kingdom and if so where they were currently registered with a General Practitioner. In addition to the vital trace status of the females in 2001, GRO were able to provide a year of last contact for the traced G1 females. This was particularly useful for the women who moved out of Scotland or died before 2001. Exact dates of death or year of emigration were not available but theoretically the year of last contact should correspond to this. In the case of women still resident in Scotland in 2001, however, it added no further useful information. The trace status, together with the year of last contact, provided additional clues as to why offspring delivery records were not found for 1512 (approximately 30%) of the 4997 potential first generation mothers.

Of the 5866 females for whom information was originally sent to GRO for tracing over 81% were registered with health boards in Scotland in 2001, with over 72% being in the Grampian region itself. 12.7% were registered with a health board outside of Scotland, either in the United Kingdom or overseas and a further 2.6% were recorded as having died prior to 2001. A small proportion (0.3%) were in prison, long term psychiatric care or in the Armed Forces and for 3.1% there was either no trace or they had no current health board registration (*Table 6.1*).

For the subset of 4997 first generation females, who were singletons with complete perinatal data, it is clear from *Table 6.2* that linkage or non-linkage to second generation deliveries was highly influenced by this vital trace status in 2001. For women who were registered with a health board in Scotland in 2001, 3254 (77%) of the 4271 had been linked to delivery records in contrast to 140 (24%) of the 584 women who had moved outside of Scotland at some time before 2001. For the 1512 (30%) of the 4997 first generation women who were not linked to any delivery records in Scotland, 444 (29.4%) were registered outside of Scotland in 2001 as opposed to only 140 (4.0%) of the 3485 women who were linked.

6.1.3 Linkage of first generation women who died or emigrated before 2001

Given that the first generation women were born between 1950 and 1955 their reproduction might have been expected to begin approximately twenty or more years later. Accordingly the first generation females were matched to second generation deliveries in the SMR2 and AMND systems over the 33 year period of 1967 to 1999. The distribution of second generation linkages according to year of delivery is detailed in *Table 6.3*. Only 1.2% of the second generation deliveries identified by the linkage occurred prior to 1970 and over half occurred in the next 12 years, before 1979. By considering the year of last contact for the women who emigrated it was found that there were no emigrations recorded prior to 1970 in the women who were linked to deliveries but had emigrated by 2001 and only 11 (8% of total 140 in that group) in that group prior to 1979. However of the 444 women who had emigrated but were not linked to deliveries 58/444 (13%) emigrated before 1970 and 167/444 (38%) emigrated before 1979. Overall within the group of G1 females who emigrated, those who were linked tended to emigrate later (closer to 2001) than those who were not linked (test for heterogeneity X^2=82.6 (39 d.f.), p<0.001).

Similarly if we consider the first generation women who had died prior to 2001, of whom there were 122 in total, 70 (57.4%) were linked to deliveries in Scotland, but 52 (43%) were not linked. If we consider when the deaths occurred, according to the year of last contact information, we find a similar pattern to the emigrations. Within the group of G1 females who died prior to 2001 but were not linked to deliveries, 6/52 (11%) of the deaths occurred before 1970 and 20/52 (38%) occurred before 1979, whereas in the linked group none of the deaths occurred before 1970 and only 1 death occurred before 1979. Overall the deaths in the linked group also tended to occur later (closer to 2001) than the non-linked group (test for heterogeneity X^2=41.8 (30 d.f.), p=0.07).

Therefore it is likely that at least 64 (4.5%) of the 1512 non-linked women had either left Scotland before 1970, and potentially reproduced entirely elsewhere where their records could not be obtained using the previously described linkage (Chapter 4), or were dead prior to reproductive age. Removing these 64 women from the age-specific fertility rate calculations would reduce the expected number of births by a further 130 (8% of the deficit in deliveries estimated in 6.1). The remaining women who emigrated or died between 1970 and 2001 may have incomplete delivery records from the linkage, but the exact nature of this deficit is more difficult to estimate. However the total number of deliveries linked to each G1 female offers a chance to explore this further.

For all of the 3485 first generation linked females, 905 (26.0%) were linked to only one second generation delivery, 1800 (51.7%) were linked to two, 601 (17.2%) were linked to three and 179 (5.1%) were linked to four or more (*Table 6.4*). It appears that the women who were linked but either emigrated or died prior to 2001 did have fewer total deliveries. The women who were linked and emigrated prior to 2001 had a mean number of 2.1 total deliveries as opposed to 2.4 total deliveries for the linked women who were in Scotland in 2001 ($p<0.001$ for test of difference of means). The women who were linked but who died before 2001 were linked to an average of 2.0 total deliveries ($p<0.001$ for test of difference of mean with those in Scotland in 2001). The lower total delivery numbers were consistent with the supposition that some of their delivery records may have been incomplete (X^2=24.8 (6 d.f.), $p<0.001$ in test for heterogeneity according to trace status).

Hence emigration and deaths in the first generation women are likely to have had a significant impact on the rate of non-linkage. The women who emigrated may or may not have reproduced, but if some or all of their reproduction took place outside of

Scotland their delivery records will not have been found using the linkage process outlined in Chapter 4.

6.1.4 Summary of assessment of the completeness of the record linkage

Therefore approximately half the estimated deficit in linkage of first generation women to second generation deliveries is explainable with updated information we have on the G1 females and the quality of the record systems. The deficit does not seem to be due to different fertility rates for Aberdeen women born in the early 1950s in comparison to Scotland as a whole. However it does seem that failure of SMR2 to capture 100% of Scottish deliveries may have contributed to at least a third of the estimated deficit in the linkage. This is a conservative estimate that cannot take full account of the higher but unknown rate of non-capture for Scottish births occurring before 1976 when the SMR2 system was purported to be much less complete. It also does not include an estimate of the deficit due to the exact matching criteria and the internal linkage required to identify second generation Aberdeen deliveries in the AMND record system. The GRO vital trace status additionally provided evidence that at least 3% of the first generation females who were not linked to deliveries had died or emigrated out of Scotland prior to reproductive age. Therefore the estimated deficit in the true rate of reproduction based on all 4997 G1 women having survived to adulthood and reproducing in Scotland was almost certainly an over-estimate.

Nonetheless linkage status is the best indicator of reproductive status that is available for the G1 females. Given that an unknown percentage of the 1512 G1 females who were not linked will have been misclassified as "non-reproducers" by using linkage as a proxy marker for reproduction that group will continue to be referred to as "non-linked" rather than "non-reproducers" at this stage. Sensitivity analyses will address this potential misclassification in Section 6.4.

6.2 Exploring the potential bias in identifying first generation reproducers

While there are plausible reasons why the rate of non-linkage may be an over-estimate of the true rate of non-reproduction there is a concern that there may be systematic bias in the inclusion of first generation women in the intergenerational analyses because of different chances of linkage according to different maternal characteristics. It is apparent that rates of successful linkage to second generation deliveries are influenced by vital trace status in 2001. Therefore the early life

characteristics of the women who had different vital trace status in adulthood are firstly considered to see if they differed. These differences are then compared to any differences in the early life characteristics associated with linkage and non-linkage in the G1 females.

6.2.1 Early life characteristics of the first generation females according to vital trace status in 2001

Three categories of vital trace status were used: firstly the 4217 women who were registered with a health board in Scotland in 2001 were considered to be "non-mobile"; secondly the 584 women who moved out of Scotland before 2001 were called "mobile"; thirdly the remaining 196 women who either died prior to or were in prison or in long term hospitalisation, or who did not have a current health board registration in 2001 were classified as "other". To consider if the women who remained in Scotland differed from those who did not, ideally it would have been useful to compare their adult characteristics, but this adult data was only available for the 3485 women who were linked to deliveries. However it was possible to consider early life characteristics to determine if women with different vital trace status in 2001 had different family environments or divergent early patterns of growth or development.

In *Table 6.5* mean measures of size at birth and size and IQ in childhood are compared for G1 females according to the three categories of trace status. In comparing the women who remained in Scotland (non-mobile) with those who emigrated prior to 2001 (mobile) there was no evidence of any significant difference in their intrauterine growth, although mean birthweight, gestational age at delivery and fetal growth all tended to be slightly higher for the mobile group. By school entry the females who were later mobile had become significantly taller and still tended to be heavier than their non-mobile peers at the same age. However they had a lower BMI at the same age, suggesting that the mobile group were relatively lighter on average for their height than the non-mobile group. The mobile group also scored 4-5 points higher on average in the standard school IQ tests at both 7 and 11 years of age. The "other" group contained the least number of women and included those who were dead or in prison or in long-term hospitalisation in 2001. They tended to have a lower mean absolute birthweight, mean fetal growth and be the shortest and lightest at school entry, but with the highest mean BMI at 4-6 years, suggesting that they were relatively heavier for their height than the other two groups. Their mean IQ score at 7 years was lower than the other two groups

but by 11 years was similar to the non-mobile group. However none of these differences reached statistical significance (*Table 6.5).*

Table 6.6 compares the distribution of G0 parental characteristics that may have influenced these early G1 growth and developmental differences across adult status groups. There was no difference in the rate of the pregnancy-specific complications of pre-eclampsia or ante-partum haemorrhage among the three status groups. However mean G0 maternal height was greatest for the mobile group as were levels of completed G0 maternal education (although this was only available for the first born females and the numbers were small). G0 paternal social class, as measured by the occupation of the child's father at the time of her birth, was highest for those G1 females who were later mobile. The "other" group had a distribution of parental characteristics similar to the non-mobile group (*Table 6.6).*

These differences in G0 parental characteristics between the first generation females may have contributed to the differential G1 childhood development of the three groups but were not reflected in differential G1 intrauterine growth. The females who moved away from Scotland (mobile) tended to have come from more advantaged family backgrounds than those who were assumed not to have moved (non-mobile), with taller mothers who completed more years of secondary education and fathers in more skilled occupations. The differences between the mobile and the non-mobile groups in particular may have lead to bias in the women who reproduced in Scotland and were therefore able to be linked to second generation deliveries.

6.2.2 Early life characteristics of the first generation females who were linked to second generation deliveries compared to those who were not linked.

Table 6.7 compares the mean measures of early life growth and development for the linked and non-linked G1 females. The 3485 linked females did not appear to differ in their own intrauterine growth from the 1512 non-linked females. There were no significant differences in their mean birthweights, gestational ages at delivery or their fetal growth. However, with respect to size in childhood, by school entry (4-6 years of age) the linked groups mean weight and height (adjusted for age at measurement) were significantly less than the means for the non-linked group. The average BMI of the two groups though was not significantly different. Developmentally whilst the two groups IQ scores were similar at 7 years of age the non-linked groups mean score was significantly higher by 11 years of age (*Table 6.7*).

In *Table 6.8* the distribution of G0 parental characteristics that might have influenced these early G1 characteristics were reviewed for both these groups. The rate of the pregnancy specific complications, pre-eclampsia and ante-partum haemorrhage, did not differ between the linked and non-linked groups. However other adult G0 maternal and paternal biological and social characteristics were different. G0 maternal adult height tended to be greater in the non-linked group, but this just failed to reach statistical significance. The most significant differences were in the distribution of G0 paternal occupational social class at the time of the G1 female's birth and the completed level of her mother's education. Overall the non-linked group tended to be from higher social class groups and be born to mothers with more years of completed education than the linked group (*Table 6.8).*

6.2.3 Comparison of the early life characteristics associated with non-linkage and with mobility in this cohort

Hence the G1 early life and G0 parental characteristics associated with non-linkage in this cohort appeared to closely parallel those associated with mobility between childhood and adulthood. Those women who were not linked to deliveries in Scotland were more likely to have been socially advantaged in childhood, which may have provided opportunities for increased family mobility out of Aberdeen and Scotland prior to reproductive age. Hence they may well have "reproduced" outside of Scotland where their records could not be traced. Alternatively they may of course have been appropriately classified as non-linked having not reproduced at all.

6.3 Early life determinants of linkage for all G1 females

A major aim of this chapter was to attempt to determine if there were any maternal early life characteristics associated with later adult reproduction. Using linkage status as a proxy indicator of reproductive status it is possible to use logistic regression to determine the estimates of effect of the maternal early life variables on odds of later linkage. Although the majority of the women who were linked to second generation deliveries were resident in Scotland in 2001, 231 (30%) of the 780 women from the mobile and "other" categories were also linked to deliveries in Scotland prior to 2001. Therefore an analysis stratified according to adult trace status is initially required to check whether summary odds ratios are appropriate, given the similarities noted between the maternal early life predictors of trace status and non-linkage.

6.3.1 Stratified analysis according to adult vital trace status in 2001

In *Table 6.9* the results of *Table 6.7* are shown separately for each of the three categories of adult trace status. A mixed pattern of maternal early growth and development was noted to be associated with linkage across the three status groups. However there was no evidence of any significant differences in birthweight between the linked and non-linked women in any of the adult trace status categories. There was a statistically significant difference in the gestational age of the linked and non-linked women in the group who were resident in Scotland in 2001, but the equivalent real difference was small and of little clinical relevance, and there was no overall evidence of a difference in fetal growth. Given the multiple statistical testing that was carried out it might be expected that some significant values might have occurred by chance therefore caution was applied in interpreting the p-values for all these analyses.

The significant differences of note that were seen between the linked and non-linked groups with respect to size in childhood in *Table 6.7* were only evident in the group of women resident in Scotland in 2001, the largest group in absolute number. The non-linked women tended to be taller and were significantly heavier on average by school entry than the linked group. The mean BMI of the non-linked women was also greater suggesting they were relatively heavier than they were tall, in contrast to the overall findings for the group who were likely to be mobile later in life (section 6.2). However in the mobile group the non-linked women who moved out of Scotland by 2001 tended to be lighter and shorter at school entry than the women linked to deliveries, but these differences did not achieve statistical significance. There was no difference though, according to linkage, in their mean BMI. The "other" group tended to be smaller overall, at birth and in childhood, but there was no significant difference between the women who were linked or not linked to deliveries later in life. With respect to educational testing, scores on IQ tests at 7 and 11 years did not vary significantly between the linked and non-linked women across all trace status groups (*Table 6.9).*

In *Table 6.10* the results of *Table 6.8* are stratified according to the three adult trace status categories. The G0 parental characteristics associated with linkage or non-linkage appeared to be more consistent across the three adult trace status groups. There was no evidence of differential rates of pregnancy complications or differences in mean G0 adult maternal height between the linked and non-linked women in any of the three trace status groups. However in each of the three groups there was a consistent pattern

of non-linkage being associated with being born to G0 mothers who had completed more years of secondary education and having G0 fathers in higher social class categories. This trend only reached statistical significance in the non-mobile group but it was also apparent in the two other groups, although with their smaller numbers they had less power to detect a statistically significant trend (*Table 6.10*).

6.3.2 Determining the odds of linkage for all the first generation women.

In order to quantify the effect of the maternal early life determinants on the odds of linkage of first generation women to second generation deliveries logistic regression was used for all 4997 women, adjusting for adult trace status in 2001. The adjustment was justified by the results of the previous section which showed no systematic differences between adult trace strata. It was also supported by formal tests for interaction. The tests excluded effect modification of explanatory variables by adult trace status (p-value provided though the statistical test is weak and the observed differences in odds ratios were also taken into account).

The results of the logistic regression analyses are presented in *Table 6.11*. They are presented for categorical variables rather than for continuous variables to provide a clearer understanding of the odds of linkage for clinically relevant explanatory variable categories and rather than "per one standard deviation difference" which is often less easily interpreted. In addition reporting the odds ratios for categorical variables means it does not assume a linear relationship between the variable of interest and the odds of linkage.

As suggested earlier, a woman's trace status in 2001 influenced her chance of being linked to second generation deliveries (*Table 6.2*). In terms of odds of linkage a woman who moved out of Scotland between childhood and 2001 had only a 9% chance of being linked to second generation delivery records in comparison to a woman who was resident in Scotland in 2001 (95% C.I. 0.08 – 0.11, $p<0.001$). A woman who was in the "other" trace status category had a 26% chance of having been linked (95% C.I. 0.19 – 0.34, $p<0.001$) by comparison. Therefore in *Table 6.11* the crude odds ratios for linkage for each category of the early life maternal characteristics are displayed together with those adjusted for adult trace status in 2001.

Overall the intrauterine growth of the first generation females did not appear to be associated with their later odds of linkage to second generation deliveries. There is some evidence to suggest that females born pre-term were less likely to be linked to deliveries

as adults with weak evidence of a differential effect of adult trace status according to whether a mother was herself born prematurely or not. However on further examination this appeared to be because this association was driven by women who remained in Scotland with the numbers in the other two trace status categories in the extremes of gestational age being relatively small, therefore summary adjusted odds were given in the table. Maternal childhood size remained an important early life determinant of later linkage with little evidence to suggest that this was due to confounding by adult trace status, particularly in terms of weight for age childhood measures. The heavier and taller a female was at school entry the lower were her odds of being linked to delivery records as an adult, though interestingly there was no evidence of an association with childhood BMI measured at the same age. This may be indicative that BMI measured in these children aged 4-6 years, was a poor measurement of their body proportion in childhood (*Chapter 11*). Even after controlling for the different ages (in months) at which height and weight were measured effect estimates and confidence intervals for BMI remained essentially unchanged (results not shown). The reduced odds of linkage in the highest IQ group at 7 years was largely explained by increased mobility out of Scotland (assumed from trace status). However at the age of 11 years mobility only partially explained the association of higher IQ with lower odds of adult linkage to delivery records.

The G0 pregnancy specific conditions of pre-eclampsia and ante-partum haemorrhage were not found to be associated with G1 females' linkage to deliveries in adulthood but G0 maternal adult height was with those born to taller mothers tending to be less likely to be linked. This association was only partially explained by the adult trace status of these females. The relationship between linkage and paternal social class in childhood was also partially confounded by adult trace status but nevertheless the association remained significant after adjusting for this. Importantly though there was no evidence of any effect modification of paternal social class by adult trace status. The level of completed maternal education showed a similar trend, but was only available for first born females (n=1504). G1 females with mothers who completed tertiary education and fathers in higher social classes were less likely to be linked to second generation deliveries (*Table 6.11*).

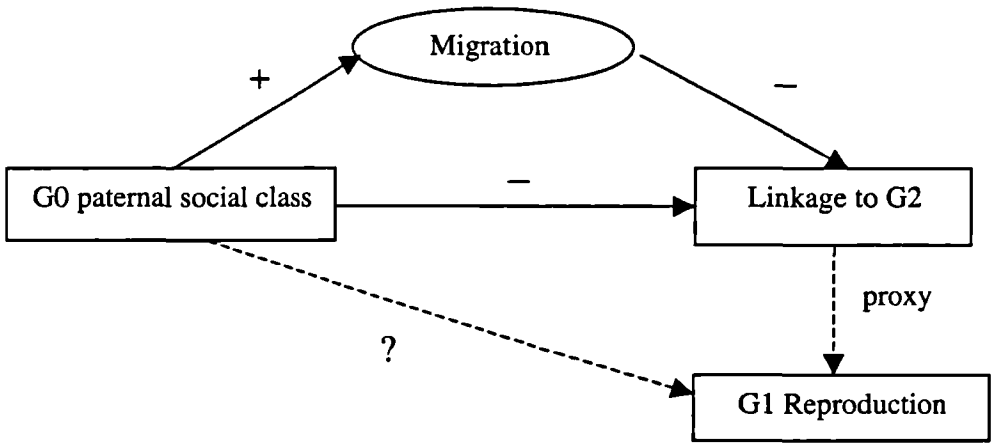
The far right hand column of *Table 6.11* displays the odds ratios for the best model considering the mutually adjusted effect of all the explanatory variables, with only the variables which had an independent statistically significant effect included. Highly

correlated variables were limited to one of a pair of correlates for this model. Therefore fetal growth and gestational age were considered but birthweight was not. Similarly height for age and BMI were considered but childhood weight for age was not and only IQ score at 11, not 7 was considered. In this final adjusted model the early life characteristics of the first generation females that remained significant predictors of her odds of later linkage to second generation deliveries were characteristics of her G0 parents alone rather than measures of her own G1 intrauterine or childhood development. In particular her G0 father's social class at the time of her birth and in early childhood and her G0 mother's adult height were the two predictor variables that remained significant after mutual adjustment. G1 females born to G0 fathers in lower social classes and to shorter G0 mothers were more likely to be linked to second generation deliveries than those in higher social classes with taller mothers, independent of their adult trace status. Size and performance on IQ tests in childhood were no longer significant after accounting for these parental characteristics *(Table 6.11)*. This is probably largely due to the strong correlation between childhood size and IQ development and parental social class and height. In this group of females, paternal social class is positively correlated with childhood height for age ($r=0.38$, $p<0.001$) and negatively correlated with childhood IQ score at the age of 11 years ($r=-0.27$, $p<0.001$). Similarly maternal adult height is positively correlated with childhood height for age ($r=0.36$, $p<0.001$). These parental relationships with childhood size will be further explored in *Chapter 11*.

6.4 Estimating the odds of reproduction for the first generation women

The original aim of this chapter was to consider whether early life characteristics of the first generation females were influential in determining whether or not they might reproduce as adults. The analyses so far have been concerned with the maternal early life characteristics of the first generation women who were linked to second generation deliveries in comparison to those who were not. For this group of women the only way to ascertain whether they had reproduced or not was by whether or not they had been linked to second generation deliveries. Section 6.1 detailed reasons why the linkage probably underestimated the true extent of reproduction in this cohort, and it is clear that the adult trace status, i.e. where a woman was living in 2001, greatly influenced her chances of being linked to deliveries, and thus of capturing her true reproductive status.

It seems that the early life determinants of linkage are similar across the three status groups and therefore summary odds ratios were calculated using logistic regression, adjusting for trace status. However the question remains whether the estimates obtained for the influence of early life characteristics on linkage is a biased estimate of their effects on reproduction, as the diagram below illustrates using the example of the early life characteristic of G0 paternal social class.



There are two further ways to estimate the effects of maternal early life characteristics on reproduction, rather than linkage, for this group of G1 women. The first is to limit the logistic regression analyses to the women who were assumed to have remained in Scotland throughout their reproductive life, namely those who were resident in Scotland in 2001. These women were not representative of all first generation women, because the females who were larger in childhood and performed better in childhood IQ tests tended to have moved outside of Scotland at a greater rate than other females (*Section 6.5*). Nonetheless this subset of first generation females offers more complete data on reproductive status than the remainder of the group because they are assumed to have remained in, and delivered in, Scotland. Further there is no reason to believe that there should be any systematic bias in the exclusion of women from the SMR2 records or from the probabilistic linkage, unlike exclusion due to selective mobility.

6.4.1 Early life predictors of the odds of "reproduction" in G1 women who were resident in Scotland in 2001

Logistic regression analyses were therefore limited to the 4217 (84% of 4997) first generation females whose trace status in 2001 found them living in Scotland to

determine the overall predictors of linkage, which are assumed to be indicative of reproduction, for this subset of G1 women.

Table 6.12 presents the crude odds of "reproduction" for this subset of first generation women according to their early life characteristics, together with the final model which is restricted to the characteristics which remain statistically significant in the mutually adjusted model. G0 paternal social class and G0 maternal adult height remained the only significant early life characteristics associated the odds of "reproducing" in adult life. This is very similar to the results obtained for all G1 females shown in *Table 6.11.* It is noteworthy that although G1 females born to taller mothers from more advantaged social class backgrounds were more likely to be excluded from this non-mobile group the gradient in the odds of reproduction related to G0 paternal childhood social class and maternal height were nonetheless evident in this subset of G1 women (*Table 6.12*).

6.4.2 Sensitivity analyses to reclassify a proportion of the non-linked females as "reproducers"

However this subset of non-mobile G1 females are not representative of all G1 females. Also the high rate of non-linkage in the mobile group (444/584) may have represented a higher proportion of misclassification of these similarly non-representative G1 females as "non-reproducers", using linkage as a proxy, than in the other two groups. Therefore to further estimate the determinants of "reproduction", rather than linkage, for all 4997 G1 women, sensitivity analyses were considered.

To simplify these analyses only the effect of G0 paternal social class on the odds of linkage to second generation deliveries was considered as this was the strongest predictor of the odds of linkage from the early life maternal characteristics analysed in *Tables 6.11* (for all women) and *6.12* (for the subset of women who were in Scotland in 2001). For simplicity this variable was recoded from eight into three categories: manual, non-manual and "other" (non-manual being social classes I to IIINM, and manual being IIIM to V, "other" was as before). This new coding led to a crude odds ratio for linkage for G1 females with G0 fathers in manual compared to non-manual classes of 1.37 (95% CI: 1.21, 1.55) and for "other" versus "non-manual" of 0.81 (95% CI: 0.62, 1.06). Adjusting the odds ratio for adult status in 2001 reduced these slightly to, respectively, 1.25 (95% CI: 1.09,1.43) and 0.75 (95% CI: 0.56,1.00). Further mutual adjustment for childhood height, maternal height and IQ score at age 11 gave odds ratios of 1.23 (95%

CI: 1.05,1.40) and 0.69 (95% CI: 0.50, 0.95). Hence having a G0 father who was in a manual occupation appeared to increase the odds of linkage to a second generation delivery by over 20%, while a father in the "other" category appeared to slightly reduce these odds. These results however cannot be directly interpreted as odds of reproduction because of the potential misclassification of the G1 females who emigrated out of Scotland.

For this reason the robustness of these estimates was examined using sensitivity analyses. These consisted of sequential re-analyses of the original data after an increasing proportion of the women who emigrated and had not been linked to second generation deliveries (444 out of 584) were re-classified as linked. The proportions reclassified varied from 5% to 70% (represented by p), in 5% steps. The maximum value of 70% reclassification would mean that the rate of overall linkage in the 584 G1 females who emigrated was equal to the rate for those who remained in Scotland (77%). For each proportion p the following steps were taken 100 times:

a) A random sample of size ($p \times 444$) of the women who had emigrated and had not been linked was reclassified as linked.
b) The adjusted odds ratios (OR) for the effect of grand-paternal social class (as defined above) were computed.
c) The log(OR) and standard error of log(OR) for each of these effects were saved.

The results of the analyses of these 100 samples for each proportion (p) of reclassification were then summarised for each level of p as mean odds ratios and 95% ranges of uncertainty, as described by Verbeke et al (Verbeke et al., 2001). The sensitivity analyses were limited to the comparison of the odds of reproduction in G1 females with manual compared to non-manual paternal social class. The mean odds ratios and 95% ranges of uncertainty results are shown graphically in *Figure 6.1* according to the proportion of reclassification (p).

The odds ratios for reproduction in G1 females who were in manual compared to non-manual households in childhood are essentially unchanged by the sequential reclassification from the adjusted odds ratio calculated using linkage status as a proxy indicator of reproductive status (point estimate of OR=1.23). Further the 95% ranges of uncertainty of the estimates do not contain the null value for any proportion of reclassification in the manual versus non-manual paternal social class comparison (*Figure 6.1*). Therefore the sensitivity analyses offer reassurance that the odds ratios

obtained for G0 paternal social class do correspond closely to the estimates of effect for reproduction, rather than just for linkage.

6.5 Summary

The linkage to second generation deliveries for all the first generation core females was almost certainly incomplete. Estimates based on the age-specific fertility rates for Scotland for woman born between 1950 and 1955 suggested that an unknown proportion of the non-linked females were probably wrongly classified as non-reproducers because they were unable to be linked to deliveries for the reasons discussed in *Section 6.1*. This loss to follow up in an intergenerational study is not unique, but it has rarely been addressed before by way of sensitivity analyses or other techniques to test the robustness of estimates of effect in the subgroup who are able to be followed up.

Klebanoff et al have considered the extent of loss to follow up in their second generation follow-up of the Danish perinatal study women (Klebanoff et al., 1993). They used a combination of interview followed by record linkage to obtain perinatal records for children born to a sample of women who were part of an original study in 1959-1961. However while they noted that women who were successfully interviewed tended to be of higher socioeconomic status than those from the original study population, they did not appear to allow for these potential biases in their analyses (Klebanoff et al., 1993).

The most plausible explanations for the misclassification of non-linked women as non-reproducers in this Aberdeen study were twofold. Either they were not linked to records in the SMR2 or AMND systems, most probably because of incomplete record systems, which should not have been subject to selection bias, or the G1 females moved out of Scotland or died before their reproductive lives began. The G1 females most likely to have moved away from Scotland, and therefore be wrongly classified as non-reproducers, tended to be from more advantaged social class backgrounds and to have grown faster in their pre-school years and performed better on childhood tests than their peers. This led to the concern that there may have been bias in the identification of first generation women who were linked to second generation deliveries.

Bias caused specifically by migration has been considered for case-control studies by Jones and Swerdlow (Jones and Swerdlow, 1996). In similar findings to the Aberdeen study they noted that migration of children born between 1965 and 1986 from

Oxfordshire was associated with higher maternal social class and lower parity, but not size at birth measures. The authors cautioned that if migration was related to "disease outcome" the impact of migration bias should be considered. This appeared to be the case for the Aberdeen study where the early life characteristics associated with non-linkage were also associated with later migration.

Therefore logistic regression analyses controlling for adult trace status (mobility) and sensitivity analyses which considered the effect of reassigning a proportion of the non-linked women who had migrated out of Scotland to the linked group were used. These confirmed the robustness of the estimated effects of maternal early life characteristics on adult reproduction. They did not appear to be an artefact of having a non-representative group of women left in Scotland available to be classified as reproducers. Most notably the odds of reproduction, after controlling for current adult status, were greatest in G1 females whose mothers were relatively short and in particular who grew up in less socially advantaged families.

One might speculate why the women who were from the most socially advantaged backgrounds in the 1950s and 1960s were less likely to reproduce. Perhaps their relative affluence allowed them the luxury of choice of reproduction and delayed childbearing which may not have been an option for less advantaged young women. Demographic studies which have considered the relationship between socioeconomic status and childlessness have debated the direction of the association between the two (dos Santos Silva and Beral, 1997). An American study by Poston (Poston, 1974) in 1974 attempted to differentiate between involuntary and voluntary childlessness. Historically rates of involuntary childlessness tend to increase as socioeconomic conditions worsen, however Poston concluded that the relationship was reversed for voluntary childlessness so that having no children "by choice" was more likely in the highest social groups. A later study in 1992 by Kravdal (Kravdal, 1992) in Norway confirmed that by the 1980s voluntary childlessness was greatest in the most highly educated groups and lowest in the least. He also re-evaluated the American data from these later decades to confirm Poston's earlier findings of voluntary childlessness being most prevalent in the most socially advantaged groups. Therefore these findings for the Aberdeen intergenerational cohort are consistent with the findings of these other studies.

The non-capture of potential reproducers who moved outside of Scotland from the first generation has potential implications for the remainder of the intergenerational analyses. It might be expected that a subset of the tallest, most highly educated females

from the first generation will not have deliveries included in the intergenerational analyses because they may have occurred outside Scotland. However given their social status they may also be less likely to have reproduced. This may narrow the differentials that are expected with respect to social class differences in second generation size at birth. Importantly however for the intergenerational analyses of offspring size at birth that follow, there was no evidence that the fetal growth of the G1 women who were linked to deliveries differed from those who were not, regardless of their adult trace status.

Table 6.1 : **Adult vital trace status in 2001 (according to health board registration) of the G1 females sent to GRO for tracing (n=5866)**

Adult trace status in 2001	Frequency (%)
Registered with Health Board in Scotland	4771 (81.3)
UK not Scotland	605 (10.3)
Emigrated outside UK	138 (2.4)
Dead	155 (2.6)
Prison/AF*/Hospital	14 (0.3)
Whereabouts unknown **	183 (3.1)
Total	**5866 (100.0)**

** **Whereabouts unknown** – includes both unable to be traced by GRO and traced but no current status available in 2001

Table 6.2 : **Linkage to G2 deliveries according to adult vital trace status in 2001 for the 4997 core G1 females**

Adult trace status in 2001	Linked to offspring		Number of core women (% of total)
	YES	NO	
Registered with HB in Scotland	3254	963	4217 (84.5)
UK not Scotland	114	354	468 (9.4)
Emigrated outside UK	26	90	116 (2.3)
Dead	70	52	122 (2.4)
Prison/ AF* /Hospital	3	9	12 (0.2)
Traced but no current status in 2001	18	44	62 (1.2)
Total	**3485 (69.7)**	**1512 (30.3)**	**4997 (100)**
Test for heterogeneity	**X^2(5 d.f.)=758.9, p<0.001**		

*AF = Armed Forces

Table 6.3 : **Distribution of year of delivery of the G2 offspring generation (n=7080)**

Year of Delivery	Frequency	Percent of total
1967-	82	1.2
1970-	1547	22.8
1975-	2580	36.4
1980-	1827	25.8
1985-	753	10.6
1990-	252	3.6
1995-	39	0.6
TOTAL	**7080**	**100.0**

Table 6.4 : **Total number of G2 deliveries per G1 linked woman, according to G1 adult vital trace status in 2001 (n=3485)**

Number of Deliveries	Trace status in 2001 n (% of total)			All linked females n (% of total)
	In Scotland	Migrated	Other	
1	818 (25.1)	51 (36.4)	36 (39.6)	905 (26.0)
2	1686 (51.8)	72 (51.4)	42 (46.1)	1800 (51.7)
3	576 (17.7)	13 (9.3)	12 (13.2)	601 (17.2)
4 or more	174 (5.4)	4 (2.9)	1 (1.1)	179 (5.1)
TOTAL	**3254**	**140**	**91**	**3485**

Table 6.5 : **Early life maternal characteristics of the G1 females according to their adult vital trace status in 2001 (n=4997)**

Maternal early life (G1) Characteristic	Non-mobile** (n=4217) Mean (SD)	Mobile* (n=584) Mean (SD)	Other*** (n=196) Mean (SD)	p-value+ (Test for heterogeneity)
Birthweight(grams)	3258 (476)	3284 (477)	3219 (495)	0.22
Gestational age (weeks)	39.3 (1.8)	39.4 (1.6)	39.3 (1.9)	0.52
Fetal growth (SD score)	-0.01 (1.0)	0.03 (1.0)	-0.08 (1.0)	0.41
Height for age score[1] at 4-6years	-0.01 (1.0)	0.16 (1.0)	-0.11 (1.0)	<0.001
Weight for age score[1] at 4-6 years	0.00 (1.0)	0.06 (1.0)	-0.07 (1.0)	0.27
BMI at 4-6yrs[1]	16.2 (1.5)	16.0 (1.3)	16.4 (1.9)	0.05
IQ score at 7 years[2]	108 (16)	112 (16)	105 (18)	<0.001
IQ score at 11 years[2]	104 (13)	109 (13)	104 (13)	<0.001

***Mobile** – refers to moved out of Scotland (including other UK)

****Non-mobile** – 2001 trace status in Scotland (assumes non-mobile)

*****Other** – All other trace status categories, including died prior to 2001

+ **p-values** from partial F-test for continuous variables

[1]**Childhood weight and height** measurements available for n=4819

[2]**Childhood IQ** available for n=4620

Table 6.6 : **G0 Parental characteristics of the G1 females according to their adult vital trace status in 2001 (n=4997)**

Parental characteristics (G0)	Non-mobile** (n=4217)	Mobile* (n=584)	Other*** (n=196)	p-value+ (Test for heterogeneity)
Pregnancy Complications: n(%)				
Maternal Hypertension	738 (17.5)	118 (20.0)	30 (15.3)	0.18 (2 df)
Maternal APH	78 (1.9)	12 (2.1)	4 (2.0)	0.93 (2 df)
Maternal height, cm				
Mean (SD)	157.8 (6.3)	160.0 (6.1)	157.3 (7.0)	<0.001
Paternal Social class n (%)				
I	72 (1.7)	25 (4.3)	5 (2.5)	
II	294 (7.0)	70 (12.0)	14 (7.1)	
IIINM	1527 (36.2)	231 (39.6)	74 (37.8)	
IIIM	845 (20.0)	100 (17.2)	36 (18.4)	
IV	578 (13.7)	69 (11.8)	26 (13.3)	
V	684 (16.2)	59 (9.9)	28 (14.3)	
Other	217 (5.2)	31 (5.3)	13 (6.6)	
				<0.001(12 df)
Maternal tertiary education n (%)[3]	16 (1.2)	6 (3.1)	2 (4.2)	0.002 (4 df)

***Mobile** – refers to moved out of Scotland (including other UK)

****Non-mobile** – 2001 trace status in Scotland (assumes non-mobile)

*****Other** – All other trace status categories, including died prior to 2001

+ p-values from partial F-test for continuous variables and X^2 test for categorical variables

[3]**Maternal** education only available for first born mothers (n=1552)

Table 6.7 : **G1 maternal early life characteristics according to linkage status of G1 females (n=4997)**

G1 Maternal early life Characteristic	Linked to offspring		p-value*
	YES (n=3485) Mean (SD)	NO (n=1512) Mean (SD)	
Birthweight (grams)	3260 (479)	3258 (473)	0.92
Gestational age (weeks)	39.3 (1.7)	39.3 (1.8)	0.09
Fetal growth (SD score)	-0.01 (1.0)	0.00(1.0)	0.64
Height for age score[1] at 4-6years	-0.01 (1.0)	0.05 (1.0)	0.04
Weight for age score[1] at 4-6 years	-0.01 (1.0)	0.05 (1.0)	0.03
BMI at 4-6yrs[1]	16.2 (1.6)	16.2 (1.5)	0.26
IQ score at 7 years[2]	108 (16)	109 (17)	0.22
IQ score at 11 years[2]	104 (13)	106 (14)	<0.01

[1]**Childhood weight and height** measurements available for n=4822

[2]**Childhood IQ** available for n=4620

* **p-values** from two sided t-test for continuous variables

Table 6.8 : **G0 parental characteristics according to linkage status of G1 females (n=4997)**

G0 Parental characteristics	Linked to offspring		p-value*
	YES n=3485	NO n=1512	
Pregnancy Complications: n(%)			
Maternal Hypertension	624 (17.9)	262 (17.3)	0.40 (1 df)
Maternal APH	67 (1.9)	27 (1.8)	0.74 (1 df)
Maternal height, cm			
Mean (SD)	157.9 (6.1)	158.2 (6.5)	0.06
Paternal Social class n (%)			
I	56 (1.6)	46 (3.0)	
II	226 (6.5)	152 (10.1)	
IIINM	1263 (36.2)	569 (37.6)	
IIIM	705 (20.2)	276 (18.3)	
IV	500 (14.4)	173 (11.4)	
V	573 (16.4)	197 (13.0)	
Other	162 (4.7)	99 (6.6)	
			<0.001(6 df)
Maternal tertiary education n (%)[3]	10 (0.9)	14 (3.1)	0.002 (2 df)

* **p-values** from two sided t-test for continuous variables and X^2 test for categorical variables

[3]**Maternal education** only available for first born mothers (n=1552)

Table 6.9 : **Comparison of the early life characteristics of linked and non-linked G1 females stratified according to vital trace status in 2001 (n=4997)**

G1 Maternal early life Characteristics	Trace status in 2001	Linked to offspring		p-value[+]
		YES Mean (SD)	NO Mean (SD)	
Birthweight (grams)	In Scotland (n=4217)	3261 (478)	3245 (468)	0.35
	Migrated (n=584)	3258 (469)	3292 (480)	0.46
	Other (n=196)	3202 (505)	3234 (487)	0.66
Gestational age (weeks)	In Scotland (n=4217)	39.3 (1.7)	39.2 (1.9)	0.02
	Migrated (n=584)	39.4 (1.5)	39.4 (1.6)	0.69
	Other (n=196)	39.2 (2.3)	39.3 (1.4)	0.67
Fetal growth (SD score)	In Scotland (n=4217)	-0.01 (1.0)	-0.01 (1.0)	0.92
	Migrated (n=584)	-0.05 (1.0)	0.06 (1.0)	0.30
	Other (n=196)	-0.07 (1.0)	-0.08 (1.1)	0.98
Height for age score[1] at 4-6years	In Scotland (n=4090)	-0.02 (1.0)	0.03 (1.0)	0.17
	Migrated (n=545)	0.24 (1.0)	0.13 (0.9)	0.26
	Other (n=187)	-0.13 (1.1)	-0.10 (1.0)	0.87
Weight for age score[1] at 4-6 years	In Scotland (n=4090)	-0.02 (1.0)	0.07 (1.1)	0.02
	Migrated (n=545)	0.12 (1.1)	0.04 (1.0)	0.43
	Other (n=187)	-0.12 (0.9)	-0.02 (1.1)	0.46
BMI at 4-6yrs[1]	In Scotland (n=4090)	16.2 (1.4)	16.3 (1.6)	0.04
	Migrated (n=545)	16.0 (1.3)	16.0 (1.3)	0.96
	Other (n=187)	16.2 (2.0)	16.3 (1.8)	0.67
IQ score at 7 years[2]	In Scotland (n=3963)	107.7 (15.7)	107.2 (17.6)	0.40
	Migrated (n=485)	113.2 (14.6)	112.3 (17.1)	0.58
	Other (n=172)	105.2 (15.6)	104.9 (20.2)	0.91
IQ score at 11 years[2]	In Scotland (n=3963)	104.2 (12.6)	105.1 (13.4)	0.07
	Migrated (n=485)	108.5 (12.3)	109.3 (13.5)	0.57
	Other (n=172)	103.0 (11.3)	105.6 (14.8)	0.21

[+]**p-values** from two sided t-test for continuous variables

[1] **Childhood weight and height** measurements available for n=4822

[2]**Childhood IQ** available for n=4620

Table 6.10 : **Comparison of G0 parental characteristics of linked and non-linked G1 females stratified according to their vital trace status in 2001 (n=4997)**

G0 Parental Characteristics	Trace status in 2001	Linked to offspring		p-value[+]
		YES n=3254	NO n=963	
Maternal Pregnancy Hypertension n(%)	In Scotland (n=4217)	582 (17.9)	156 (16.2)	0.22 (1 df)
	Migrated (n=584)	90 (20.0)	90 (20.2)	0.95 (1 df)
	Other (n=196)	14 (15.4)	16 (15.2)	0.98 (1 df)
Maternal APH n(%)	In Scotland (n=4217)	17 (1.9)	17 (1.8)	0.83 (1 df)
	Migrated (n=584)	4 (2.9)	8 (1.8)	0.44 (1 df)
	Other (n=196)	2 (2.2)	2 (1.9)	0.89 (1 df)
Maternal height, cm Mean (SD)	In Scotland (n=4217)	157.8 (6.2)	158.0 (6.6)	0.33
	Migrated (n=584)	159.0 (6.5)	159.0 (6.0)	0.94
	Other (n=196)	158.0 (6.5)	156.8 (7.4)	0.25
Maternal tertiary education* n(%)	In Scotland (n=1308)	9 (0.9)	7 (2.5)	0.09 (2 df)
	Migrated (n=196)	1 (1.9)	5 (3.5)	0.56 (2 df)
	Other (n=48)	0 (0.0)	2 (8.0)	0.08 (2 df)
Paternal Social class n(%)	In Scotland (n=4217)			
	I	51 (1.6)	21 (2.2)	
	II	209 (6.4)	85 (8.8)	
	IIINM	1176 (36.1)	351 (36.5)	
	IIIM	661 (20.3)	184 (19.1)	
	IV	468 (14.4)	110 (11.4)	
	V	543 (16.7)	141 (14.6)	
	Other	146 (4.5)	71 (7.4)	<0.001(6 df)
	Migrated (n=584)			
	I	5 (3.6)	20 (4.5)	
	II	13 (9.3)	57 (12.8)	
	IIINM	49 (35.0)	182 (41.0)	
	IIIM	27 (19.3)	73 (16.4)	
	IV	22 (15.70	47 (10.6)	
	V	14 (10.0)	44 (9.9)	
	Other	10 (7.1)	21 (4.7)	0.39 (6 df)
	Other (n=196)			
	I	0 (0.0)	5 (4.8)	
	II	4 (4.4)	10 (9.5)	
	IIINM	38 (41.8)	36 (34.3)	
	IIIM	17 (18.7)	19 (18.1)	
	IV	10 (11.0)	16 (15.2)	
	V	16 (17.6)	12 (11.4)	
	Other	6 (6.6)	7 (6.7)	0.18 (6 df)

[+] **p-values** from two sided t-test for continuous variables and X^2 test for categorical variables

* **Maternal education** – only available for first born mothers (n=1552)

Table 6.11 : **Odds of linkage to second generation deliveries according to maternal early life characteristics (n=4997)**

Early life Characteristic	Odds Ratio of Linkage to second generation deliveries (G1)		
	Crude OR (95% CI)	Adjusted for adult trace status in 2001 OR (95% CI)	Final Model[3] Mutually adjusted OR (95% CI)
G1 Birthweight categories			
LBW (<2500g)	1.00	1.00	—
Apt BW (2500-4000g)	0.97 (0.75 , 1.27)	0.99 (0.75 , 1.32)	
HBW (>4000g)	0.88 (0.60 , 1.30)	0.95 (0.62 , 1.45)	
*Test for linear trend**	*p=0.48*	*p=0.79*	
Test for interaction with status		p=0.76	
G1 Gestational age categories			
Preterm (<37 weeks)	1.00	1.00	—
Term (37-41 weeks)	1.20 (0.94 , 1.54)	1.30 (1.00 , 1.69)	
Post term (>41 weeks)	1.20 (0.86 , 1.68)	1.33 (0.92 , 1.91)	
Test for linear trend	*p=0.30*	*p=0.13*	
Test for interaction with status		p=0.04	
G1 Fetal growth fourths			
1	1.00	1.00	—
2	0.82 (0.69 , 0.97)	0.81 (0.68 , 0.98)	
3	0.85 (0.72 , 1.01)	0.87 (0.73 , 1.05)	
4	0.96 (0.81 , 1.13)	0.97 (0.82 , 1.16)	
Test for linear trend	*p=0.69*	*p=0.91*	
Test for interaction with status		p=0.93	
G1 Weight for age at 4-6yrs+ (fourths)			
1	1.00	1.00	—
2	0.92 (0.77 , 1.10)	0.92 (0.76 , 1.12)	
3	0.90 (0.76 , 1.08)	0.89 (0.73 , 1.08)	
4	0.83 (0.70 , 0.99)	0.83 (0.69 , 1.01)	
Test for linear trend	*p=0.04*	*p=0.06*	
Test for interaction with status		p=0.49	
G1 Height for age at 4-6yrs+ (fourths)			
1	1.00	1.00	—
2	0.85 (0.71 , 1.01)	0.89 (0.73 , 1.07)	
3	0.93 (0.78 , 1.11)	0.97 (0.80 , 1.17)	
4	0.78 (0.65 , 0.94)	0.85 (0.70 , 1.03)	
Test for linear trend	*p=0.03*	*p=0.21*	
Test for interaction with status		p=0.18	

G1 BMI at 4-6yrs (fourths) [+]			
1	1.00	1.00	—
2	0.95 (0.79 , 1.14)	0.96 (0.79 , 1.17)	
3	0.99 (0.82 , 1.18)	0.96 (0.79 , 1.16)	
4	0.98 (0.82 , 1.17)	0.91 (0.76 , 1.11)	
Test for linear trend	*p=0.96*	*p=0.37*	
Test for interaction with status		p=0.72	
G1 IQ score at 7 (fourths)			
1	1.00	1.00	
2	1.12 (0.93 , 1.34)	1.24 (1.02 , 1.50)	—
3	1.17 (0.98 , 1.40)	1.31 (1.08 , 1.59)	
4	0.82 (0.69 , 0.97)	1.01 (0.84 , 1.22)	
Test for linear trend	*p=0.03*	*p=0.87*	
Test for interaction with status		p=0.90	
G1 IQ score at 11 (fourths)			
1	1.00	1.00	
2	1.01 (0.84 , 1.22)	1.05 (0.86 , 1.29)	—
3	0.99 (0.82 , 1.20)	1.11 (0.91 , 1.36)	
4	0.69 (0.57 , 0.83)	0.83 (0.57 , 0.83)	
Test for linear trend	*p<0.001*	*p=0.07*	
Test for interaction with status		p=0.86	
G0 Maternal pre-eclampsia			
None	1.00	1.00	
Other hypertension	1.00 (0.84 , 1.19)	1.05 (0.87 , 1.26)	—
Pre-eclampsia	1.24 (0.87 , 1.77)	1.39 (0.94 , 2.01)	
Test for linear trend	*p=0.41*	*p=0.15*	
Test for interaction with status		p=0.67	
G0 Maternal APH (no/yes)	1.08 (0.69 , 1.69)	1.14 (0.69 , 1.86)	—
	p=0.74	*p=0.61*	
G0 Maternal Adult Height (fourths)			
1	1.00	1.00	1.00
2	0.66 (0.55 , 0.79)	0.67 (0.55 , 0.81)	0.71 (0.59 , 0.86)
3	0.78 (0.66 , 0.93)	0.81 (0.67 , 0.97)	0.87 (0.71 , 1.06)
4	0.70 (0.57 , 0.84)	0.78 (0.63 , 0.96)	0.79 (0.63 , 0.99)
Test for linear trend	*p=0.004*	*p=0.11*	*p=0.003*
Test for interaction with status		p=0.36	
G0 Paternal social class			
I (baseline)	1.00	1.00	1.00
II	1.22 (0.79 , 1.89)	1.07 (0.66 , 1.75)	1.19 (0.58 , 1.98)
IIINM	1.82 (1.22 , 2.72)	1.48 (0.95 , 2.32)	1.42 (0.81 , 2.52)
IIIM	2.09 (1.39 , 3.12)	1.62 (1.02 , 2.56)	1.66 (0.93 , 2.97)
IV	2.37 (1.55 , 3.64)	1 87 (1.17 , 3.01)	1.81 (1.00 , 3.28)
V	2.39 (1.57 , 3.64)	1.73 (1.08 , 2.76)	1.60 (0.88 , 2.66)
Other	1.34 (0.85 , 2.14)	1.02 (0.62 , 1.73)	0.96 (0.51 , 1.82)
Test for linear trend	*p<0.001*	*p=0.003*	*p=0.001*
Test for interaction with status		p=0.18	

G0 Maternal Education [++]			
MSLA*	1.00	1.00	
Secondary completed	0.80 (0.58 , 1.09)	0.92 (0.65 , 1.30)	—
Tertiary completed	0.28 (0.12 , 0.63)	0.33 (0.14 , 0.81)	
Test for linear trend	*p=0.003*	*p=0.07*	
Test for interaction with status		p=0.07	

[+] **Childhood height and weight** measures available for 4821 first generation females.

[++]**Maternal education** only available for first born mothers (n=1504).

***MSLA** stands for minimum school leaving age.

****Other** status refers to dead, in prison, hospitalised (long term), in Armed Forces or status unknown in 2001.

Test for linear trend applies to crude OR and OR adjusted for status but the p value in the mutually adjusted analysis is the value for the significance of the variable in the final best model predicting linkage.

[3] **Final model** – only includes ORs for the variables that have a significant effect on reproduction after mutual adjustment for all potential explanatory variables found to be significant in univariate analyses.

Table 6.12 : **Odds of "reproduction" according to maternal early life characteristics restricted to G1 females resident in Scotland in 2001(n=4217)**

Early life Characteristic	Odds Ratio of having reproduced as an adult (G1)	
	Crude OR (95% CI)	Final model[3] OR (95% CI)
G1 Birthweight categories		
LBW (<2500g)	1.00	
Apt BW (2500-4000g)	1.03 (0.75 , 1.40)	—
HBW (>4000g)	1.06 (0.66 , 1.69)	
Test for linear trend	*p=0.83*	
G1 Gestational age categories		
Preterm (<37 weeks)	1.00	
Term (37-41 weeks)	1.45 (1.10 , 1.92)	—
Post term (>41 weeks)	1.40 (0.95 , 2.07)	
Test for linear trend	*p=0.08*	
G1 Fetal growth (fourths)		
1	1.00	
2	0.82 (0.67 , 1.00)	—
3	0.87 (0.71 , 1.07)	
4	0.99 (0.82 , 1.21)	
Test for linear trend	*p=0.93*	
G1 Weight for age at 4-6yrs[1] (fourths)		
1	1.00	—
2	0.93 (0.75 , 1.14)	
3	0.84 (0.68 , 1.03)	
4	0.80 (0.65 , 0.98)	
Test for linear trend	*p=0.02*	
G1 Height for age at 4-6yrs[1] (fourths)		
1	1.00	—
2	0.90 (0.73 , 1.11)	
3	0.99 (0.80 , 1.23)	
4	0.78 (0.63 , 0.97)	
Test for linear trend	*p=0.07*	
G1 BMI at 4-6yrs (fourths)[1]		
1	1.00	
2	0.95 (0.76 , 1.18)	—
3	0.94 (0.75 , 1.16)	
4	0.89 (0.72 , 1.10)	
Test for linear trend	*p=0.40*	
G1 IQ score at 7 (fourths)[1]		
1	1.00	
2	1.28 (1.04 , 1.59)	—
3	1.32 (1.07 , 1.63)	
4	1.01 (0.82 , 1.23)	
Test for linear trend	*p=0.10*	

G1 IQ score at 11 (fourths)		
1	1.00	
2	1.02 (0.83 , 1.27)	—
3	1.11 (0.89 , 1.39)	
4	0.81 (0.66 , 1.00)	
Test for linear trend	*p=0.10*	
G0 Maternal pre-eclampsia		
None	1.00	
Other hypertension	1.10 (0.89 , 1.36)	—
Pre-eclampsia	1.25 (0.81 , 1.94)	
Test for linear trend	*p=0.19*	
G0 Maternal APH (no/yes)	1.06 (0.62 , 1.83)	—
	p=0.82	
G0 Maternal Adult Height		
1	1.00	1.00
2	0.72 (0.58 , 0.88)	0.74 (0.59 , 0.92)
3	0.85 (0.69 , 1.04)	0.88 (0.71 , 1.08)
4	0.76 (0.61 , 0.96)	0.80 (0.62 , 1.02)
Test for linear trend	*p=0.09*	*p=0.04*
G0 Paternal social class		
I (baseline)	1.00	1.00
II	1.01 (0.57 , 1.79)	0.95 (0.46 , 1.94)
IIINM	1.38 (0.82 , 2.33)	1.26 (0.64 , 2.47)
IIIM	1.48 (0.87 , 2.52)	1.42 (0.72 , 2.81)
IV	1.75 (1.01 , 3.03)	1.59 (0.79 , 3.18)
V	1.59 (0.92 , 2.72)	1.38 (0.69 , 2.74)
Other	0.85 (0.47 , 1.51)	0.75 (0.36 , 1.60)
Test for linear trend	*p=0.001***	*p=0.002***
G0 Maternal Education [++]		
MSLA*	1.00	
Secondary completed	0.99 (0.67 , 1.47)	—
Tertiary completed	0.35 (0.13 , 0.94)	
Test for linear trend	*p=0.24*	

[+] **Childhood height and weight** measures available for 4091 first generation females.

[++]**Maternal education** only available for first born mothers (n=1308).

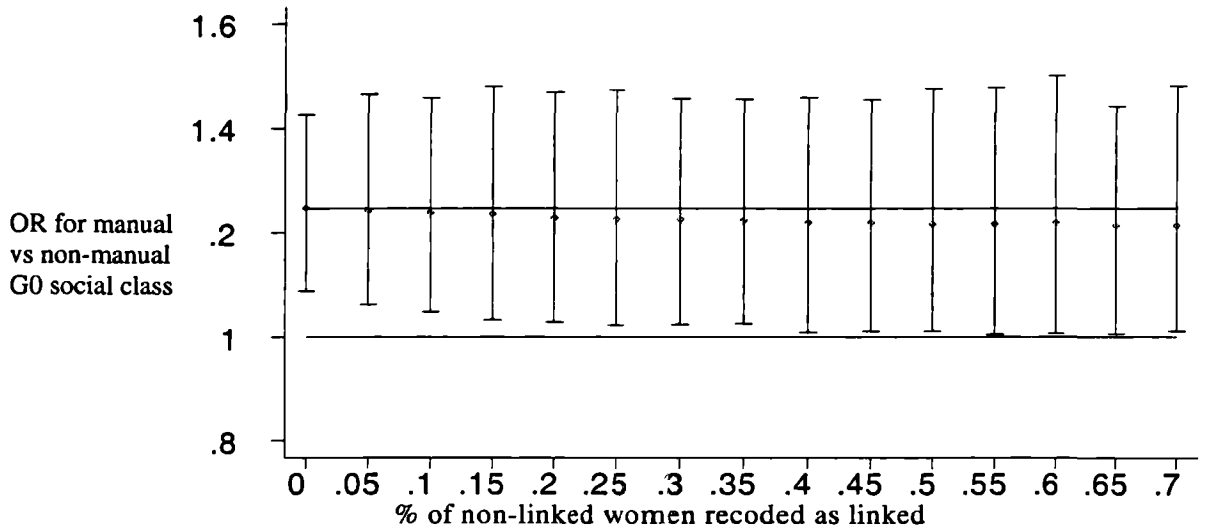
***MSLA** stands for minimum school leaving age.

Test for linear trend applies to crude OR but the p value in the mutually adjusted analysis is the value for the significance of the variable in the final best model predicting linkage for this subset of females.

***Test for trend* excludes other catgory

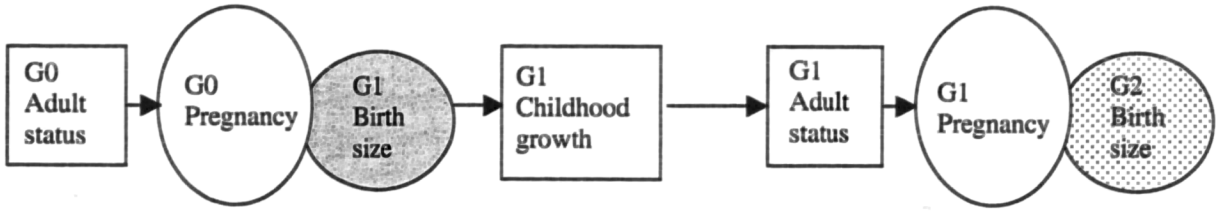
[3] ***Final model*** – only includes ORs for the variables that have a significant effect on reproduction after mutual adjustment for all potential explanatory variables found to be significant in univariate analyses.

Figure 6.1 : **Mean odds ratios (OR) and 95% ranges of uncertainty for the effect of manual versus non-manual G0 paternal social class on G1 female reproduction - estimated using different proportions of reclassification of 444 non-linked emigrated G1 females to linked status**



Chapter 7:

Cross-sectional Measures of Size at Birth of the First (G1) and Second (G2) Generations



The next two chapters explore the within generation measures and determinants of size at birth for each of the two generations in this intergenerational dataset. This chapter specifically examines the distribution of size at birth of the G2 (second generation) infants who are defined entirely because of their relationship to their first generation mothers. There were 7080 such viable*, singleton G2 deliveries linked to the 3485 first generation reproducers. However the description of second generation size at birth excludes stillborn infants and is limited to the 7014 (99.1% of 7080) liveborn infants. Cross-sectional comparisons of G1 and G2 distributions of size at birth measures are made in the body of the text.

7.1 The size at birth of the second generation (G2) offspring

The description of size at birth for the second generation parallels that of the description of the first generation females' size at birth in Chapter 3. The distribution of absolute birthweight is described for the 7014 liveborn second generation infants with complete birthweight information (as for the 5718 first generation females with validated birthweight information in Chapter 3). The gestational age and fetal growth distributions are restricted to the 6954 second generation infants with complete information on gestational age at delivery as well as birthweight (as for the 5210 core first generation females in Chapter 3).

Three first generation (G1) groups are used for the cross-sectional comparisons of absolute birthweight and gestational age at delivery. Firstly all first generation females, regardless of linkage to second generation deliveries, are compared to all females in the second generation.

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* Viable refers to a birthweight of 500grams or more and a gestational age of at least 24 completed weeks at delivery

Secondly the comparison with G2 females is restricted to the 3485 G1 females who were identified as having reproduced by the linkage outlined in Chapter 4. This is a prelude to the intergenerational comparisons in Chapter 9. Thirdly the categorisations of birthweight and gestational age of all male and female G1 infants in the original Child Development Study, with complete perinatal information, are compared to the categorisations for all male and female G2 deliveries. Fetal growth is directly comparable for males and females, so all second generation males and females are compared to all first generation males and females for this measure. For each of the size at birth measures (birthweight, gestational age and fetal growth) the distribution of G2 size will firstly be considered, followed by the cross-sectional comparison with the G1 distribution. These cross-sectional comparisons consider size of singleton live births over two distinct time periods. Many of the comparisons are graphical and absolute frequencies are used throughout so as to maintain the sense of relative size of the comparison groups.

A. Birthweight

Birthweight of second generation (G2) infants was abstracted either from the SMR2 maternity discharge record or the AMND perinatal record. The validation of this birthweight formed an integral part of the construction of the second generation dataset described in *Chapter 4.* To reiterate briefly, birthweight was recorded to the nearest gram in both the record systems and was validated for all records by checking the plausibility of the weight for the given gestational age at delivery and by comparing the recorded birthweight from the two data sources where duplicates were available. The SMR2 and AMND records extract their data from the same original maternity record but the information is coded separately for the two systems, therefore a primary aim of these checks was to detect transcription errors.

i. Distribution of second generation (G2) absolute birthweight

The distribution of the absolute birthweight of all 7014 second generation liveborn singleton, male and female infants was approximately normal with an overall mean of 3312g and a standard deviation of 533g (*Figure 7.1(a)*). Birthweight ranged from 750 to 5305grams for this group of infants. The 3610 male infants were 133grams heavier on average than the 3404 females at birth (mean male birthweight of 3377g (SD=545) versus a female mean of 3244g (SD=510), $p<0.001$ for two-sided t-test). *Table 7.1(b)*

categorises the distribution of absolute birthweight according to the standard clinical categories of extremely low birth weight (less than 1000g), very low birth weight (less than 1500g), low birth weight (less than 2500grams), appropriate birth weight (2500 to 4000grams) and high birth weight (greater than 4000grams). For this group of second generation infants 397/7014 (5.7%) were low birthweight at delivery, 40 (0.6% of all births) were very low birthweight, and 604/7014 (8.6%) weighed more than 4000grams at delivery.

ii. Comparison between first (G1) and second (G2) generation absolute birthweight distributions

The cross-sectional comparison of absolute birthweight across the two generations was limited to females so that comparisons were meaningful given the gender differences in intrauterine growth and subsequent absolute size at birth, both in general and in particular as demonstrated above for this group of second generation infants. Therefore the distribution of absolute birthweight of the 3404 G2 females was compared with all 5718 G1 females with birthweight information, and with the subset of 3485 G1 reproducers identified in Chapter 6 (*Figure 7.1 (b)*). Superimposing the absolute birthweight distributions for these three groups it was clear firstly that the distribution of absolute birthweight for both generations appeared to be quite similar, allowing for the differences in absolute numbers in each group. Further within the first generation the distributions for all 5718 first generation females and the subset of 3485 first generation females identified as mothers were also similar.

The most notable difference between the two generations was in the range of absolute birthweight (*Table 7.1(a)*). This difference was accentuated when the comparison between G2 and G1 was restricted in the first generation to G1 females who later reproduced (n=3485). The minimum birthweight in the G1 reproducers group was 568 grams heavier than the 750g minimum for their 3404 G2 female offspring. At the other extreme of the distribution, maximum birthweight for all three groups was more uniform. The measures of central tendency for the three groups suggested that overall the G2 females tended to be slightly lighter at birth on average than the G1 females (*Table 7.1(a)*). The standard deviation was however slightly greater for the second generation, as might be expected given the greater range of birthweight in this group.

Considering the standard birthweight categories 4/3404 (0.1%) of the liveborn singleton G2 female infants were extremely low birthweight (that is less than 1000

grams at delivery) whereas none of the G1 females were this light at birth (*Figure 7.1(b)*). There was also a greater proportion of G2 females in the high birthweight category than in the first generation, 5.8% of the G2 females had a birthweight of greater than 4000g as compared to 4.5% of all the G1 females *(Figure 7.1(b))*. Therefore there was some variation in the absolute birthweight distributions for the two generations of females, in particular the G2 females tended to be lighter on average at birth but have greater proportions of infants in both extremes of the birthweight distribution.

B. Gestational age at delivery

Gestational age at delivery for the second generation (G2) was measured in completed weeks from the mother's date of her last menstrual period and confirmed by an early ultrasound scan assessment, if this was available. Further it was judged to be certain or uncertain according to the clinical opinion of the obstetrician in charge of each woman's antenatal care. As for absolute birthweight, the details of the validation of gestational age at delivery for the second generation were largely provided in Chapter 4 in the description of the record linkage. Briefly, during the linkage process implausible values of gestational age alone were removed (that is greater than 44 weeks or less than 24 weeks) and gestational age was then checked in relation to birthweight. As for the first generation validation of gestational age in Chapter 3, birth weights were divided into 500g intervals and the gestational age distribution within those groups was examined using the centiles for all Scottish births between 1975 and 1990 as the frame of reference (Maconochie, 1995). Gestational age at delivery was either not available or was judged uncertain for 60 (less than 1%) of the 7014 liveborn infants, therefore analyses were restricted to the 6954 liveborn, singleton second generation infants with complete validated measurements for both birthweight and gestational age at delivery.

i. Distribution of second generation (G2) gestational age

The distribution of gestational age at delivery for the 6954 singleton, liveborn second generation male and female infants was highly skewed to the left with the range of age at delivery being 25 to 43 or more completed weeks of gestation (*Figure 7.2 (a)*). Most deliveries occurred at term (between 37 and 41 weeks gestation) with a median gestational age at delivery of 40.0 weeks. As the distribution of gestational age was highly skewed, the mean was not the best measure of central tendency, however it was

interesting in that it differed according to the sex of the G2 infant. Mean gestational age at delivery for the 3374 G2 females was 39.6 weeks (SD =1.8 weeks) but for male infants it was 39.5 weeks (SD=1.9 weeks). Although this gender difference was of trivial clinical significance it was statistically significant (p=0.02, two-sided t-test for difference of means).

In terms of the clinically relevant gestational age categories there were 381/6954 (5.5%) pre-term deliveries (born at less than 37 completed weeks of gestation) and 378/6954 (5.4%) post-term deliveries (born at greater than 41 weeks gestation) in the second generation (*Table 7.2 (b)*).

ii. Comparison between first (G1) and second (G2) generation gestational age distribution

The comparison of gestational age at delivery for the first and second generations was also limited to females in both generations. While generally accepted that males are heavier on average than females at birth gender is not usually considered to be a predictor of duration of gestation (Macfarlane and Mugford, 2000), although it is a well known predictor of differences in fetal growth rate. Some twin studies have suggested that male-male twins may have a shorter gestation than female-female twin pregnancies, but this was not found to be the case for a large Swedish study of over 3,400 twin pairs (Rydhstrom, 1992). Nonetheless for this group of G2 infants there was a statistically significant gender difference in mean gestational age, with the females tending to be born at slightly later gestations than the males, as described above. There was also evidence that G1 females tended to be born at a slightly later mean gestational age than G1 males. The 5600 first generation males had a mean gestational age at delivery of 39.2 weeks (SD=1.8 weeks) whereas the mean gestational age at delivery of the 5210 first generation females was 39.3 weeks (SD=1.7 weeks), ($p<0.001$ for two-sided t-test for difference of the means). The gender differences were clinically trivial in each case but were statistically significant and consistent in their direction across generations. Therefore for comparability, and consistency with absolute birthweight, further comparison of gestational age at delivery was restricted to the females of both generations (*Figure 7.2(b)*).

The distributions of gestational age at delivery for the three groups of females appeared similar when superimposed on the same axes, taking into account the different absolute numbers of females in each group (*Figure 7.2(b)*), although the second

generation deliveries tended to occur slightly later overall. The distribution of gestational age at delivery for the second generation had a greater range than the first generation with more infants in the far left-hand tail of the distribution (*Table 7.2(a)*). The absolute numbers were small in the lowest gestational age groups (less than 32 weeks) so this difference was difficult to detect graphically. Measures of central tendency tended to be similar, with median gestational age at delivery being 40 weeks for all groups, but the mean gestational age at delivery of G2 females was slightly higher than for the G1 females (*Table 7.2(a)*). Despite the number of liveborn second generation infants born at very low gestational ages and their higher mean gestational age there was however no evidence that there were more second generation infants overall who were either pre-term or post-term (*Table 7.2(b)*). Within the first generation females were slightly less likely to have reproduced if they were born pre-term themselves, (only 5.5% of the G1 reproducers were pre-term as compared to 6.0% of all G1 females).

The G2 distribution of gestational age was curtailed to the right, as was the G1 distribution and maximum gestational age at delivery was the same for both generations. This was probably largely due to the practise of artificially inducing delivery in post-term pregnancies, because of the acknowledged increased risks of prolonged gestation to mother and infant (Fleisher et al., 1985).

C. Fetal growth (SD scores)

Fetal growth measures of birthweight for gestational age were calculated for the second generation to provide a measure of size at birth that was independent of sex and gestational age at delivery. However, the internal standardisation process used to calculate this measure for the first generation (Chapter 3), was not appropriate for the second generation. The first generation represented a cohort of survivors of all births over a six year period in the geographically defined area of Aberdeen, Scotland whereas the second generation births occurred throughout Scotland over a greater than thirty year period and included only a subset of all the viable, liveborn, singleton deliveries during that time.

i. Comparability of the second generation deliveries to all Scottish deliveries between 1975 and 1990

In order to calculate fetal growth measures the distribution of second generation birthweight for gestational age was therefore referred to the distribution of all liveborn, singleton Scottish births between 1975 and 1990 (a total of 877061 births) (Maconochie, 1995). This was considered the most appropriate reference group for these births given the relative period and the geographical location of the deliveries. Although the second generation births occurred over a more extended time period than the reference births, over half of the 23% of births that occurred prior to 1975 were in the immediate two years prior to 1975, and less than 2% of the G2 births occurred after 1990. As mentioned in Chapter 4 the SMR2 system was only felt to be close to 100% complete after 1975, hence the start date for the reference group.

Table 7.3 details the mean birthweight for each week of completed gestational age separately for the 3610 male and the 3404 female liveborn G2 infants. *Table 7.4* shows the same information for all the singleton liveborn Scottish births between 1975 and 1990 calculated using all such births in the SMR2 system. The two distributions are compared graphically in *Figure 7.3(a)*, where it is clear that the mean birthweights were very similar, despite the difference in the absolute number of deliveries, except at gestational ages of less than 32 weeks, where the second generation delivery numbers were particularly small. Further, the relationship between birthweight and gestational age was approximately linear, until the gestations become post-term (greater than 41 completed weeks).

The similarity between the two distributions had two important implications. Firstly this reference population was considered suitable for calculating the fetal growth SD scores for the second generation deliveries. Secondly that whilst the 6954 second generation infants were a proportionally small subset of all the singleton liveborn deliveries that occurred in Scotland over more than a thirty year period, nevertheless they were largely representative of the size at birth of all deliveries over that time, particularly for gestations of greater than 32 weeks (*Figure 7.3(a)*).

ii. Calculating fetal growth (SD scores) for the second generation

Therefore the population of all Scottish singleton liveborn births between 1975 and 1990 was used as the external standard to which the birthweight of each second generation (G2) infant of a given gestational age and sex was referred. Fetal growth

(SD) scores were calculated separately for males and females using the same method as was described in Chapter 2. To test that fetal growth had stayed reasonably constant over the period from 1967 to 1999 the fetal growth scores so calculated were examined to see if there was any consistent trend in mean fetal growth according to G2 year of delivery. There was a crude positive association between mean G2 fetal growth and year of delivery (regression coefficient of 0.03 per year, $p<0.001$ for trend) but this was completely explained by the increases in G1 maternal age and G1 parity at delivery over time (adjusted regression coefficient = -0.01, $p=0.33$).

iii. Distribution of second generation fetal growth

The fetal growth scores for the second generation were normally distributed with a mean SD score of -0.06, a standard deviation of 1.0 and a range of –3.9 to 4.3 (*Figure 7.4(a)*). Hence this second generation had a slightly lower mean size at birth than the whole Scottish population born over the entire birth period (1975 to 1990) but the same standard deviation. From *Figure 7.3(a)* it appears that the second generation deliveries in the very pre-term (<33 weeks gestation) and the post-term (>41 weeks) gestations in particular tended to have reduced mean fetal growth when compared to all 1975 – 1990 Scottish deliveries.

iv. Comparison between the fetal growth of the first (G1) and second (G2) generations

An advantage of using fetal growth as a measure of size at birth is that it allows a direct comparison of growth independent of sex. Therefore, unlike absolute birthweight and gestational age, the fetal growth of males and female infants in both generations were considered together. However for fetal growth SD scores to be directly comparable across generations the same reference population would need to have been used to calculate the fetal SD scores for both generations and this was not the case here. The G1 fetal growth scores were calculated using an internal standardisation process as outlined in Chapter 3 whereas the G2 fetal growth scores were calculated using an external reference population.

The distributions of mean birthweight for each week of gestational age are however directly comparable and are shown in *Figure 7.3(b)*, together with the external reference population of all Scottish births between 1975 and 1990 used for the calculation of the G2 fetal growth SD scores. It is apparent from this figure that the mean birthweight of

the first generation was greater than the second for all gestational ages less than term (i.e. less than 37 completed weeks gestation). Similarly at these early gestations the first generations mean birthweight for each week of gestational age was also consistently higher than the reference population of all the Scottish births.

The distribution of the fetal growth SD scores for the two generations are compared graphically in *Figure 7.4(b).* Allowing for the differences in the absolute numbers and considering that different reference populations were used to calculate the scores in each generation the distributions were nevertheless quite similar. The mean fetal growth of all the G1 female infants (n=5210) was 0 with a standard deviation of 1, as expected after using an internal standardisation process (*Table 7.5(a)).* Similarly the percentage of all G1 infants (n=10810) born either small for gestational age or large for gestational age was approximately 10% in both cases (*Table 7.5(b)).* For the subset of G1 female reproducers (n=3485) the mean and median fetal growth was slightly less than for all the G1 core females (n=5210), but the range and standard deviations were the same (*Table 7.5(a)).* In the second generation mean G2 fetal growth was less than zero for males and females, so that overall they tended to be smaller than all Scottish births. The mean was also less than their G1 mothers, albeit using different reference populations. The standard deviation though was equal to 1.0 (*Table 7.5(a)).* Of note for the intergenerational analyses that follow was that the two different standardisation processes had produced similar distributions of fetal growth scores with the same standard deviation in particular for both generations.

7.2 Summary of the comparison of the size at birth of the first (G1) and second (G2) generation

The differences in the measures of size at birth for the two generations emphasise the fact that these two groups of births are defined by different parameters. These different parameters provide two plausible reasons why the G2 liveborn infants were smaller on average with respect to absolute birthweight and fetal growth than the G1 infants.

The first generation were a group of liveborn infants who had additionally survived infancy to attend a primary school in Aberdeen in 1962 (aged 7-12 years), whereas the second generation were only required to be liveborn at delivery. Given that infants who are lightest and smallest have the highest chance of death in the perinatal and infant periods we might therefore expect that the G2 infants, having not yet had to survive

these periods, might be smaller on average at birth than the G1 infants who had survived to enter primary school (Macfarlane and Mugford, 2000).

Secondly the two generations were born over different time periods, with the second in particular being born during a time of rapid improvement in the ability to artificially support evermore premature and light-for-date infants, especially in the immediate perinatal period. Between 1950 and 1990, stillbirths fell from 40/1000 births to less than 10/1000 in Scotland, with a greater number of very low birthweight infants surviving and being classified as liveborn when previously they would have been classified as stillborn (Macfarlane and Mugford, 2000).

In the light of these changes, there were more liveborn singleton infants in the extremely preterm categories of gestational age (less than 32 weeks) in the second generation than there were in the group of first generation survivors as we might have expected. However the mean gestational age of the second generation is slightly higher than the mean of the first and there are proportionally less females overall in the second generation pre-term category (less than 37 completed weeks), perhaps contrary to expectation. With respect to the higher mean gestational age, the difference in terms of days of gestation amounts to only 1-2 days greater on average (being 0.1-0.2 of a week) for the second generation. This difference could be accounted for by the greater mean maternal height of the G1 mothers of the second generation in comparison to the mean maternal height of G0 mothers of the first generation (159.4cm versus 158.2 cm, $p<0.001$), given that taller women tend to have longer gestations on average. The median gestational age at delivery, which is a more appropriate summary measure for these highly skewed distributions, is nevertheless the same for both generations. The lower mean absolute birthweight coupled with the slightly higher mean gestational age of the second generation does however predict lower mean fetal growth of the second generation overall relative to the first.

The sex differences in mean gestation at delivery were unexpected. They might be explained by a greater mean intrauterine growth rate of male infants and therefore a slightly earlier gestation at delivery because of the limits of maternal capacity. However this is speculative and whether this is a phenomenon that is unique to this cohort requires further investigation. It was however a consistent, statistically significant gender difference found in both generations.

Overall the mean fetal growth of the second generation was lower than for all Scotland births as a whole over approximately the same time period. This may have

been a consequence of the migration out of Scotland of the most socially advantaged G1 females who, if they reproduced, will therefore not have had their birth records captured in the linkage, as discussed in Chapter 6. In general there is a socioeconomic gradient in size at birth, whereby the largest infants tend to be born to the most socially advantaged women. It is therefore likely that these larger infants are under-represented in the second generation in comparison to the total population of Scottish births, which is likely to include the infants of more advantaged women who similarly moved into Scotland before reproductive age but who were not born in Aberdeen and so were not included in the original Child Development Study. The nature of the relationship between size at birth and parental biological and social characteristics for these two generations will be explored further in Chapter 8.

This chapter has compared the distributions of the measures of size at birth for the first and second generations for all males and females as well as specifically for the mothers in the first generation and their offspring. The chapters that follow will concentrate on the latter group, being the intergenerational dataset defined in Chapter 5, with the extent of the intergenerational continuity in size at birth being explored further in Chapter 9. The next chapter will present a cross-sectional comparison of the patterning of size at birth measures according to adult parental characteristics within both generations.

Figure 7.1(a) : **Distribution of absolute birthweight of second generation (G2) liveborn males and females (n=7014)**

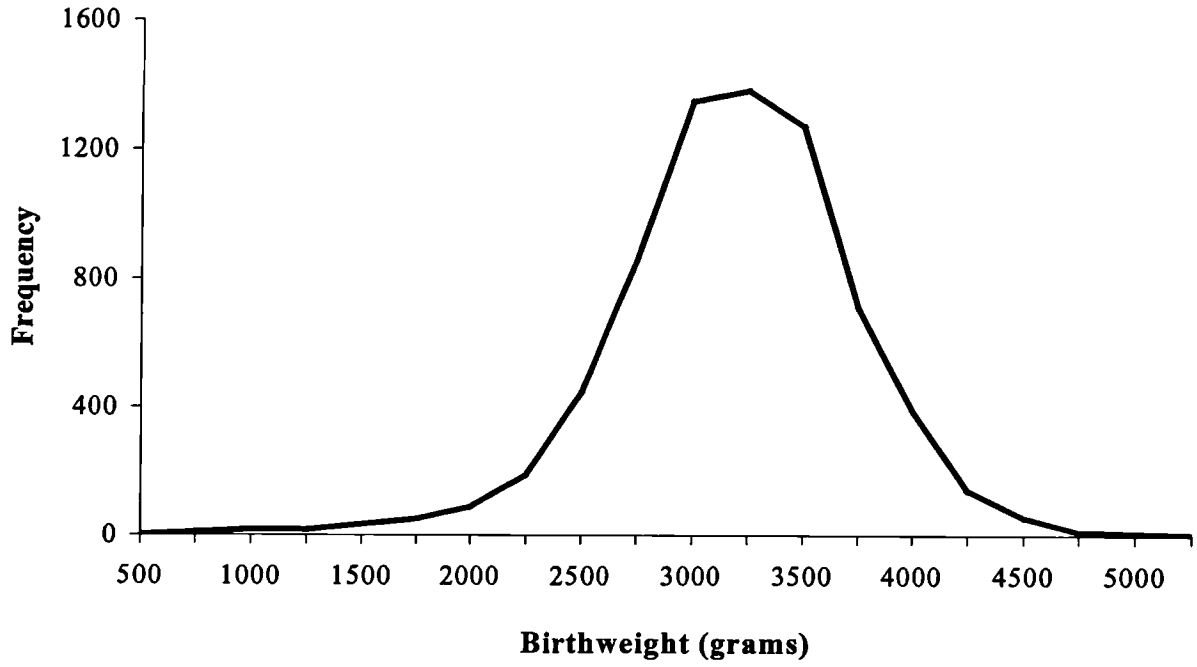


Figure 7.1(b) : **Absolute birthweight distribution for first (G1) and second (G2) generation liveborn females**

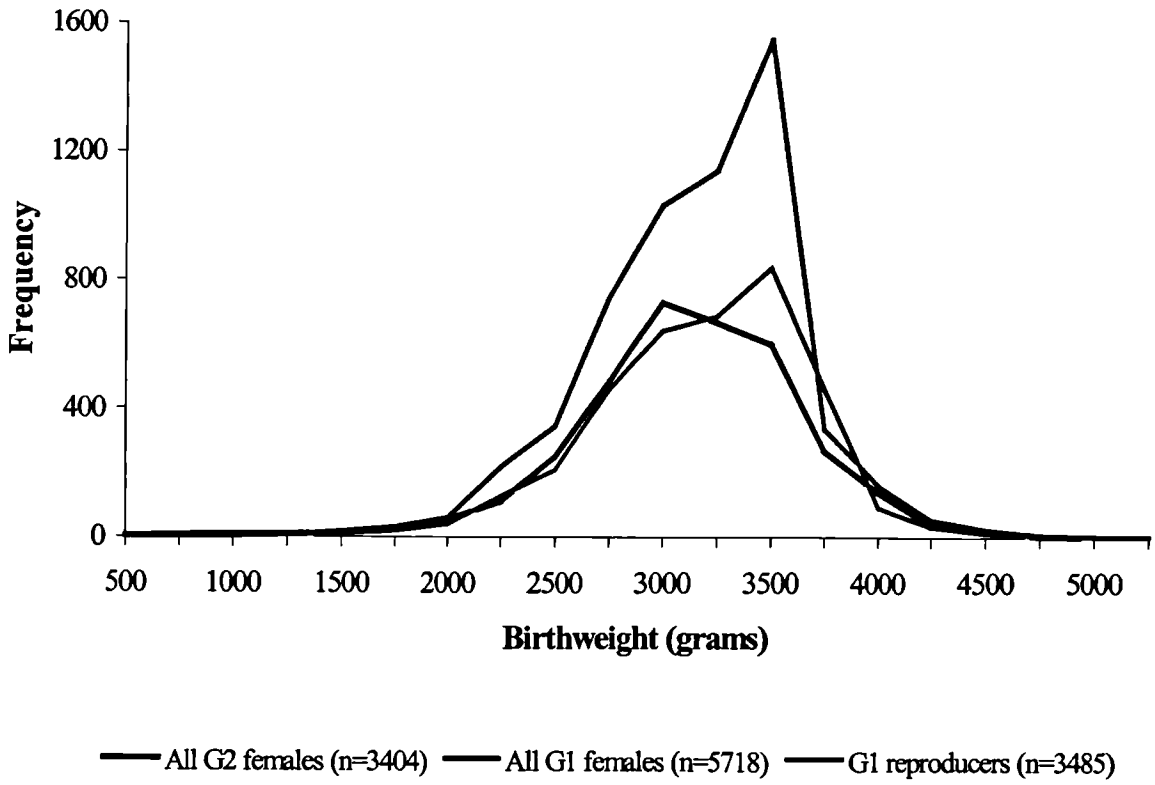


Table 7.1 (a) : **Absolute birthweight parameters for first (G1) and second (G2) generation singleton, liveborn females**

Absolute Birthweight (grams)	All G1 females (n=5718)	G1 reproducers (n=3485)	All G2 females (n=3404)
Minimum	1049	1318	750
Maximum	5557	5557	5305
Mean	3257	3260	3244
Median	3288	3288	3250
Standard deviation	484	479	510

Table 7.1 (b) : **Distribution of absolute birthweight categories for the first (G1) and second (G2) generation singleton, liveborn males (M) and females (F) and females only**

Birthweight category	Frequency (%)				
	G1			G2	
	All M + F	Females only	Reproducers only	All M + F	Females only
ELBW	0 (0.0)	0 (0.0)	0 (0.0)	8 (0.1)	4 (0.1)
VLBW	21 (0.2)	11 (0.2)	5 (0.1)	32 (0.5)	15 (0.4)
LBW	573 (4.8)	323 (5.6)	190 (5.5)	357 (5.1)	202 (5.9)
Appropriate BWT	10501 (88.7)	5129 (89.7)	3150 (90.4)	6013 (85.7)	2985 (87.8)
High BWT	738 (6.3)	255 (4.5)	140 (4.0)	604 (8.6)	198 (5.8)
TOTAL	11833 (100.0)	5718 (100.0)	3485 (100.0)	7014 (100.0)	3404 (100.0)

ELBW = extremely low birth weight (<1000g)
VLBW = very low birth weight (1000g - 1499g)
LBW = low birth weight (1500g - 2499g)
Appropriate BWT = 2500g – 4000g
High BWT = birth weight greater than 4000g

Figure 7.2(a) : **Distribution of gestational age at delivery of second generation (G2) males and females (n=6954)**

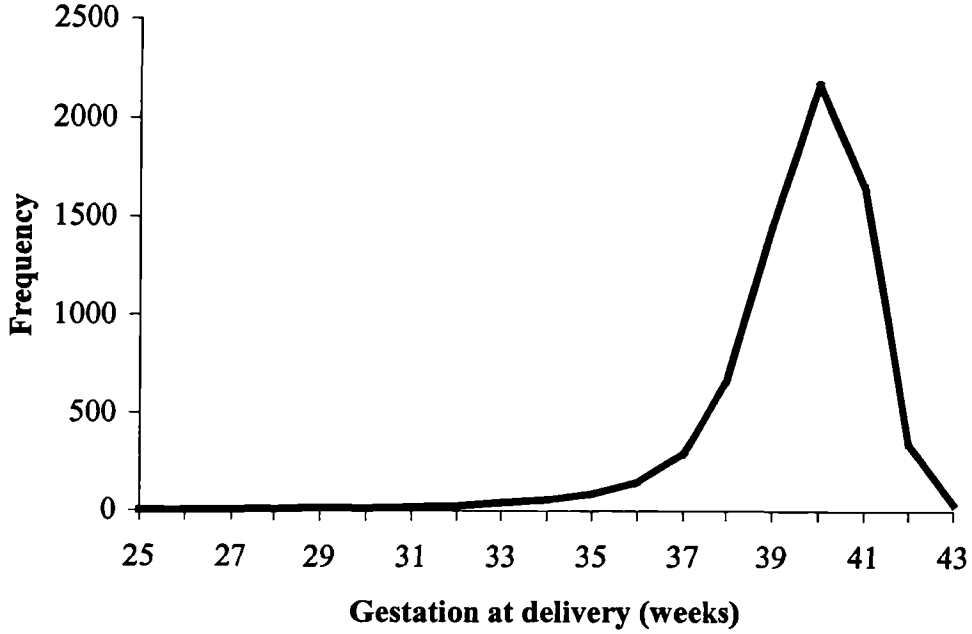


Figure 7.2(b) : **Gestational age at delivery of first (G1) and second (G2) generation females**

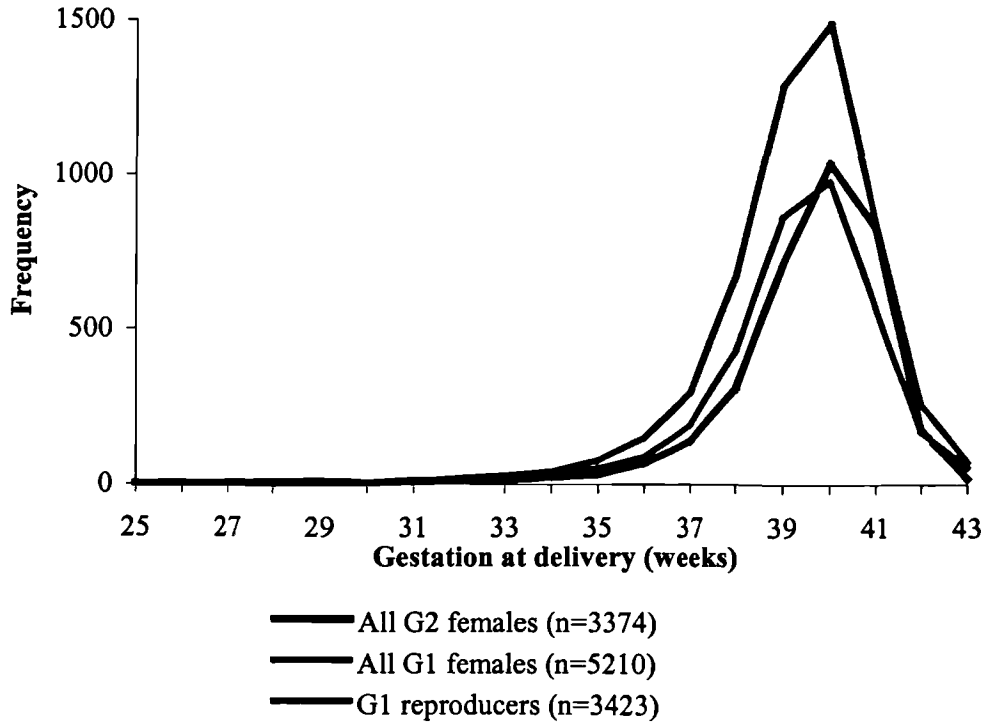


Table 7.2 (a) : **Parameters of gestational age at delivery for first (G1) and second (G2) generation singleton, liveborn females**

Gestational Age (completed weeks)	All G1 females (n=5210)	G1 reproducers (n=3485)	All G2 females (n=3374)
Minimum	28	28	25
Maximum	43	43	43
Mean	39.3	39.4	39.6
Median	40.0	40.0	40.0
Standard deviation	1.7	1.7	1.8

Table 7.2 (b) : **Distribution of gestational age categories for the first (G1) and second (G2) generation singleton, liveborn males (M) and females (F) and females only**

Gestational Age Category	Frequency (%)				
	G1			G2	
	All M + F	Females only	Reproducers only	All M + F	Females only
Preterm (<37 weeks)	692 (6.4)	312 (6.0)	189 (5.5)	381 (5.5)	164 (4.9)
Term (37- 41 weeks)	9407 (87.0)	4569 (87.7)	3013 (88.0)	6195 (89.1)	3014 (89.3)
Post term (>41 weeks)	711 (6.6)	329 (6.3)	221 (6.5)	378 (5.4)	196 (5.8)
TOTAL	10810 (100.0)	5210 (100.0)	3423 (100.0)	6954 (100.0)	3374 (100.0)

Table 7.3 : **Mean and standard deviation of birthweight for each completed week of gestation at delivery for 7014 singleton liveborn G2 second generation infants according to sex**

Gestational Age (in completed weeks)	G2 FEMALES		G2 MALES	
	Frequency	Birthweight Mean (Standard deviation)	Frequency	Birthweight Mean (Standard deviation)
25	0	- (-)	1	790 (-)
26	1	879 (-)	1	945 (-)
27	1	980 (-)	2	1070 (99)
28	5	1038 (211)	3	1117 (58)
29	7	1249 (153)	6	1267 (305)
30	2	1153 (66)	2	1312 (392)
31	10	1851 (548)	6	1762 (439)
32	8	2160 (575)	12	1779 (287)
33	13	2036 (374)	24	1992 (450)
34	21	2158 (563)	29	2465 (518)
35	30	2475 (356)	50	2613 (459)
36	66	2776 (418)	78	2794 (382)
37	138	2880 (464)	149	3007 (472)
38	306	3043 (432)	352	3230 (439)
39	710	3216 (436)	729	3367 (453)
40	1036	3340 (434)	1131	3489 (454)
41	824	3430 (426)	820	3575 (451)
42	177	3398 (438)	165	3582 (439)
43	19	3276 (488)	17	3487 (424)
Gestation uncertain	30	3235 (382)	30	3322 (655)
Total	**3404**	**3244 (510)**	**3610**	**3377 (545)**

Table 7.4 : **Mean and standard deviation birthweight for each completed week of gestation at delivery for all liveborn singleton females and males in Scotland, 1975 – 1990 (Maconochie, 1995)**

Gestational Age (in completed weeks)	FEMALES		MALES	
	Frequency	Birthweight Mean (Standard deviation)	Frequency	Birthweight Mean (Standard deviation)
25	99	881 (417)	136	851 (233)
26	239	916 (332)	300	1000 (239)
27	217	1020 (326)	261	1122 (355)
28	440	1218 (429)	526	1239 (355)
29	416	1304 (341)	518	1381 (429)
30	625	1518 (427)	806	1578 (436)
31	683	1667 (498)	813	1730 (453)
32	1281	1827 (447)	1477	1908 (420)
33	1347	2010 (460)	1738	2110 (445)
34	2584	2203 (430)	3018	2289 (450)
35	3616	2447 (458)	4304	2519 (458)
36	8595	2661 (461)	10161	2750 (471)
37	15962	2891 (464)	18674	2991 (471)
38	44614	3092 (443)	49683	3210 (456)
39	82111	3246 (433)	88387	3376 (448)
40	170928	3363 (435)	176962	3501 (454)
41	76154	3471 (436)	77451	3621 (455)
42	11446	3505 (452)	11551	3659 (468)
43	4112	3499 (460)	4623	3630 (471)
Total	**425551**	**3265 (511)**	**451510**	**3382 (541)**

Figure 7.3(a) : **Mean birthweight for gestational age for all Scottish livebirths (1975 – 1990) and all G2 second generation livebirths (1967-1999)**

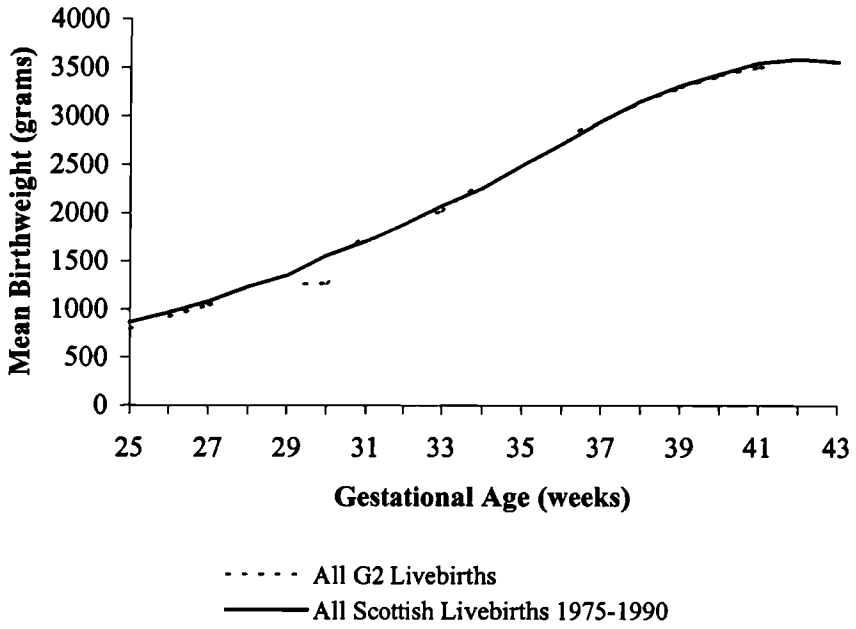


Figure 7.3(b) : **Mean birthweight for gestation age for all Scottish singleton livebirths (1975-1990), all G2 (1967-1999) and all G1 (1950-1955) singleton livebirths**

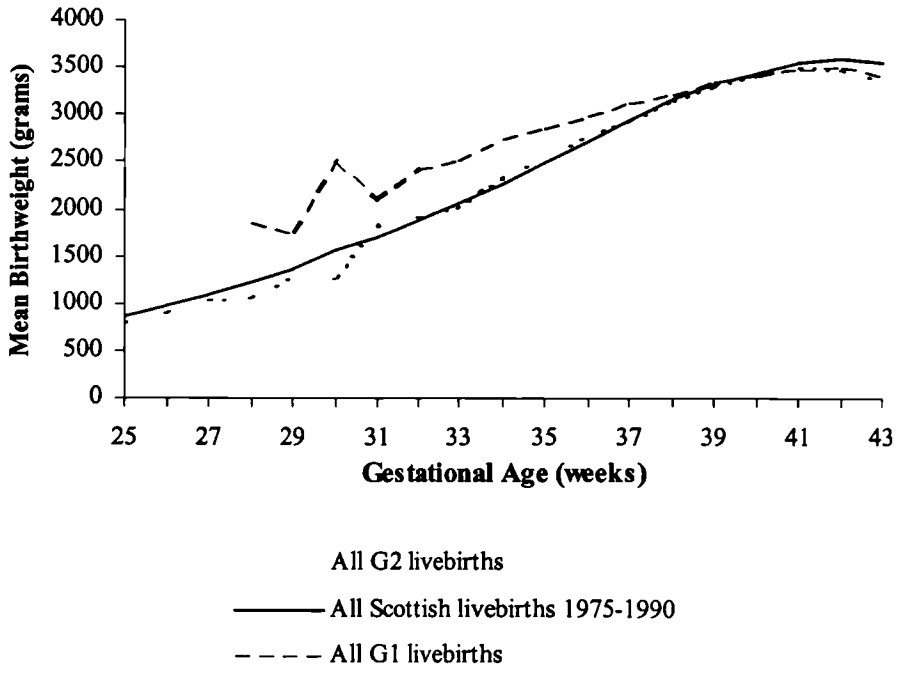


Figure 7.4(a) : **Distribution of second (G2) generation fetal growth (SD score) (n=6954)**

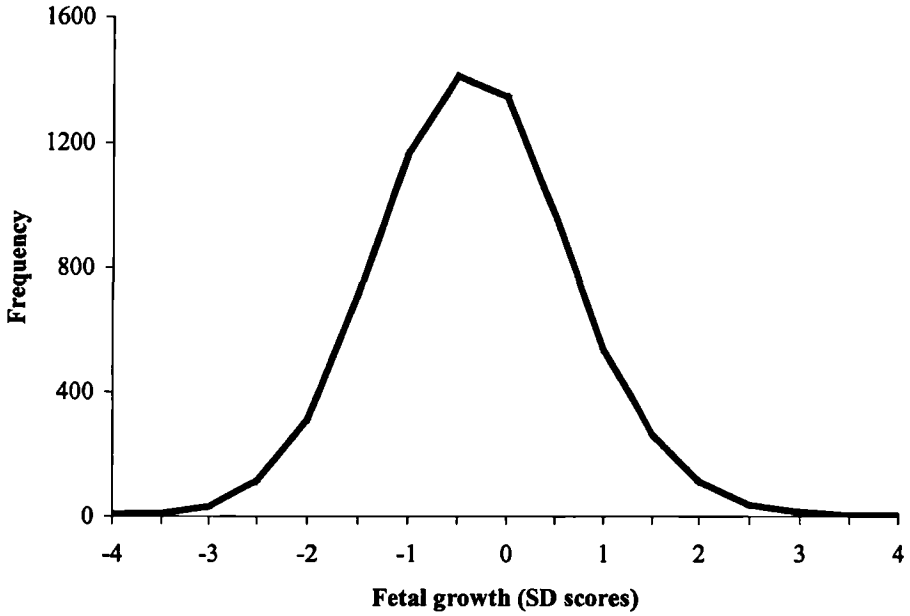


Figure 7.4(b) : **Distribution of fetal growth (SD score) of first (G1) and second (G2) generation**

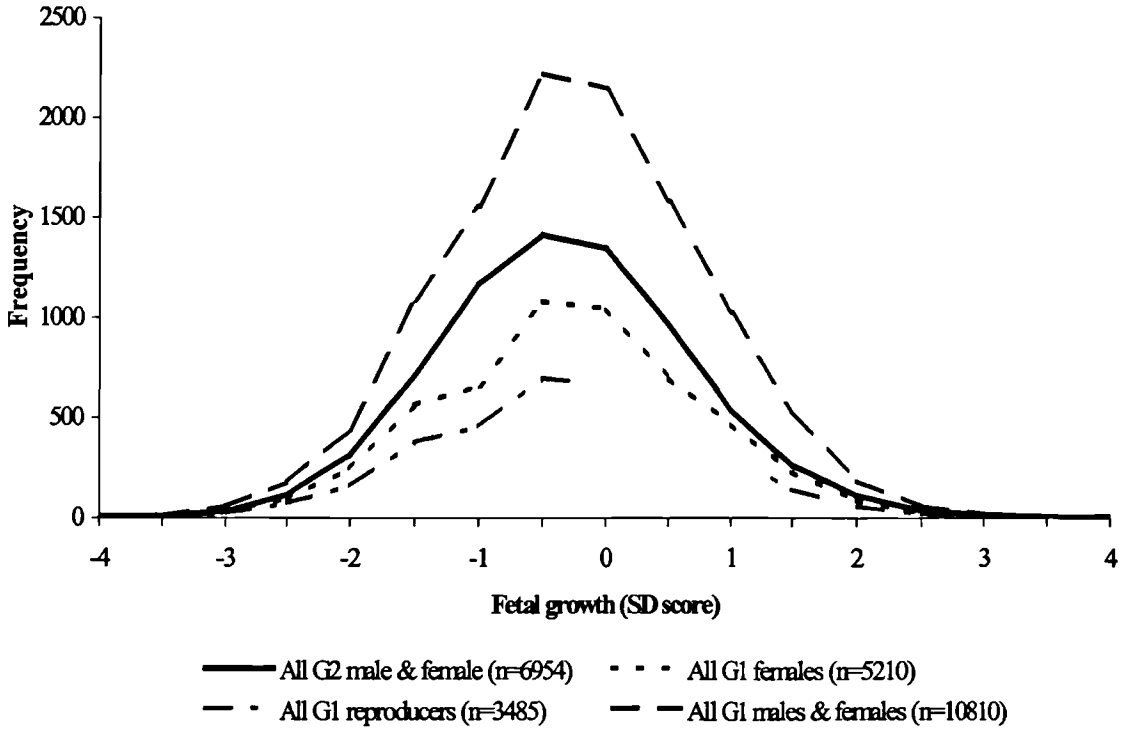


Table 7.5 (a) : **Parameters of fetal growth (SD score) for all first (G1) and second (G2) generation singleton, live births**

Fetal growth (SD score)	All G1 females (n=5210)	G1 reproducers (n=3485)	All G2 males and females (n=6954)	All G2 females (n=3374)
Minimum	-3.8	-3.8	-3.9	-3.7
Maximum	4.4	4.4	4.3	4.2
Mean	0	-0.01	-0.06	-0.07
Median	-0.02	-0.12	-0.08	-0.10
Standard deviation	1.0	1.0	1.0	1.0

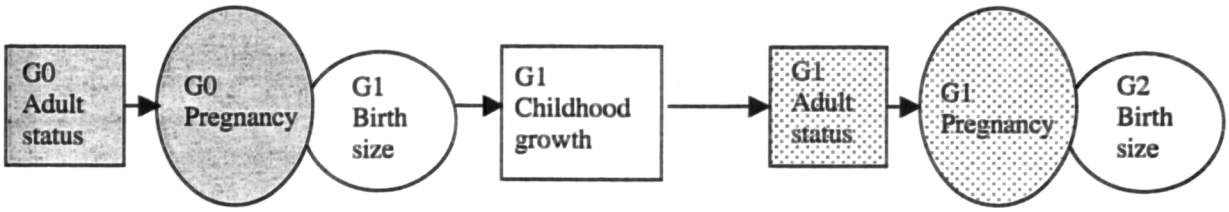
Table 7.5 (b) : **Comparison of fetal growth categories for first (G1) and second (G2) generation singleton, live births**

Fetal growth Category	Frequency n (%)				
	G1			G2	
	All M + F	Core Females only	Reproducers only	All M + F	Females only
SGA (< 10^{th} centile)	1080 (10.0)	465 (8.9)	324 (9.4)	670 (9.6)	340 (10.1)
AGA (10^{th} – 90^{th} centile)	8563 (79.2)	4229 (81.2)	2717 (79.4)	5584 (80.3)	2711 (80.3)
LGA (>90^{th} centile)	1167 (10.8)	516 (9.9)	382 (11.2)	700 (10.1)	323 (9.6)
TOTAL	10810 (100.0)	5210 (100.0)	3423 (100.0)	6954 (100.0)	3374 (100.0)

SGA= small for gestational age
AGA= appropriate for gestational age
LGA= large for gestational age

Chapter 8:

Adult Determinants of Size at Birth for the First (G1) and Second (G2) Generations



Having considered the distributions of measures of size at birth for the second generation (G2) and compared these to the distributions of first generation (G1) measures of size at birth, this chapter considers the associations of adult parental biological and social characteristics with size at birth within both generations. There is an extensive literature on the determinants of size at birth that was overviewed in Chapter 1. For most populations there is a gradient in size at birth according to parental characteristics concurrent with the pregnancy itself. These include a positive gradient with respect to adult maternal height and parity and to a large extent with respect to maternal age, although the relationship is often slightly skewed at high maternal age, and a positive gradient with respect to paternal social class (whereby infants born to fathers in higher social classes tend to be larger on average at birth). Size at birth is also influenced by pregnancy specific maternal diseases, gestational hypertension in particular, and maternal behaviours such as smoking.

The association between these adult parental characteristics and the size at birth of both the first generation mothers (G1) and of their offspring (G2) are considered to check the consistency of patterning in this cohort with the trends described in the perinatal literature. The analyses are restricted to the *intergenerational dataset* described in Chapter 5, that is 3231 first generation mothers (G1) and their 6539 offspring (G2), who have complete parental and perinatal data on the outcome and the main explanatory variables of interest*. Maternal smoking information is only available

* Complete birthweight and gestational age for offspring and maternal age, height, parity, pregnancy hypertension and paternal social class for parents.

for a subset of the G1 females, so is only considered with respect to the second generation (G2) size at birth.

The outcomes of interest in these analyses are mean measures of size at birth for each category of explanatory variable rather than proportions of infants who fall into the clinically significant categories of low birth weight, pre-term delivery or small for gestational age groups.

8.1 Adult patterning of size at birth of the first generation "reproducers" (G1)

As for all the intergenerational analyses the first generation is limited to the females who were linked to the second generation deliveries and for whom all data is available (n=3231). These females are referred to as "reproducers", although in Chapter 6 it was acknowledged that there was almost certainly an unspecified rate of misclassification of non-linked women as non-reproducers. However size at birth measures did not differ significantly between linked and unlinked first generation females and further sensitivity analyses suggested that the maternal early life determinants of reproduction within the group of women who were linked were nevertheless robust to adjustments for possible misclassification.

The mean measures of G1 size at birth are tabulated for the adult G0 parental characteristics of maternal height, age, parity, hypertension in pregnancy and paternal social class for all G1 reproducers. Multivariate regression is used to consider which of these G0 adult parental characteristics are most influential in determining G1 measures of size at birth. For the regression analyses the size at birth outcome is restricted to fetal growth scores.

8.1.1 Distribution of size at birth of G1 according to G0 maternal adult characteristics

The mean and standard deviations of measures of G1 size at birth detailed according to categories of G0 parental characteristics for the 3231 first generation females who were identified as reproducers in adulthood, are shown in *Table 8.1.* Taller, multiparous G0 females tended to have heavier first generation female (G1) infants. Absolute birthweight also tended to increase with G0 maternal age up to 40 years, with a slight fall-off thereafter. Gestational age at delivery was not associated with differences in maternal age or parity but taller mothers tended to have longer gestations *(Table 8.1).* The patterning of fetal growth according to these characteristics was as for absolute

birthweight. Taller G0 mothers tended to have both larger G1 infants and longer gestations. The positive gradient in fetal growth (G2) with increasing maternal adult height (G1) suggested that the increased mean birthweight was due mostly to an increased growth rate in-utero rather than simply to a longer gestation.

8.1.2 Distribution of size at birth of G1 according to G0 pregnancy-specific maternal characteristics

In addition to the maternal adult characteristics of height, age and parity, which are determined as pregnancy begins, there are pregnancy-induced maternal conditions which influence fetal size. The most common of these is hypertension in pregnancy, and pre-eclampsia in particular.

Hypertension in pregnancy was divided into two categories. "Pre-eclampsia" was defined as hypertension occurring after 20 weeks gestation and requiring both a systolic rise in blood pressure to over 140mm Hg on more than one occasion and/or a rise in diastolic blood pressure to over 90mmHg together with significant proteinuria (over 300mg/L in 24 hours)[+]. "Other hypertension" was defined as either pre-existing maternal hypertension or hypertension in pregnancy occurring either before 20 weeks gestation or without proteinuria. Due to possible inconsistencies in the clinical application of the definition over time, women who were classified as having "mild" pre-eclampsia were analysed with the "other hypertension" group and only moderate or severe pre-eclampsia were included in the "pre-eclampsia" category for these analyses.

Moderate to severe pre-eclampsia complicated the pregnancies of 105/3231 (3.3%) of the G0 mothers' pregnancies, with a further 469/3231 (14.5%) G0 pregnancies being complicated by other hypertension. Comparing the rates of pre-eclampsia in G0 mothers of different heights, age at delivery and parity, pre-eclampsia was more common in primiparous (X^2=280 (8 d.f.), p<0.001), younger (X^2=45 (10 d.f.), p<0.001) and shorter (X^2=12 (6d.f.), p=0.05) G0 women. G1 females born to G0 mothers with pre-eclampsia were lighter than those born to mothers with no hypertension and tended to be born at younger gestational ages with reduced fetal growth overall. G1 females born to G0 mothers with "other hypertension" tended to have mean size at birth measures that were

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[+] The definition of pre-eclampsia has been the subject of some debate but is based here on the AMND definition as recommended by Redman and Jefferies (Redman and Jefferies, 1988).

intermediate to the infants born to G0 women with either no hypertension or pre-eclampsia (*Table 8.1*).

8.1.3 Distribution of size at birth of G1 according to G0 parental socioeconomic characteristics

Mean birthweight of first generation (G1) female infants was positively associated with paternal (G0) social class measured at the time of the G1 female's birth. Females born to fathers in Social class V weighed 130grams less on average than those born to fathers in Social class I and 221grams less on average than those born to fathers in Social class II. There was also a statistically significant association between higher paternal social class and longer gestational age but this was probably due to differences in maternal height, as taller mothers tended to have partners in higher social classes. Mean fetal (G1) growth was also positively associated with paternal (G0) social class. Infants born to non-manual fathers had 0.20 SD ($p<0.001$ for mean difference) greater fetal growth on average than those born to fathers in manual occupations. Females born to fathers in the "other" category had the lowest measures of mean size at birth overall (*Table 8.1*). The "other" category for the G0 parents included single mothers and fathers who were disabled or were unemployed and the reduced fetal growth of the infants born in this category suggest that this denotes greater social disadvantage than any employment category. Mean measures of size at birth were also tabulated for markers of maternal socioeconomic status in *Table 8.1*. The gradients in offspring size at birth according to markers of maternal status were very similar to those seen according to paternal status, despite the maternal information being less complete (maternal education was only available for primiparae). In particular G0 mothers who were more highly educated and had a higher premarital social class (according to their occupation) had larger G1 infants on average. G0 women with higher status occupations also tended to have longer gestations, as was seen for paternal social class, no doubt largely because these females tended to be taller in adulthood. G0 paternal social class, measured at the time of the G1 infants birth, was maintained as the marker of the socioeconomic environment for the multivariate analyses as the information was available for all 3231 first generation female reproducers.

8.1.4 Adult parental (G0) determinants of size at birth of first generation (G1) reproducers - multivariate associations

The univariate patterns of association described above are broadly consistent with the trends reported in the perinatal literature. However many of the adult parental variables that are associated with size at birth are not independent.

The G0 maternal adult characteristics, with the exception of hypertension in pregnancy, were strongly socially patterned by current G0 paternal social class (*Figure 8.1 (a)-(c)*). The higher the social class of a woman's partner in adulthood the taller she was likely to be on average and the older she was likely to be when she entered her first pregnancy. Using the total family size information collected in 1962 when she was aged 7-12 years*, her paternal social class also influenced the total number of pregnancies she was likely to have during her reproductive life ($p<0.001$ for all trends with respect to adult paternal social class).

Linear regression was therefore used to mutually adjust for these related parental adult explanatory variables and to quantify the effect of and mutually adjust for the adult G0 influences on G1 size at birth. The outcome measure of size at birth was restricted to fetal growth SD scores, where one standard deviation increase in fetal growth was approximately equivalent to a 600g increase in birthweight, for a G1 infant born at 40 weeks. This comparison is provided throughout this section for familiarity with the meaning of a one standard deviation change in fetal growth score for this generation, but comparisons will not continue to be given throughout.

G0 maternal predictor variables of height, age at delivery and parity were treated as continuous, after checking that a linear relationship was appropriate between each explanatory variable and the main outcome variable, fetal growth. Only for maternal age at delivery was there any evidence of departure from linearity and therefore a quadratic maternal age term was included (*Table 8.2*). Maternal pre-eclampsia was treated as a binary variable (yes/no) with "other hypertension" included with no hypertension. Paternal social class was treated as a categorical variable with five levels, I &II, IIINM, IIIM, IV & V and "Other".

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* Total family size is likely to be an underestimate of total number of G0 pregnancies because it was collected when the G0 women were still reproducing, a more up-to-date estimate is used in Chapter 10 but this information was only available for a subset of the G1 females.

The crude relationships between G0 parental characteristics and measures of G1 size at birth confirm those suggested in the categorical breakdown shown in *Table 8.1,* as each G0 parental variable was univariately significantly associated with G1 fetal growth. In particular lower G0 paternal social class status was associated with decreased G1 fetal growth on average. The decrease was approximately equivalent to a loss of 30 grams at 40 weeks of gestation, for a one level drop in each social class grade from I to V, including IIINM and IIIM, and the "other" category. For each centimetre increase in maternal adult height there was an average 0.04 SD increase in fetal growth, equivalent to approximately 24 grams in birthweight for each centimetre at 40 weeks gestation. Each unit increase in maternal parity lead to a 0.10 SD average increase in fetal growth, approximately 60 grams increase in birthweight at 40 weeks gestation. Maternal age was also related to fetal growth with a smaller effect of a 0.08 SD average increase for every five year increase in G0 maternal age. There was additionally a small but significant negative coefficient for the quadratic age term, reflecting the decline in fetal growth as maternal age increased beyond 34 years, evident in *Table 8.1.* Pre-eclampsia during pregnancy was associated with an average 0.43 SD drop in fetal growth for moderate to severe disease as compared to no or "other hypertension".

In the mutually adjusted model (*Table 8.2*) G0 paternal social class, maternal height, maternal parity and pre-eclampsia in pregnancy remained important determinants of G1 fetal growth, but maternal age was no longer significant. Its effect was probably explained largely by maternal parity with which it was positively correlated ($r=0.49$, $p<0.001$). Of particular note was that the effect of G0 paternal social class on G1 fetal growth was not fully explained by the differences in the adult G0 maternal biological variables, the gradients in the coefficients being diminished but not eliminated in the mutually adjusted model (*Table 8.2*). Smoking status, which is known to be an important independent influence on offspring size at birth, was unavailable for this generation but is considered for the G1 females in their own pregnancies.

8.2 Adult patterning of size at birth of the second generation (G2)

This section considers the size at birth of the second generation (G2) infants according to the G1 adult maternal characteristics of their 3231 first generation mothers and their partners' social class at the time of their delivery. The analyses are restricted to the G1 pregnancies of the 6539 G2 live born infants for whom complete perinatal and parental information was available (*Intergenerational dataset,* Chapter 5).

The G2 generation was necessarily different in the way it was defined from the first generation females described in Section 8.1. The second generation included male and female infants and births were not confined to a particular time period or isolated geographical area. Rather they were defined by the identity of their mothers and the necessity that they were born in Scotland between the years of 1967 and 1999. Further they were not required to survive infancy or reach adulthood and reproduce as the first generation (G1) females must necessarily have to be included in the *Intergenerational dataset*. The distribution of the G2 measures of size at birth in terms of their G1 maternal and paternal characteristics are considered initially, as was the case for the first generation, and in Section 8.3 the distributions of size at birth according to adult characteristics are compared for both generations of infants.

8.2.1 Distribution of size at birth of G2 according to G1 maternal adult characteristics

Mean and standard deviations of measures of size at birth for the 6539 G2 infants according to categorical adult characteristics of their 3231 G1 mothers are tabulated in *Table 8.3*. Older, taller G1 mothers of higher parity had heavier G2 infants on average than younger, shorter women of lower parity. Gestational age at delivery of the second generation infants was less strongly patterned by G1 adult maternal characteristics but tended to be significantly longer in taller mothers and slightly shorter in older, multiparous mothers (*Table 8.3).* Fetal growth increased as maternal height, age and parity increased, with no fall off for mothers over 40 years of age at delivery for this group of G2 infants.

8.2.2 Distribution of size at birth of G2 according to G1 pregnancy-specific maternal characteristics

Information on smoking in pregnancy was available for G1 adult females whose linkage to second generation deliveries was made through the AMND system, but this data was not collected routinely by ISD (SMR2 forms) until after 1996. Therefore information on smoking was available for 3665 (56%) of the 6539 second generation pregnancies. As discussed in Chapter 4 there was no evidence to suggest that the delivery records found in AMND were systematically different from those found in SMR2, once year of delivery was accounted for.

Smoking was categorised in terms of the number of cigarettes a woman smoked per day during pregnancy into: none, less than ten, between ten and twenty, and greater than twenty. *Table 8.3* illustrates the dose-dependent association between G2 size at birth and G1 maternal smoking in pregnancy. Both mean G2 birthweight and fetal growth decreased as the number of cigarettes smoked per day by the G1 mother increased, with length of gestation unaffected. These results are often only reported for smoking as a binary variable (no/yes), but for this subgroup of G1 mothers the smoking information obtained from the AMND obstetric records was more detailed.

Hypertension in pregnancy was categorised in the same way for the G1 mothers as it was for the G0 females: no hypertension, other hypertension or pre-eclampsia. Of the 6539 second generation pregnancies, 182 (2.8%) were complicated by moderate to severe pre-eclampsia and a further 1491 (22.8%) were complicated by "other hypertension"[4]. Pre-eclampsia was more common in primiparous (X^2=271.3 (8d.f.), p<0.001) and younger (X^2=38.4 (10 d.f.), p<0.001) G1 mothers, but there was no clear relationship with height for this generation (X^2=9.0 (6d.f.), p=0.17). Mothers of offspring who smoked during pregnancy were less likely to develop pre-eclampsia (X^2=29.1 (3 d.f.), p<0.001 for trend) with the heaviest smokers having the least risk. G2 infants born to G1 mothers with pre-eclampsia in pregnancy were lighter, born earlier and had reduced fetal growth on average relative to G2 infants born to mothers without pre-eclampsia (*Table 8.3*). Infants born to mothers with "other hypertension" though were similar in size to those born to mothers with no hypertensive problems. In the case of fetal growth the G2 infants in the "other hypertension" category tended to have grown at a faster mean rate in-utero than those born to unaffected pregnancies. This differs from the findings for the G1 infants, where size at birth for "other hypertension" was intermediate to the other two categories and fewer pregnancies were classified in this way. However a recent large study in Canada found that infants born to hypertensive mothers delivered at term did not differ in measures of birthweight for gestational age from those born to mothers who were normotensive throughout pregnancy (Xiong et al., 2002).

[4] Other hypertension refers to either pre-existing hypertension or hypertension in pregnancy before 20 weeks and/or without proteinuria

8.2.3 Distribution of size at birth of G2 according to G1 parental socioeconomic characteristics

Mean G2 size at birth showed a positive association with G1 paternal social class at the time of the infant's birth for the second generation male and female infants. There was a mean birthweight difference of 184 grams between infants born to fathers in Social class I and infants born to fathers in Social class V ($p<0.001$ for mean difference). There was a weak association of paternal social class with length of gestation in this generation, but fetal growth nevertheless increased as social class status increased (*Table 8.3).* The G1 paternal social class "other" category differed from the "other" category for G0 social class. For the G1 parents of the second generation the "other" category referred to being either in the Armed Forces or in an unspecified occupation or having no partner (i.e. single mother). Therefore it was a more diverse category than for the G0 parental generation, and more difficult to rank in terms of relative social disadvantage. The mean G2 size at birth measures for the G1 "other" paternal social class category tend to be similar to the overall G2 mean measures rather than indicative of a more disadvantaged social category, as was the case for the G0 "other" category. Maternal occupational social class codes are missing for almost 50% of the adult first generation (G1) females. Unlike the G0 maternal occupational measures recording of maternal occupation was largely the result of maternal preference for these women (Campbell 2001, *Personal communication*). Nevertheless the mean measures of size at birth according to the maternal social class (G1) showed similar patterns as for paternal social class measures, although overall the G2 size at birth tended to be reduced. This appeared to be because the mean measures for the women missing maternal social class information were greater than the means for the entire second generation. This may have been because a high proportion of women with social class information missing had partners in social classes I & II for whom size at birth was increased on average.

8.2.4 Adult parental (G1) determinants of size at birth of first generation (G2) reproducers – multivariate associations

The patterning of measures of G2 size at birth with respect to adult G1 parental characteristics was also consistent with the trends reported in the perinatal literature. However the maternal and paternal G1 adult characteristics that were associated with G2 size at birth were again not independent. The G1 maternal adult characteristics, with

the exception of hypertension in pregnancy, were socially patterned by current G1 paternal social class (*Figure 8.2 (a)-(d)*). The higher the social class of a woman's partner in adulthood the taller she was likely to be on average and the older she was likely to be when she entered her first pregnancy ($p<0.001$ for both trends with respect to adult paternal social class). The relationship with total number of pregnancies was weaker in this generation than in the earlier G0 generation, but there was still a trend towards a higher number of pregnancies overall for G1 females with partners in lower social classes. In addition for this generation, the percentage of G1 mothers who smoked in pregnancy was socially patterned with G1 females in lower social classes being more likely to smoke than their more advantaged peers (*Figure 8.2(d)*, $X^2=83$ (6 d.f.), $p<0.001$).

Linear regression was used to mutually adjust for these related explanatory variables and to quantify the effect of and mutually adjust for the adult G1 determinants of G2 size at birth. The outcome measure of size at birth was restricted to G2 fetal growth SD scores, where one standard deviation increase in fetal growth was approximately equivalent to a 560 gram increase in birthweight, at 40 weeks gestation for female G2 infants (further estimates in grams will not be given). G1 maternal height, age and parity were treated as continuous, after checking that a linear relationship was appropriate between each explanatory variable and fetal growth. There was no evidence of any departure from linearity for G1 maternal age in this cohort. G1 paternal social class was treated as categorical (with the same groups as for G0 social class) and maternal pre-eclampsia was similarly treated as a binary variable. The analyses were carried out initially for all G2 infants (*Table 8.4*, n=6539) and then restricted to the subset of G2 infants for whom information on G1 maternal smoking was available (*Table 8.5*, n=3665). The crude relationships between G1 parental characteristics and measures of G2 size at birth were very similar for both sets of G2 infants and confirm those suggested for parental categorical characteristics detailed in *Table 8.3*, with each G1 parental variable univariately significantly associated with G2 fetal growth. For all G2 infants there was an average decrease of 0.20 SD in fetal growth per social class difference for infants born to fathers from social class I to social class V. For each centimetre increase in maternal height there was an average 0.04 SD increase in fetal growth and a 0.14 SD average increase in fetal growth per unit of maternal parity. Maternal age was also related to fetal growth with a 0.14 SD average increase in fetal growth score for every five year increase in maternal age. Pregnancy specific

characteristics were important univariately with an average decrease of 0.19 SD in fetal growth for pregnancies complicated by moderate to severe pre-eclampsia, as opposed to no or other hypertension for this generation (*Table 8.4*).

In the mutually adjusted model for all G2 infants all the G1 parental variables remained important determinants of G2 fetal growth, except for maternal pre-eclampsia which just failed to reach statistical significance at the 0.05 level. However the numbers of G1 pregnancies complicated by moderate to severe pre-eclampsia was relatively small (2.8%). There was evidence of confounding for the correlated variables of maternal age and parity but the effect of each remained independently significant. The gradient in G2 fetal growth according to G1 paternal social class was diminished but remained a significant independent determinant of G2 fetal growth (*Table 8.4)* in the mutually adjusted model. The regression analyses were repeated for all G1 pregnancies with information on maternal smoking status (*Table 8.5,* n=3665). The mutually adjusted coefficients of the parental characteristics remained similar for this subset of G2 infants. Increasing rates of G1 maternal smoking in pregnancy were univariately associated with reduced G2 fetal growth and this effect was only slightly diminished after controlling for other parental characteristics. However G1 maternal smoking status did not fully explain the effect of G1 paternal social class in this subset. Despite the fact that maternal smoking status was related to paternal social class, (the Social class I rate was 17% versus 60% rate of maternal smoking in social class V), the association remained significant and G2 infants born to fathers in lower social classes had reduced mean fetal growth after mutual adjustment for all the G1 maternal variables. Including smoking status in the model increased the positive effect of maternal parity and the negative effect of maternal pre-eclampsia so that in the latter case it too reached statistical significance in the fully adjusted model. This is not unexpected as mean fetal growth increases with maternal parity but pre-eclampsia is commonest in primigravidae. Similarly maternal smoking is protective against pre-eclampsia although the mechanism underlying this remains poorly understood (*Table 8.5*).

8.3 Comparison of the distribution of measures of size at birth according to parental characteristics for the first generation reproducers (G1) and the second generation offspring (G2).

The comparison of the distribution of measures of size at birth according to parental characteristics for these two generations must be carried out bearing in mind the

differences in the parameters defining the two generations. To reiterate the 3231 members of the first generation (G1) in this chapter are all core first generation females who were linked to second generation deliveries, as outlined in Chapter 4. Therefore they were survivors to adulthood and they reproduced in Scotland between 1967 and 1999. The first generation females who were linked to deliveries were however not representative of all the first generation females in the original Child Development Study (Chapter 6). Females from less advantaged social backgrounds were more likely to reproduce than women from more advantaged childhood environments. By contrast the 6539 second generation infants were both male and female and were limited only in having to be liveborn. They were entirely defined by the identity of their mothers and their place of birth, and were neither a cross-sectional nor a population-based birth cohort.

Nevertheless in terms of the broad patterning of measures of size at birth with respect to parental characteristics both generations behaved in ways that were consistent with the trends reported in the perinatal literature. However the exact nature of the relationship of size at birth according to parental characteristics differs across generations perhaps as a result of the different parameters that defined the two generations.

8.3.1 Similarities and differences in the association of size at birth with parental characteristics between generations

In both generations taller mothers had longer mean gestations and delivered infants who were heavier on average with greater mean fetal growth. Similarly increasing maternal parity was associated with increasing absolute birthweight and fetal growth, but no significant difference in length of gestation in both generations. Increasing G0 maternal age, especially for mothers aged over 34 years, was associated with a decline in G1 absolute birthweight and fetal growth, but there was no equivalent decline in size at birth with increasing maternal age in G1 mothers. This is not easily explained by other differences in parental characteristics between the generations. The most notable differences in parental characteristics were that more G1 mothers delivered their infants at less than 25 years of age than G0 mothers (46.9% versus 37.6%), and less G1 women delivered infants over the age of 34 years than G0 mothers (5.4% versus 11.1% of all deliveries). G1 mothers tended to be taller on average than G0 mothers (5.1% versus 2.4% over 170cm tall) but were less likely to have partners in non-manual occupations

(33.1% versus 44.8%). However 82.8% of all G2 infants were born to G1 mothers in their first or second recorded pregnancy as compared to 64.2% of G1 infants to G0 mothers. In terms of the relationship of birth size with maternal age, in G1 pregnancies at 35 years or over, 32% of the mothers had partners in social classes I or II, as compared to only 13% of the G0 mothers of the same age. This difference in social advantage is the most likely contributor to the decline in G1 size at birth with respect to G0 maternal age over 34 years.

The rates of "other hypertension" in the pregnancies differed between the generations. In the pregnancies of the G1 mothers the rate was 22.8% compared to 14.5% in the G0 pregnancies, with no parallel change in the rate of moderate to severe pre-eclampsia. This may reflect changes in recognition of hypertension or in the coding of hypertension over time, or it may reflect a real change in incidence. The effect of moderate to severe hypertension was also more apparent in terms of reducing the fetal growth of the G1 infants compared to the G2 infants. This may suggest that the clinical management of the condition has changed over time, perhaps in terms of medication and/or early delivery of infants in cases of severe maternal disease, despite the progression of the disease still being poorly understood.

An alternative explanation for the higher rate of "other hypertension" in G2 pregnancies is that in this intergenerational context it might be due to the different constituency of the two generations. A woman can only be included in the G1 generation if she has successfully carried a viable G2 pregnancy herself, which has not yet been established for the G2 infants born of hypertensive pregnancies. There are indications that the development of hypertension in pregnancy may have a genetic basis which might be linked to other vascular insufficiencies (Irgens et al., 2001). Therefore it is plausible that there may be higher rates of early pregnancy loss and infertility in adult women whose own intrauterine development was affected by gestational hypertension. Hence in this intergenerational comparison we might expect to see a lower percentage of G0 pregnancy hypertension than G1. It remains to be established in the future how many of the G2 infants affected by pregnancy hypertension will be able to successfully reproduce themselves. Chapter 10 will consider the intergenerational determinants of hypertension in pregnancy in more detail.

8.3.2 Socioeconomic inequalities in offspring size at birth in both generations

In both generations size at birth was significantly associated with paternal social class measured at the time of the infants birth. In neither generation were these differences fully explained by socially patterned differences in adult maternal or pregnancy specific characteristics. Infants born to less socially advantaged parents tended to grow less well on average in-utero regardless of the distribution of their maternal characteristics. In other studies adjusting for maternal smoking in pregnancy has largely explained the effect of social class on size at birth (Brooke et al., 1989; Nordstrom and Cnattingius, 1996). However this is not the case for this intergenerational cohort in which a significant gradient remains in the G2 size at birth according to paternal social class after adjustment for G1 graded smoking status (*Table 8.5*). The inequalities in G2 size at birth that are evident with respect to social class measures will be considered further in Chapter 12.

8.4 Summary

Within each generation the patterning of measures of size at birth according to adult parental characteristics were broadly consistent with the trends reported in the perinatal literature. Despite the different parameters that defined the two generations and the secular trends in adult size (Kuh et al., 1991) and in fertility patterns (dos Santos Silva and Beral, 1997) the influence of each parental characteristic has essentially remained stable, both in their univariate and multivariate associations, with size at birth. There have been some differences in the rates of pregnancy complications but the reasons for this can only be speculated upon using this population-level data.

Hence within these two generations the parental adult determinants of offspring size at birth are similar when the two groups of temporally distinct births are compared cross-sectionally. However they are not simply two cross-sectional sets of births but are linked by the G1 mothers who are both the product of the G0 pregnancies and the conduits for the G2 pregnancies. Therefore in order to better understand the origin of the gradients in size at birth with respect to adult characteristics the intergenerational associations and continuities in offspring size at birth and in the adult determinants of size at birth will be considered in Chapters 9 and 10 respectively.

Table 8.1 : **Distribution of G1 size at birth measures according to G0 parental adult characteristics (n=3231)**

Parental Characteristic (G0)	Frequency(%)	G1 Mean (standard deviation)		
		Birthweight (grams)	Gestational Age (weeks)	Fetal growth (SD score)
Total	3231	3260 (480)	39.4 (1.7)	-0.01 (1.0)
Maternal Height categories (cm)				
<150	273 (8.5)	3087 (451)	39.1 (1.8)	-0.35 (1.0)
150-	1656 (51.2)	3221 (474)	39.3 (1.8)	-0.10 (1.0)
160-	1224 (37.9)	3331 (471)	39.4 (1.6)	0.14 (1.0)
170+	78 (2.4)	3568 (513)	39.5 (1.4)	0.64 (1.0)
p-value (for linear trend)		p<0.001	p<0.001	p<0.001
Maternal Age at delivery (completed years)				
<20	128 (4.0)	3152 (467)	39.2 (2.3)	-0.17 (0.9)
20-24	1085 (33.6)	3208 (450)	39.4 (1.8)	-0.13 (0.9)
25-29	1026 (31.8)	3272 (500)	39.4 (1.6)	0.01 (1.1)
30-34	629 (19.4)	3319 (472)	39.2 (1.7)	0.14 (1.0)
35-39	288 (8.9)	3323 (488)	39.4 (1.5)	0.10 (1.0)
40+	75 (2.3)	3276 (551)	39.3 (1.7)	0.02 (1.1)
p-value (for heterogenity)		p<0.001	p=0.46	p<0.001
Maternal Parity				
0	1120 (34.6)	3201 (450)	39.4 (1.7)	-0.15 (0.9)
1	956 (29.6)	3268 (473)	39.3 (1.7)	0.01 (1.0)
2	567 (17.6)	3291 (470)	39.3 (1.7)	0.08 (1.0)
3	300 (9.3)	3293 (543)	39.4 (1.8)	0.08 (1.1)
4+	288 (8.9)	3365 (533)	39.5 (1.7)	0.21 (1.1)
p-value (for linear trend)		p<0.001	p=0.64	p<0.001

Maternal Pregnancy Hypertension				
None	2657 (82.2)	3273 (477)	39.4 (1.7)	0.01 (1.0)
Mild or other	469 (14.5)	3254 (450)	39.3 (1.5)	-0.02 (1.0)
Pre-eclampsia	105 (3.3)	2943 (562)	38.2 (2.4)	-0.40 (1.0)
p-value (for linear trend)		p<0.001	p<0.001	p=0.001
Paternal Social Class at child's birth				
I & II	265 (8.2)	3402 (441)	39.5 (1.4)	0.32 (1.0)
IIINM	1183 (36.6)	3302 (460)	39.4 (1.6)	0.06 (1.0)
IIIM	651 (20.2)	3208 (488)	39.4 (1.8)	-0.13 (1.0)
IV & V	983 (30.4)	3224 (491)	39.3 (1.9)	-0.08 (1.1)
Other*	149 (4.6)	3123 (495)	38.9 (2.0)	-0.17 (1.0)
p-value (for linear trend)		p<0.001	p<0.001	p<0.001
Maternal Education (information only for parity=0)				
Minimum School leaving age	883 (27.3)	3194 (458)	39.4(1.7)	-0.17 (0.9)
Higher Sec school	131 (4.1)	3226 (397)	39.5 (1.6)	-0.13 (0.9)
Higher Education	9 (0.3)	3616 (509)	39.4 (0.7)	0.75 (1.2)
Missing	2208 (68.3)	3286 (489)	39.3 (1.7)	0.06 (1.0)
p-value (for linear trend)		p=0.05	p=0.85	p=0.07
Maternal Premarital Social Class (by occupation)				
I & II	91 (2.8)	3371 (447)	39.5 (1.5)	0.20 (1.0)
IIINM	572 (17.7)	3300 (412)	39.5 (1.5)	0.05 (0.9)
IIIM	1257 (38.9)	3266 (488)	39.4 (1.7)	-0.01 (1.0)
IV & V	1101 (34.1)	3229 (498)	39.3 (1.8)	-0.05 (1.0)
Missing	210 (6.5)	3225 (502)	39.2 (1.7)	-0.06 (1.1)
p-value (for linear trend)		p<0.001	p=0.004	p=0.008

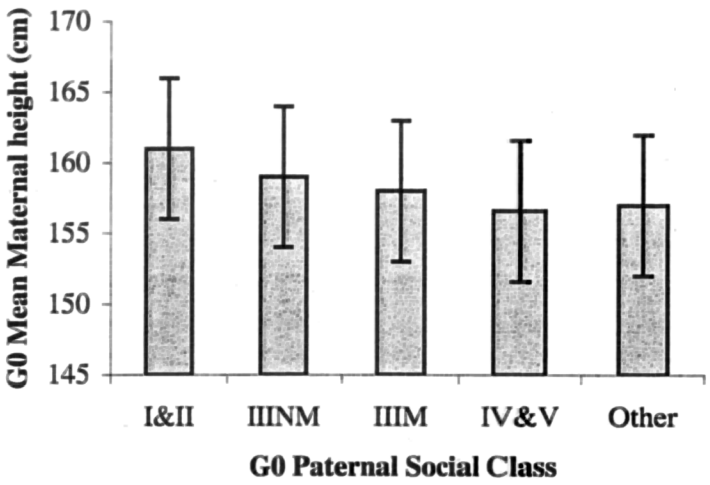
* **"Other" G0 paternal social class** refers to father unemployed, disabled or deceased

p-values – Likelihood ratio test used for test of linear trend, F-test used for test of heterogeneity

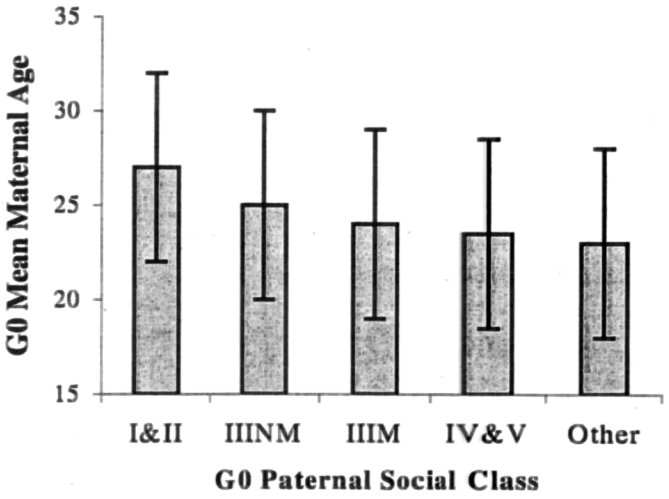
Figure 8.1 (a) – (c) : **Mean G0 adult maternal characteristic according to category of G0 adult paternal social class (n=3231).**

[**Note:** Error bars shown represent plus or minus one standard deviation.]

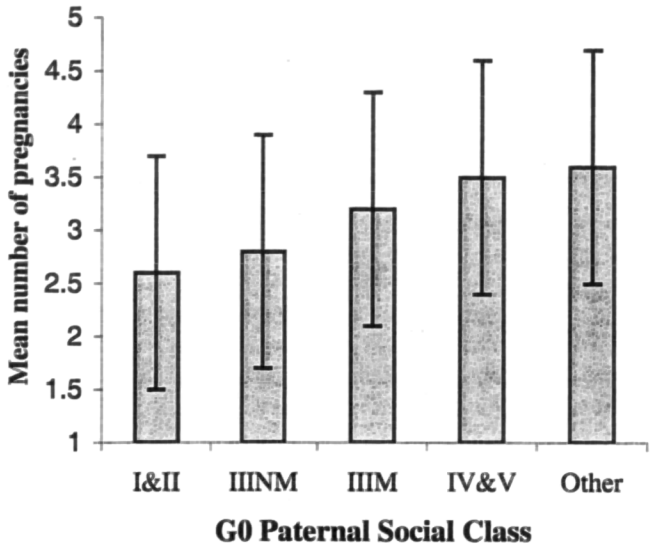
(a) G0 Maternal Adult Height



(b) G0 Age at first pregnancy (years)



*(c) Total number of G0 pregnancies **



*Estimated from **total family size** of G1 mother in 1962 (aged 7 – 12 years)

Table 8.2 : **G0 parental adult determinants of G1 fetal growth (n=3231)**

G0 Parental Characteristic	G1 Fetal growth (SD score) Regression coefficient (95% Confidence Interval)	
	Crude	Mutually Adjusted
Paternal Social Class		
I&II (reference)	0.0	0.0
IIINM	-0.21 (-0.34 , -0.08)	-0.13 (-0.26 , -0.01)
IIIM	-0.39 (-0.54 , -0.25)	-0.30 (-0.44 , -0.16)
IV&V	-0.33 (-0.47 , -0.20)	-0.25 (-0.38 , -0.11)
Other	-0.48 (-0.68 , -0.28)	-0.36 (-0.57 , -0.17)
p-value (linear trend)	p<0.001	p<0.001
Maternal Height (per cm)	0.04 (0.03 , 0.04) **	0.04 (0.03 , 0.04) ***
Maternal Age (per 5 years)	0.08 (0.05 , 0.12) ***	0.01 (-0.02 , 0.05) NS
Maternal Age^2 (quadratic term)	-0.0006 (-0.002 , -0.0001) *	-0.001 (-0.002 , 0.0003) NS
Maternal Parity (per birth)	0.10 (0.06 , 0.11) ***	0.09 (0.06 , 0.12) ***
Maternal Pre-eclampsia$^+$	-0.43 (-0.63 , -0.24) ***	-0.31 (-0.50 , -0.12) **

$^+$ Treated as a binary variable – none and "other" hypertension treated as no pre-eclampsia

*** Significant at p<0.05 level**

**** Significant at p<0.01 level**

***** Significant at p<0.001 level**

NS = not significant

Table 8.3 : **Distribution of G2 size at birth measures according to G1 parental adult characteristics (n=6539)**

Parental Characteristic (G1)	Frequency(%)	G2 Mean (standard deviation)		
		Birthweight (grams)	Gestational Age (weeks)	Fetal growth (SD score)
Total	6539 (100.0)	3310 (531)	39.5 (1.8)	-0.06 (1.0)
Maternal Height categories (cm)				
<150	289 (4.4)	3027 (527)	38.9 (2.3)	-0.47 (0.9)
150-	2985 (45.7)	3230 (511)	39.5 (1.8)	-0.23 (1.0)
160-	2929 (44.8)	3397 (528)	39.6 (1.8)	0.11 (1.0)
170+	336 (5.1)	3509 (520)	39.5 (1.8)	0.37 (1.0)
p-value (for linear trend)		p<0.001	p=0.001	p<0.001
Maternal Age at delivery (years)				
<20	732 (11.2)	3178 (545)	39.4 (2.3)	-0.24 (1.0)
20-24	2336 (35.7)	3282 (502)	39.6 (1.7)	-0.16 (1.0)
25-29	2150 (32.9)	3324 (528)	39.5 (1.7)	-0.04 (1.0)
30-34	969 (14.8)	3399 (551)	39.4 (1.8)	0.15 (1.0)
35-39	305 (4.7)	3450 (566)	39.3 (1.8)	0.31 (1.0)
40+	47 (0.7)	3408 (617)	38.9 (1.7)	0.34 (1.1)
p-value (for linear trend)		p<0.001	p=0.05	p<0.001
Maternal Parity				
0	2887 (44.1)	3230 (532)	39.4 (2.0)	-0.20 (1.0)
1	2528 (38.7)	3371 (517)	39.6 (1.7)	0.04 (1.0)
2	868 (13.3)	3370 (526)	39.5 (1.7)	0.06 (1.0)
3	188 (2.9)	3410 (512)	39.3 (1.5)	0.17 (1.1)
4+	68 (1.0)	3474 (644)	39.2 (1.7)	0.40 (1.3)
p-value (linear trend)		p=0.006	p=0.46	p<0.001

Maternal Pregnancy Hypertension				
None	4866 (74.4)	3312 (531)	39.5 (1.8)	-0.06 (1.0)
Mild or other	1491 (22.8)	3334 (509)	39.5 (1.7)	-0.03 (1.0)
Pre-eclampsia	182 (2.8)	3086 (651)	38.7 (2.3)	-0.24 (1.0)
p-value (heterogeneity)		p=0.26	p=0.04	p=0.14
Maternal Smoking in Pregnancy (number of cigarettes per day)				
None	2275 (34.8)	3396 (522)	39.5 (1.8)	0.12 (1.0)
<10	401 (6.1)	3246 (500)	39.5 (1.9)	-0.19 (0.9)
10-20	797 (12.2)	3180 (539)	39.5 (2.0)	-0.34 (1.0)
>20	192 (2.9)	3103 (532)	39.5 (1.9)	-0.51 (1.0)
Unknown	2874 (44.0)	3302 (527)	39.5 (1.8)	-0.07 (1.0)
p-value (linear trend) +		p<0.001	p=0.80	p<0.001
Paternal Social Class at child's birth				
I&II	1468 (22.4)	3392 (532)	39.5 (1.7)	0.11 (1.0)
IIINM	699 (10.7)	3378 (503)	39.7 (1.6)	0.02 (0.9)
IIIM	2249 (34.4)	3304 (518)	39.5 (1.8)	-0.08 (1.0)
IV&V	1613 (24.7)	3216 (543)	39.4 (2.0)	-0.22 (1.0)
Other*	510 (7.8)	3310 (534)	39.4 (1.7)	-0.03 (1.0)
p-value (linear trend)		p<0.001	p=0.02	p<0.001
Maternal Premarital Social Class (by occupation)				
I&II	737 (11.3)	3337 (549)	39.4 (1.8)	0.03 (1.0)
IIINM	1628 (24.9)	3278 (515)	39.5 (1.9)	-0.12 (0.9)
IIIM	314 (4.8)	3266 (566)	39.4 (2.0)	-0.11 (1.0)
IV&V	732 (11.2)	3225 (518)	39.4 (1.9)	-0.22 (1.0)
Missing	3128 (47.8)	3367 (522)	39.5 (1.7)	0.04 (1.0)
p-value (linear trend)		p<0.001	p=0.33	p=0.007

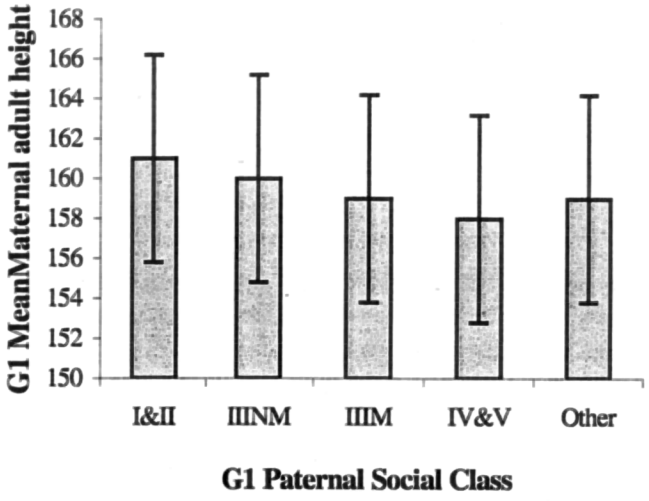
* **Other paternal social class (G1)** refers to social class not specified or father in Armed Forces (not classified in occupational social class) or single mother

+ **Test for trend** restricted to n=3665 with smoking information (excludes unknown)

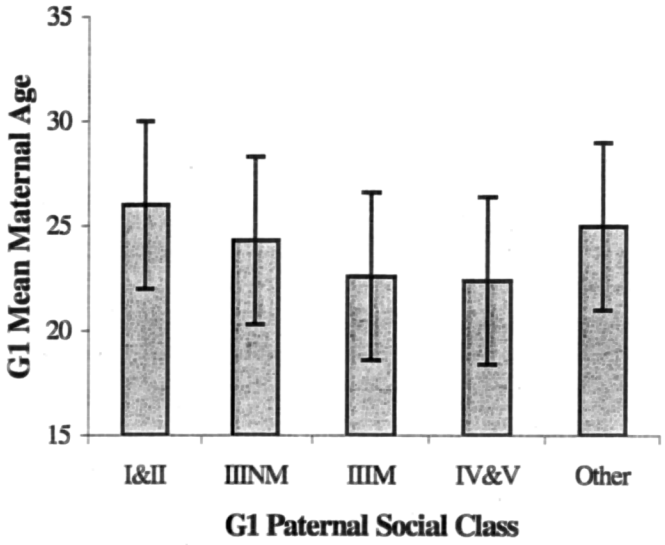
Figure 8.2 (a) – (d) : **Mean G1 adult maternal characteristics according to category of G1 adult paternal social class (n=3231)**

[**Note:** Error bars shown represent plus or minus one standard deviation.]

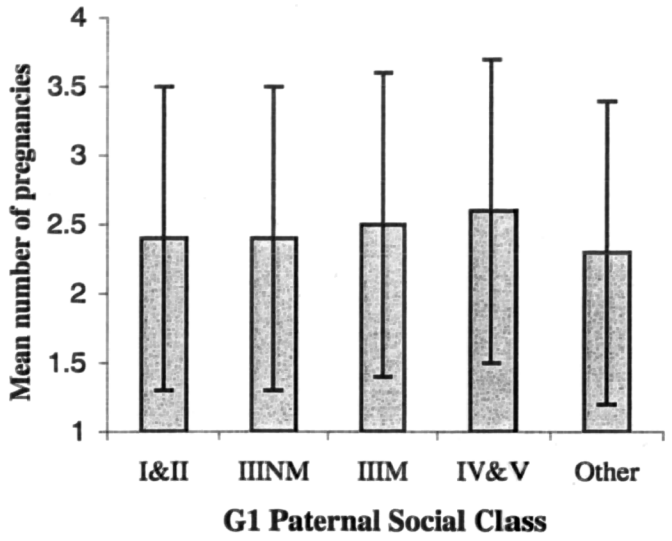
(a) G1 Maternal Adult Height (cms)



(b) G1 Age at first pregnancy (years)



(c) Total number of G2 pregnancies



(d) Percentage of G1 smokers in pregnancy (available for 3665 G2 pregnancies)

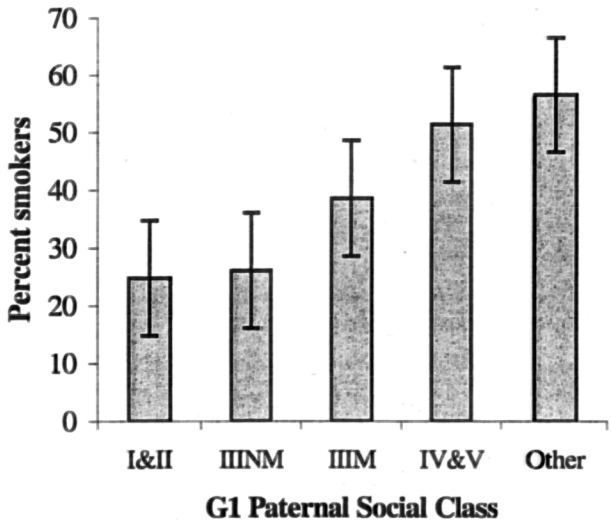


Table 8.4 : **G1 adult determinants of G2 offspring fetal growth (n= 6539)**

G1 Parental Characteristic	G2 Fetal growth (SD score) Regression coefficient (95% Confidence Interval)	
	Crude	**Mutually Adjusted**
Paternal Social Class		
I&II (reference)	0.0	0.0
IIINM	-0.09 (-0.17 , 0.00)	-0.04 (-0.12 , 0.04)
IIIM	-0.19 (-0.25 , -0.12)	-0.08 (-0.14 , -0.02)
IV&V	-0.33 (-0.40 , -0.26)	-0.21 (-0.28 , -0.14)
Other	-0.14 (-0.23 , -0.04)	-0.13 (-0.22 , -0.03)
p-value (linear trend)	p<0.001	p<0.001
Maternal Height (per cm)	0.04 (0.03 , 0.04) ***	0.04 (0.03 , 0.04) ***
Maternal Age (per 5 years)	0.14 (0.11 , 0.16) ***	0.05 (0.03 , 0.08) ***
Maternal Parity (per birth)	0.14 (0.12 , 0.17) ***	0.12 (0.09 , 0.15) ***
Maternal Pre-eclampsia⁺	-0.19 (-0.33 , -0.04) *	-0.09 (-0.23 , 0.04) NS

⁺**Treated as a binary variable** – none and "other" hypertension classified as no pre-eclampsia

*** Significant at p<0.05 level**

**** Significant at p<0.01 level**

***** Significant at p<0.001 level**

NS = not significant

Table 8.5 : **G1 adult determinants of G2 offspring fetal growth restricted to G1 mothers with smoking information (n= 3665)**

G1 Parental Characteristic	G2 Fetal growth (SD score) Regression coefficient (95% Confidence Interval)	
	Crude	Mutually Adjusted
Paternal Social Class		
I&II (reference)	0.0	0.0
IIINM	-0.08 (-0.20 , 0.04)	-0.03 (-0.14 , 0.08)
IIIM	-0.20 (-0.28 , -0.11)	-0.06 (-0.15 , 0.02)
IV&V	-0.36 (-0.46 , -0.27)	-0.16 (-0.25 , 0.05)
Other	-0.14 (-0.30 , 0.03)	-0.03 (-0.18 , 0.13)
p-value (linear trend)	p<0.001	p=0.006
Maternal Height (per cm)	0.04 (0.03 , 0.04) ***	0.04 (0.03 , 0.04) ***
Maternal Age (per 5 years)	0.15 (0.12 , 0.18) ***	0.03 (0.00 , 0.07) *
Maternal Parity (per birth)	0.16 (0.12 , 0.19) ***	0.14 (0.11 , 0.18) ***
Maternal Pre-eclampsia[+]	-0.22 (-0.38 , -0.06) **	-0.15 (-0.30 , 0.00) *
Maternal smoking in pregnancy		
None (reference)	0.0	0.0
<10/day	-0.31 (-0.41 , -0.21)	-0.27 (-0.37 , -0.18)
10-20 per day	-0.46 (-0.54 , -0.38)	-0.42 (-0.49 , -0.34)
20+ per day	-0.63 (-0.77 , -0.49)	-0.54 (-0.68 , -0.41)
p-value (linear trend)	p<0.001	p<0.001

[+] **Treated as a binary variable** – none and "other" hypertension classified as no pre-eclampsia

*** Significant at p<0.05 level**

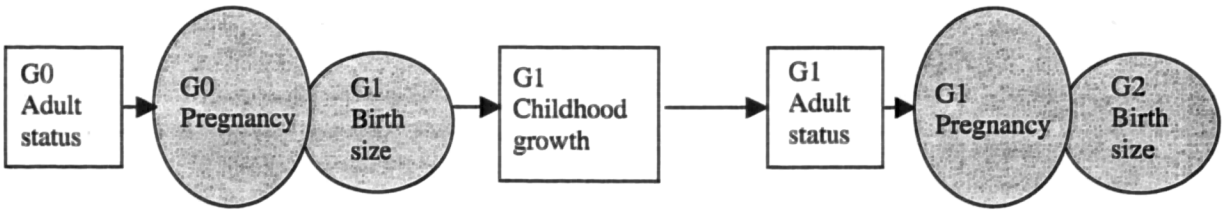
**** Significant at p<0.01 level**

***** Significant at p<0.001 level**

NS = not significant

Chapter 9:

Intergenerational Associations and Continuities in Measures of Size at Birth



It is evident that within each generation in this intergenerational cohort an infant's size at birth is influenced by parental adult social and biological characteristics. In addition to these adult predictors of size at birth studies have also consistently demonstrated a positive association between maternal size at birth and her offspring's size at birth (*Table 1.1*). The next two chapters therefore explore the extent of the continuity and association in the measures and determinants of size at birth across the two generations. Studies considering intergenerational continuity in size at birth across generations have rarely included complete, reliable information on the full range of gestational age at delivery in addition to birthweight for large numbers of births in two generations. The Aberdeen cohort includes all these data collected from perinatal records for a population-based intergenerational cohort together with extensive parental information. This chapter therefore examines the intergenerational continuities in measures of size at birth of the Aberdeen G1 mothers and their Scottish-born G2 offspring.

9.1 Suitability of the Aberdeen intergenerational cohort for considering continuity in size at birth across generations

This intergenerational cohort has significant advantages over other studies which have previously considered and quantified intergenerational associations in measures of size at birth (*Table 1.1*). The first generation mothers (G1) were a subset of a population-based group of all live survivors to primary school age in Aberdeen, Scotland born between 1950 and 1955 for whom detailed perinatal and parental information was retrieved from their obstetric records at the time of the original Aberdeen Child Development Study. This was a high quality data collection with low rates of missing data and clinically validated perinatal measures. Record linkage was used to obtain second generation perinatal data using the SMR2 and AMND record systems for births throughout Scotland. This record linkage was not dependent on first

generation interview or questionnaire response and was more complete than many other studies of this kind, despite the loss of some G1 women due to migration out of Scotland (described in Chapter 6). The first generation (G1) Aberdeen women were aged 46-51 years of age when the SMR2 and AMND linkages were undertaken, using record systems that were established in 1969 and 1967 respectively. It follows that all second generation (G2) Scottish deliveries were potentially able to be captured, rather than restricting to either the first-born or most recent delivery in the second generation or collecting the second generation data when potential mothers were in their early thirties. The AMND records included G0 and G1 parental social information as well as biological data for the G1 and G2 deliveries. Importantly measures of birthweight and gestational age were abstracted from obstetric records for both generations, rather than being obtained through later recall. Gestational age was available for the normal population range for both generations, rather than being limited either to term deliveries or stored as a categorical variable which would have restricted analyses to at risk groups (e.g. low birthweight (LBW) or pre-term infants).

The cohort does however share some of the limitations of other intergenerational studies. In Chapter 6 it was acknowledged that the description of second generation deliveries to all the first generation reproducers is nevertheless incomplete, largely because of migration out of Scotland. However this was not because of incomplete questionnaire response which tends to exclude the most disadvantaged women (Hennessy and Alberman, 1998a). The G1 mothers were from a geographically isolated population, which might be a limitation in terms of generalisability of results, particularly if G1 Aberdeen women were different in terms of maternal and perinatal characteristics than other women in the United Kingdom in particular. Chapter 6 comparisons were however reassuring in terms of G1 measures of size at birth and childhood size. In that case the geographical isolation could be seen as advantageous in considering the determinants of offspring size at birth. If G1 women were exposed to similar environmental conditions and societal norms during their childhood and early adult life these external factors should not have contributed to differential pregnancy outcomes, which may not be the case for geographically diverse populations. Another possible limitation is that information is only available for G1 anthropometric measures and not G1 paternal measures in childhood and adult life. Whilst it is acknowledged that the maternal characteristics have a stronger influence that paternal (Little, 1987), an analysis with both parental characteristics might have been informative.

Therefore, overall and in comparison to previous intergenerational studies, this intergenerational dataset is in a position of considerable strength to examine the intergenerational associations and continuities in G1 and G2 offspring fetal growth.

9.2 Continuity in size at birth across generations

The investigation of continuity in size at birth across generations is restricted to the 3231 first generation female reproducers (G1) and their 6539 second generation offspring (G2), as for Chapter 8. Intergenerational correlations in the measures of size and maturity at birth are examined for this intergenerational cohort, and linear regression is used to consider the influence of G1 maternal measures of size at birth on G2 infant size at birth after adjusting for adult G1 parental determinants of infant size. Percent frequencies are used in graphical comparisons to compare the relative proportions of infants in each strata of size at birth measure.

A. Birthweight

There was a positive association between G1 maternal and G2 offspring absolute birth weight. This relationship existed for the entire range of birthweight and was not restricted to extremes of the distribution. This was demonstrated by the proportion of G2 offspring in each birthweight quintile being associated with their mother's G1 maternal birthweight quintile (*Table 9.1*, X^2 =389 (16d.f.), p<0.001). The mean birthweight of offspring similarly showed a strong positive association according to maternal quintile of birthweight (*Table 9.2*, p<0.001 for trend). However the standard deviation did not alter appreciably across groups so that for each increasing G1 maternal birthweight quintile the distribution of G2 offspring birthweight was similar in shape but was shifted progressively to the right (*Figure 9.1*).

Linear regression predicted that G2 offspring birthweight increased by an average of 25 grams for every 100 gram increase in G1 maternal birthweight (*Table 9.7*). After adjusting for G1 maternal age, adult height, parity, hypertension in pregnancy, paternal social class and G2 infant sex the association was reduced slightly to 19 grams for every 100grams of maternal birthweight but G1 maternal birthweight remained a highly significant independent predictor of G2 absolute birthweight (*Table 9.7*). These adult parental characteristics were treated as continuous variables in the regression analyses after confirming that there was no evidence of departure from linearity in the univariate

relationships. Further there was no evidence of any interaction between the explanatory variables and G2 infant size at birth.

In the subset of intergenerational pairs with maternal smoking status in pregnancy (n=3665) the relationship was largely unchanged (*Table 9.7*). G2 offspring birthweight similarly increased on average by 20grams for every 100gram increase in G1 maternal birthweight after adjusting for all G1 adult parental variables including G1 maternal smoking.

B. Gestational age at delivery

There was a positive intergenerational association between G1 maternal gestational age at delivery and G2 offspring gestational age at delivery but it was weaker than the intergenerational association observed for absolute birthweight. The association was demonstrated by the patterning of offspring gestational age according to the gestational age categorisation of the mother herself at her birth (*Table 9.3*, X^2 =56.2 (9d.f.), $p<0.001$). Most deliveries in both generations occurred at term (37-41 completed weeks of gestation) and there were relatively few deliveries at the extremes of gestation. Despite the small numbers of infants in the pre-term gestational age categories, particularly in the G1 generation, there was a clear trend in intergenerational transmission of length of gestation between G1 mothers and their G2 offspring (*Table 9.4*, $p<0.001$ for trend).

Linear regression predicted that G2 offspring gestational age increased by 0.11 week on average for every 1 week increase in G1 gestational age at delivery (*Table 9.7*). The association existed over the entire range of gestation from pre-term to post-term, independently of differences in adult maternal characteristics (after adjustment for G1 adult height, maternal age, parity, hypertension in pregnancy, paternal social class and G2 offspring sex). Further in the subset of intergenerational pairs (n=3655) for whom G1 maternal smoking information was available the association remained of the same magnitude and significance in the mutually adjusted regression model including G1 maternal smoking (*Table 9.7*).

C. Fetal growth (SD scores)

Considering the intergenerational relationship in fetal growth allowed a consideration of size at birth independent of any gestational age or gender differences between a G1 mother and her G2 offspring. There was a strong positive association between fetal

growth of the G1 mother and fetal growth of her G2 offspring. This positive association existed across the entire range of fetal growth with the proportion of offspring in each quintile of G2 offspring fetal growth being related to the quintile of fetal growth of the G1 mother herself at birth (*Table 9.5*, X^2 =338.1 (16d.f.), p<0.001). The mean offspring G2 fetal growth for each G1 maternal quintile of fetal growth also showed a strong positive association across generations (*Table 9.6*, p<0.001 for trend). As was the case for absolute birthweight, the distribution of G2 fetal growth according to maternal quintile of fetal growth was shifted progressively to the right, with changing means but with similar standard deviations for each G1 maternal fetal growth quintile (*Figure 9.2).* Linear regression predicted an average increase in G2 fetal growth of 0.23 SD (standard deviations) for every 1 SD increase in G1 maternal fetal growth (*Table 9.7*). Given that offspring fetal growth is strongly associated with maternal parity the intergenerational comparison was restricted to infants born to primiparous mothers in both generations (n=1701 pairs). For these pairs the intergenerational association in fetal growth was slightly stronger, with regression predicting that first born offspring fetal growth increased by 0.27 SD on average for each 1 SD increase in first born maternal fetal growth (p<0.001). For G1 mothers and G0 grandmothers who were both multiparous the estimated average increase in G2 fetal growth per 1 SD of G1 maternal fetal growth was reduced to 0.21 SD but it nevertheless remained a significant intergenerational association (p<0.001). Mutually adjusting for G1 adult height, maternal age, parity, hypertension in pregnancy, maternal smoking in pregnancy and paternal social class the intergenerational association remained significant but was diminished slightly to an average of 0.19 SD increase in fetal growth per 1 SD of maternal fetal growth (*Table 9.7*).

9.2.1 Translating intergenerational continuity into intergenerational risk

The intergenerational continuities in size at birth between G1 mothers and their G2 offspring may also be expressed as risks of transmission of the clinically important categories of size at birth and maturity. The extreme categories, particularly at the lower end of the scale, define groups of infants who are at increased risk of perinatal morbidity and mortality (*Table 9.8).* Logistic regression was used to compare the repeated risk of falling into these categories across generations.

If a G1 mother was born low birth weight (i.e. she weighed less than 2500g at birth) then she was 1.7 times more likely to have a low birth weight infant herself than if she

had been born with a birthweight greater than 2500grams (p=0.006). If a mother was born prematurely (i.e. at less than 37 weeks completed gestation) she was more than twice as likely to deliver a preterm infant than if she had been born at a gestational age of greater than or equal to 37 completed weeks (p<0.001). The intergenerational relationship was seen most strongly for fetal growth. If a G1 mother was born small for gestational age (in the lowest 10^{th} centile of birthweight for her gestational age at delivery) her own offspring were 2.7 times more likely to also have reduced fetal growth than if she had been appropriate or large for gestational age (p<0.001). These relationships were strongest in first born G2 infants, who are known to be at greatest risk of intrauterine growth retardation (Winkvist et al., 1998). Even after adjusting for known maternal adult risk factors for small offspring size at birth the intergenerational relationship remained significant for transmission of reduced fetal growth and prematurity but just failed to remain significant for intergenerational continuity in low birthweight (*Table 9.8).* The intergenerational continuity in reduced fetal growth and preterm delivery also remained as strong and as significant after adjusting for maternal smoking in addition to the other parental adult characteristics in the 3665 intergenerational pairs for whom this information was available (results not shown).

9.2.2 Risk in consecutive deliveries to the same first generation mother

An advantage of this intergenerational dataset over many others is that it had the potential to capture all deliveries that occurred to first generation women throughout their entire reproductive history, up to the ages of 46-51 years. Many other intergenerational studies have been limited to either first born second generation infants (Carr-Hill et al., 1987) or have ascertained reproductive histories when first generation women were aged in their early thirties (Emanuel et al., 1992; Alberman et al., 1992; Hennessy and Alberman, 1998a; Hennessy and Alberman, 1998b). Therefore for this intergenerational cohort it was possible to consider the risk of repeating adverse birth outcomes in second and later pregnancies if the infant of a first pregnancy was either preterm or had reduced intrauterine growth (classified either as low birthweight or small for gestational age). For the 6539 intergenerational pairs of first generation mothers (G1) and second generation infants (G2), 3308 represented deliveries of second or higher birth order G2 infants. The risk of repeating an adverse outcome in a subsequent pregnancy if the first was already affected was examined for this subset of intergenerational pairs.

If a first born sibling was born preterm, the risk of a subsequent delivery to the same mother also occurring before 37 weeks of completed gestation was three and a half times greater than if her first born infant was delivered at term. Similarly if a first born sibling weighed less than 2500 grams the risk of a subsequent sibling also being low birthweight was over five times greater than if the first born infant weighed 2500grams or more at delivery. The greatest risk for repetition of risk in consecutive pregnancies to the same mother was with respect to small for gestational age deliveries. If a mother's first child weighed less than the tenth centile for it's gestational age the risk was increased over five fold for a subsequent sibling to also be small for gestational age as compared to being appropriate or large for gestational age (*Table 9.9).* These risks of repeating adverse outcomes remained highly significant after adjusting for known adult maternal determinants of reduced size at birth (*Table 9.9).*

These familial patterns have been previously described for a Swedish intergenerational population (Winkvist et al., 1998), which also found that the risks of preterm delivery were increased if a mother's sister had previously delivered a preterm infant. It is not unusual to note correlation in birthweight between siblings, in fact large correlations of between 0.4-0.5 have been found by several authors including Khoury et al (Khoury et al., 1989) and previously by Bakketeig et al (Bakketeig et al., 1979). But of interest here is that adverse birth outcomes tend to be repeated for the same mother, independently of the adult specific influences on each pregnancy such as maternal age, parity or gestational hypertension. This suggests that there is something about the mother's own development that may be more influential than her adult pregnancy-specific characteristics. A study of risk factors for recurrent small for gestational age deliveries in Australian women previously concluded that isolated SGA deliveries were more likely to occur because of obstetric conditions, pre-eclampsia in particular, whereas recurrent SGA deliveries tended to be associated with maternal social disadvantage (Read and Stanley, 1993). Continuities in maternal social disadvantage will be considered in terms of their influence on continuities in size at birth in *Chapter 10.*

9.3 Aberdeen intergenerational associations compared to findings in previous intergenerational studies

For this intergenerational cohort the established positive intergenerational association between maternal and infant absolute birthweight has been confirmed as existing across

the full range of birthweight, including preterm infants, and independent of maternal adult characteristics known to influence birthweight. Further a positive significant association has been shown for fetal growth across generations, where for both generations fetal growth has been calculated as birthweight for gestational age standard deviation scores unlike many previous studies where gestational age has either been unavailable (Little, 1987; Ounsted et al., 1988; Coutinho et al., 1997) or unreliable for one or more generations (Emanuel et al., 1999) or subject to recall bias (Alberman et al., 1992; Emanuel et al., 1992). A significant positive association in length of gestation was also demonstrated across the two generations, which was larger than had been previously described (Magnus et al., 1993; Hennessy and Alberman, 1998b).

In terms of intergenerational transmission of clinically at risk categories of birth size and maturity this study also confirmed the relationship in reduced intrauterine growth across generations, measured either as the risk of transmission of low birth weight or small size for gestational age. However in addition it found a significantly increased doubled risk of preterm delivery in offspring of mothers who were themselves preterm. Previous studies, largely in Scandinavian countries, had shown mixed results for the association in preterm delivery across generations (Klebanoff et al., 1989; Magnus et al., 1993; Klebanoff et al., 1997; Winkvist et al., 1998).

In general studies which did not have reliable information on maternal gestational age had been unable to conclude which aspect of low maternal birthweight predisposed her infants to be at increased risk of both small size for gestational age and preterm delivery. Many had postulated that the mechanism was likely to be through reduced intrauterine growth since the intergenerational relationship between fetal growth and maternal birthweight was stronger than between fetal maturity and maternal birthweight. However gestational age measures are more likely to be imprecise than measures of absolute birthweight, which would generally lessen the chance of finding a strong association between maternal measures and offspring gestational ages. The results in this intergenerational cohort support both reduced growth in utero and the propensity to be delivered preterm as important mechanisms for transmission of intergenerational risk of reduced offspring size at birth.

Of note here in transmission of risk are the differences in composition of these two generations of infants because of the changes that have occurred in obstetric and neonatal care in the last half century. G1 mothers who were themselves low birthweight, preterm or small for gestational age are likely to represent the healthiest of their

generation born in each of these categories, given the limited perinatal support available for immature and small infants born in the 1950s. Yet they still carried the highest risk of transmission of these "at risk" perinatal characteristics to their offspring. Given the changes in care available in the last few decades it is likely that less "robust" infants will now be supported through the perinatal period with the chance of reaching adulthood to reproduce. It might be hypothesised that this group might carry an even greater risk of transmission of growth restriction, with its possible implications for later adult health (Power, 1994).

9.4 Summary

The Aberdeen intergenerational cohort is well equipped to address the intergenerational continuities in measures of size at birth, having several advantages over other previous intergenerational studies and sharing few of their limitations.

The intergenerational analyses for this cohort confirm that there is intergenerational continuity in size at birth between the G1 mothers and their G2 offspring, not just in terms of absolute birthweight but also in terms of length of gestation and fetal growth. These continuities exist across the entire range of birthweight and gestational age but are of particular importance clinically because of the intergenerational transmission of risk of falling into the extreme categories of size or maturity, independent of other known adult maternal risk factors.

Size at birth is the result of a complex mix of genetic and environmental factors, the contribution of each and the exact mechanisms of transmission being poorly understood. Within each generation offspring size at birth is patterned by adult characteristics concurrent with the pregnancy (*Chapter 8*). It is therefore conceivable that the intergenerational continuities demonstrated in size at birth might reflect continuities in the adult parental characteristics that influence size at birth. Chapter 10 will consider this possibility in this Aberdeen intergenerational cohort.

Table 9.1 : **Frequency distribution of G2 offspring birthweight according to G1 maternal birthweight quintile**

Maternal(G1) birthweight quintiles	Offspring (G2) birthweight quintiles Frequency (%)					
	1	2	3	4	5	Total
1	254 (32.4)	176 (22.5)	162 (20.7)	110 (14.1)	81 (10.3)	783 (100)
2	214 (25.7)	185 (22.2)	173 (20.7)	140 (16.8)	122 (14.6)	834 (100)
3	230 (19.4)	290 (24.5)	273 (23.1)	210 (17.7)	181 (15.3)	1184 (100)
4	393 (16.7)	434 (18.4)	507 (21.5)	523 (22.2)	498 (21.2)	2355 (100)
5	147 (10.6)	194 (14.0)	279 (20.2)	340 (24.6)	423 (30.6)	1383 (100)
Total	1238 (18.9)	1279 (19.6)	1394 (21.3)	1323 (20.2)	1305 (20.0)	6539 (100)

Table 9.2 : **Mean and standard deviation of G2 offspring birthweight according to G1 maternal birthweight quintile**

Maternal (G1) Birthweight Quintiles	Offspring (G2) Birthweight (grams)	
	Frequency	Mean (standard deviation)
1	783	3097 (564)
2	834	3201 (525)
3	1184	3259 (477)
4	2355	3348 (509)
5	1383	3476 (535)
Total	6539	3310 (531)

Figure 9.1 : **Distribution of G2 offspring absolute birthweight according to G1 maternal absolute birthweight quintile**

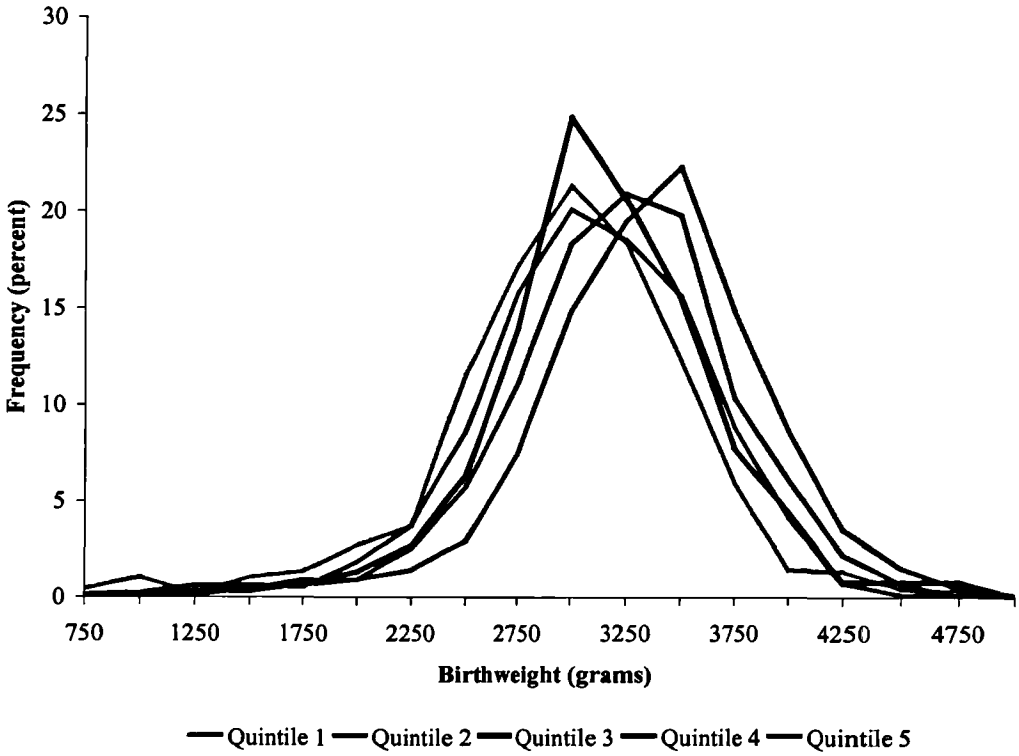


Table 9.3 : **G2 offspring gestational age category according to G1 maternal gestational age category**

Maternal (G1) gestational age category	Offspring(G2) gestational age category Frequency (%)			
	<37 weeks	37-41	>41 weeks	Total
<37 weeks	39 (10.8)	308 (85.1)	15 (4.1)	362 (100)
37-41	305 (5.3)	5149 (89.5)	297 (5.2)	5751 (100)
>41 weeks	17 (4.0)	378 (88.7)	31 (7.3)	426 (100)
Total	361 (5.5)	5835 (89.2)	343 (5.3)	6539 (100)

Gestational age categories are for completed weeks and are defined according to the traditional clinical cut-offs for pre-term, term and post-term deliveries.

Table 9.4 : **Mean length of gestation of G2 offspring according to G1 maternal gestational age categories at delivery**

Maternal (G1) Gestational Age categories	Offspring (G2) gestational age (weeks)	
	Frequency	Mean (standard deviation)
<32 weeks	15	37.4 (4.5)
32-36 weeks	347	39.0 (2.2)
37-41 weeks	5751	39.5 (1.8)
>41 weeks	426	39.8 (1.7)
Total	6539	39.5 (1.8)

Table 9.5 : **Frequency distribution of G2 offspring fetal growth according to quintile of G1 maternal fetal growth**

Maternal (G1) fetal growth quintiles	Offspring (G2) fetal growth quintiles Frequency (%)					
	1	2	3	4	5	Total
1	407 (29.4)	331 (24.0)	269 (19.5)	202 (14.7)	171 (12.4)	1380 (100)
2	317 (23.9)	285 (21.5)	270 (20.4)	238 (18.0)	214 (16.2)	1324 (100)
3	209 (15.9)	268 (20.4)	266 (20.3)	308 (23.5)	261 (20.0)	1312 (100)
4	211 (16.6)	256 (20.1)	247 (19.4)	284 (22.3)	276 (21.7)	1274 (100)
5	129 (10.4)	194 (15.5)	255 (20.4)	285 (22.8)	386 (30.8)	1249 (100)
Total	1273 (19.5)	1334 (20.4)	1307 (20.0)	1317 (20.1)	1308 (20.0)	6539 (100)

Table 9.6 : **Mean and standard deviation of G2 offspring fetal growth according to quintile of G1 maternal fetal growth**

Maternal (G1) Fetal growth quintiles	Offspring (G2) Fetal growth	
	Frequency	Mean (standard deviation)
1	1380	-0.36 (0.98)
2	1324	-0.21 (0.96)
3	1312	0.0 (0.91)
4	1274	0.02 (0.98)
5	1249	0.30 (0.97)
Total	6539	-0.06 (1.0)

Figure 9.2 : **Distribution of G2 offspring fetal growth according to G1 maternal fetal growth quintile**

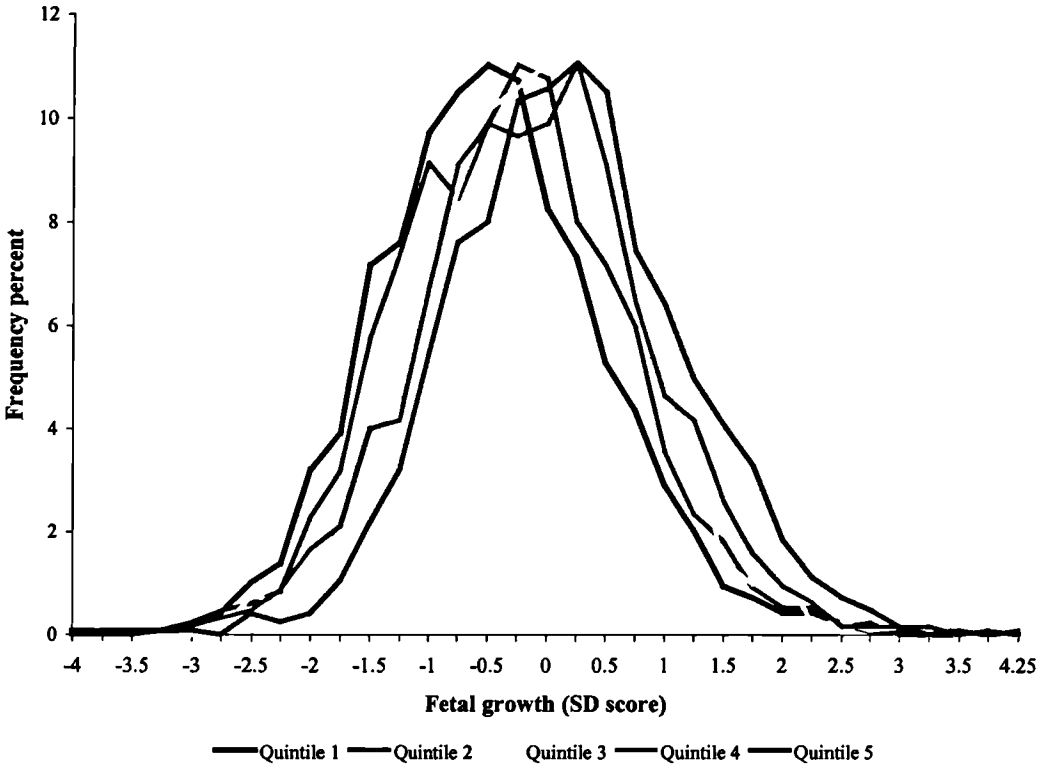


Table 9.7 : **Summary of intergenerational associations in measures of size and maturity at birth**

Intergenerational relationship in birth measure	Regression coefficient (95% C.I.)				
	Crude n=6539 pairs	Adjusted* n=6539 pairs	Crude n=3665 pairs	Adjusted* n=3665 pairs	Adjusted* + smoking n=3665 pairs
G2 Birthweight (gram) -per 1 gram G1 birthweight	0.25 (0.22 , 0.28) p<0.001	0.19 (0.17 , 0.22) p<0.001	0.27 (0.24 , 0.31) p<0.001	0.20 (0.17 , 0.25) p<0.001	0.20 (0.17 , 0.25) p<0.001
G2 Gestational age (weeks) -per 1 week G1 gestational age	0.11 (0.08 , 0.14) p<0.001	0.11 (0.08 , 0.13) p<0.001	0.12 (0.08 , 0.16) p<0.001	0.11 (0.08 , 0.15) p<0.001	0.11 (0.08 , 0.15) p<0.001
G2 Fetal growth (SD) -per 1 SD G1 fetal growth	0.23 (0.21 , 0.26) p<0.001	0.18 (0.16 , 0.20) p<0.001	0.25 (0.22 , 0.28) p<0.001	0.19 (0.16 , 0.22) p<0.001	0.19 (0.15 , 0.22) p<0.001

* **Adjusted** for G1 maternal adult height, age, parity and hypertension at pregnancy, paternal adult social class and infant sex

Note: Crude and mutually adjusted regression coefficients are displayed for all intergenerational pairs (n=6539) and for the subset of G1 mothers that have smoking information available (n=3665). There is no evidence that this subset is not representative of the total group.

Table 9.8 : **Intergenerational odds ratio for clinically significant G2 birth outcomes according to G1 birth outcome**

G1 Birth Characteristic	Odds Ratio for repeating characteristic in G2 delivery (95% Confidence Interval)	
	Crude	Adjusted [+]
LBW (<2500g)	1.7 (1.1 , 2.4)**	1.4 (1.0 , 2.0) NS
Pre-term (<37 weeks)	2.2 (1.5 , 3.1)**	2.1 (1.5 , 3.1)**
SGA (<10th centile)*	2.7 (2.2 , 3.4)**	2.3 (1.8 , 3.0)**

** Significant at the p<0.01 level

NS not significant

* The centiles are based on the distribution of SD scores for each generation, as previously described.

[+] Adjusted for maternal age, height, parity, hypertension in pregnancy, paternal current social class and infant sex

Table 9.9 : **Within G2 generation odds ratios of clinically significant birth outcomes (n=3308 pairs)**

Characteristic of first born G2 infant	Odds of repeated characteristic in subsequent G2 delivery Odds Ratio (95% Confidence Interval)	
	Crude	Adjusted [+]
LBW (<2500g)	5.2 (3.5 , 7.9)***	4.9 (3.3 , 7.5)***
Pre-term (<37 weeks)	3.6 (2.3 , 5.6)***	3.7 (2.4 , 5.9)***
SGA (<10th centile)*	5.4 (4.1 , 7.1)***	4.6 (3.5 , 6.1)***

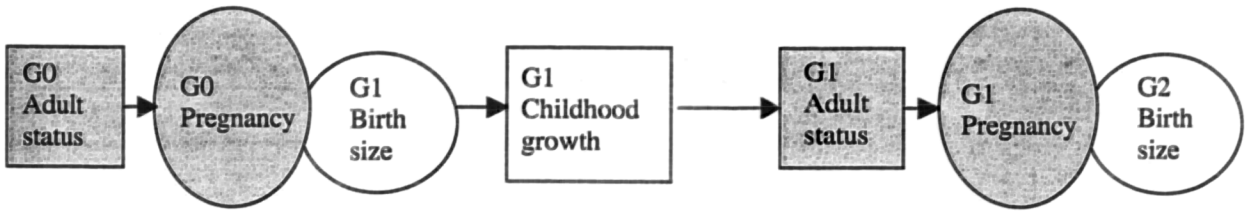
*** Significant at the p<0.001 level

* The centiles are based on the distribution of SD scores for each generation, as previously described.

[+] Adjusted for maternal age, height, parity, hypertension in pregnancy, paternal current social class and infant sex

Chapter 10:

Intergenerational Continuities in Adult Determinants of Size at Birth



Within each generation there are gradients in size at birth according to adult parental biological and social characteristics that are concurrent with the pregnancy itself. In particular there is a gradient in size at birth according to parental social class measured at the time of the pregnancy. For this cohort it was established that paternal social class remains a significant predictor of infant size at birth even after adjusting for differences in other concurrently measured socially patterned biological characteristics, such as maternal height, age and parity, and behaviours including maternal smoking within each generation (Chapter 8). There is also intergenerational continuity in size at birth measures across the two generations in this cohort, in terms of measures of fetal growth and maturity, which persist after adjusting for the adult characteristics that are known to influence size at birth (Chapter 9). However an individual mother's intrauterine growth is subject to the adult influences of her own mother at the time of pregnancy. Therefore the intergenerational continuities that are seen in size at birth may be due to intergenerational continuities in the adult maternal environment and behaviours. This chapter explores the extent of the continuities in adult determinants of size at birth across the generations in this cohort and considers the contribution these make to the intergenerational continuity seen in size at birth. The final section of the chapter compares the effect of intergenerational continuity with intergenerational discontinuity of socioeconomic environment on offspring size at birth.

10.1 Intergenerational continuities in maternal adult predictors of size at birth

Maternal adult and pregnancy-specific determinants of infant size at birth are initially examined for evidence of intergenerational continuity. The measures to be considered are maternal adult height and age at first pregnancy (primigravidity) and hypertension in pregnancy. Continuities in the social environment contemporary to the pregnancies are examined following the discussion of the maternal characteristics. The analyses are

restricted to the *intergenerational dataset* considered in the previous two chapters, with 6539 G2 offspring and 3231 G1 mothers.

10.1.1 Continuities in maternal adult height across generations

It is well established that adult height is highly correlated across generations, and further that within a generation infant size at birth is positively associated with both maternal and paternal adult height (Cawley et al., 1954). It was also the case for this intergenerational cohort that G1 maternal adult height was positively associated with G0 maternal adult height (Pearson correlation coefficient of $r=0.52$, $p<0.001$). The relationship existed across the entire range of maternal height and was not confined to extreme groups (*Table 10.1*, $X^2=691$ (12d.f.), $p<0.001$). Further the mean G1 maternal adult height increased with increasing G0 maternal adult height category (*Table 10.2*, $p<0.001$ for trend). Linear regression predicted that for every 1cm increase in adult G0 maternal height there was an average 0.49cm increase in the G1 maternal adult height ($p<0.001$).

Final adult height in both generations reflects a complex mixture of genetic and environmental influences. Mean adult height tends to be greatest in highest social classes and least in the lowest social classes (Kuh and Wadsworth, 1989). The continuity that is seen in maternal height across generations is no doubt strongly influenced by genetic continuity, but two generations are also likely to share very similar childhood social environments which also have the potential to shape final adult height in both generations (Wales et al., 1992).

10.1.2 Continuities in age at first pregnancy

Age at first pregnancy was compared for G0 and G1 mothers as this measurement signifies the beginning of a female's successful reproductive career. Continuities in the timing of subsequent pregnancies raises issues concerning pregnancy spacing which is subject to many pressures, some social and some biological (Erickson and Bjerkedal, 1978). This data has a limited capacity to explore these issues because of a lack of information about the timing of all the G0 pregnancies. However it is able to ascertain maternal age at first pregnancy for primigravidae in both generations.

Gravidity and number of previous abortions are recorded in both the AMND and SMR2 pregnancy records in addition to parity for both generations of mothers. Using information from a combination of these variables the analyses were restricted to 1012

intergenerational pairs of G0 and G1 mothers who delivered liveborn infants as primigravidae (therefore parity zero women who had had previous early recognised pregnancy loss were excluded). There was a positive association between G0 maternal age at first pregnancy and G1 maternal (daughters) age at her own first pregnancy across the two generations (*Table 10.3,* p<0.001 for linear trend). In particular if a G0 mother was under 25 when she had her first pregnancy as opposed to over 25, logistic regression predicted that there was a twofold increased odds that her G1 daughter would also deliver her first child before the age of 25 years as opposed to after (OR=2.0, 95% CI 1.6-2.6, p<0.001).

This positive intergenerational association was also seen between G0 paternal and G1 maternal age at first pregnancy. The younger a G0 father was during the G0 mother's first pregnancy the younger the G1 daughter was also likely to be at her first pregnancy (*Table 10.4*, p<0.001 for linear trend). If the G0 father was under 25 during the G0 mother's first pregnancy, as opposed to over 25 years, the odds were increased more than two-fold that the G1 daughter would also reproduce before the same age (OR=2.4, 95% CI 1.8-3.2, p<0.001) as compared to 25 years or later. The intergenerational relationship between G0 paternal age and G1 maternal age appeared slightly stronger than between G0 maternal and G1 maternal age. Univariate regression analyses predicted that G1 maternal age at first pregnancy increased by 0.89 years on average per 5 year increase in G0 maternal age (p<0.001) compared to 1.0 year for every 5 years of G0 paternal age (p<0.001). The two G0 parental ages were highly correlated (Pearson correlation coefficient=0.60, p<0.001) but nevertheless in the mutually adjusted regression model G0 paternal age remained a significant predictor of G1 maternal age, whereas G0 maternal age became non-significant (*Table 10.5*). One possible interpretation of these results is that the continuity seen in age at first pregnancy across generations is perhaps driven as much by environmental as biological influences. Paternal age may be more indicative of social status than maternal age, so that having an older father during a first pregnancy may lead to a more advantaged childhood and a later age at first pregnancy for the daughter. However if the analyses are additionally adjusted for G0 paternal social class then G0 paternal age does not seem to be acting as a proxy for his social status (*Table 10.5).* The effect of paternal age remains significant and only slightly diminished after accounting for G0 paternal social class. This is an intriguing and unanticipated finding. However there is some evidence from the 1958 British Birth Cohort that paternal age may be more influential than maternal age at predicting reproductive outcome. Paternal age was found to be more influential than

maternal age in predicting offspring size at birth by Hennessy and Alberman in the 1958 cohort who were born during the same decade as the first generation (G1) Aberdeen females (Hennessy and Alberman, 1998a). The authors concluded that the stronger effect of paternal age might be associated with "good antenatal habits of the mother" in the British cohort. However they did not have shared maternal and paternal information for the same infant therefore this could not be confirmed. The underlying mechanism for the association in the Aberdeen cohort also remains unclear.

10.1.3 Continuities in the total number of pregnancies (total gravidity) across generations

To consider intergenerational continuity in the total gravidity for G0 and G1 mothers it is necessary to ascertain the total number of pregnancies for all the G0 mothers together with the total number of pregnancies for all the G1 daughters. However, this information was not complete for all G0 mothers of the original Aberdeen Child Development Study cohort members. The G1 children were recruited as 7-12 year olds in 1962 and whilst total family size of the mother in 1962 was available for all G1 females their mothers may not have completed their child-bearing at that time. However for a 20% randomly selected subset of the members of the original Child Development Study details of all the G0 maternal pregnancies up to 1964 were obtained in a follow-up parental interview by the original researchers two years after the original study. Hence for 1264 (19%) of the intergenerational G0 and G1 maternal pairs data was available on gravidity of the G0 mother up to 1964 and total gravidity could be estimated for the G1 mothers from the linkage to all Scottish births between 1967 and 1999 (Chapter 4).

The total mean number of pregnancies per mother was greater in the G0 generation than for the generation of G1 mothers, even though it was more likely that the total G0 maternal pregnancy numbers were incomplete. In 1964 G0 maternal age ranged from 27 to 57 years with a mean age of 39 years (SD=5.8 years), therefore it was possible that some women had not completed their childbearing at that time. However the first generation mothers were aged 46-51 years at the time of the SMR2 record linkage so their reproductive histories should have been largely complete.

In the G0 maternal generation the mean total number of pregnancies per woman was 3.7 (SD=1.9) with a range of 1 to 14, and for the G1 maternal generation the mean total number of pregnancies was 2.8 (SD=1.3) with a narrower range of 1 to 10. This difference might have been due in part to the introduction of chemical contraceptive methods for

women in the 1960s or to temporal trends in childbearing due to other cultural factors that lead to the downsizing of the family and a reduction in total pregnancy number.

Despite the probable partial enumeration of the total G0 maternal pregnancy numbers there was a positive association between the total number of pregnancies between the two generations. The chances of a G1 mother having only one or two liveborn children were almost doubled if her G0 mother had only one or two children as opposed to 3 or more (OR=1.8, 95% CI 1.4-2.2, p<0.001). The small numbers of women for whom this information is available though make it difficult to look at these intergenerational continuities in further detail. However there was some evidence in this subset of females to suggest that total family size was repeated across generations.

10.2 Continuities in pregnancy specific maternal conditions

The similarity in family size across generations probably reflects a complex mix of shared biological and social factors. However if the course of maternal pregnancy across two generations is similar this might be a contributory factor to the family size similarities. Similarities in the course of pregnancy may be particularly relevant if pregnancy is complicated by maternal disease in both generations. The most common maternal complication arising in the course of pregnancy is gestational hypertension, with more than 10% of all pregnancies being affected by this, although recent research suggests this may be an underestimate in the Scottish population (Wilson et al., 2000).[#]

As a further step in understanding intergenerational continuities in offspring size at birth the intergenerational continuities in hypertension in pregnancy are explored for this cohort.

10.2.1 Hypertension in pregnancy

Familial clustering of hypertensive disorders in pregnancy has been recognised for several decades (Zhang et al., 1997; Mogren et al., 1999), with siblings of women who have had pregnancies affected by hypertension being at increased risk of developing the same complications in their own pregnancies. A 1997 study using information from the 1958 British Birth cohort provided evidence that a woman's own reduced intrauterine

[#] It is acknowledged that the variation in incidence of hypertension in pregnancy may be attributable to differences in definition, population composition or obstetric characteristics as well as actual incidence (Zhang et al., 1997).

growth was associated with an increased risk of developing hypertension in her adult pregnancies (Hennessy and Alberman, 1997). However the women were only 33 years of age at the time of the study and gestational hypertension was self-reported. A later study by Klebanoff et al, which used record linkage for a Danish birth cohort born between 1959 and 1961, confirmed the increased risk of pregnancy hypertension in women born small for gestational age at birth (Klebanoff et al., 1999). A cohort study in Aberdeen, Scotland followed up women with a history of hypertension in pregnancy and found that they were at increased risk of developing hypertension in later adult life (Wilson et al., 2000) compared to women who had not had any hypertension in pregnancy. A more recent study in Norway concluded that women who specifically developed pre-eclampsia during their pregnancies were at increased risk of death particularly from cardiovascular disease compared to women who did not have pre-eclampsia (Irgens et al., 2001).

The conclusions of these separate studies are consistent with the "fetal origins of adult disease" hypothesis which links reduced intrauterine growth to an increased risk of hypertension, among other chronic conditions, in later adult life. It might be extrapolated from these separate studies that reduced intrauterine growth may lead to an increased risk of pre-eclampsia in pregnancy which is then associated with later hypertension and an increased risk of mortality from cardiovascular disease. However there are as yet no studies that have enough data on women followed prospectively from birth to old age, including details of their full reproductive histories, to test this in practice. It appears that the physiological stress of pregnancy has the capacity to unmask the future potential for chronic disease. However the causes of pre-eclampsia remain poorly understood and it may be that the pathway suggested by these individual studies is not a causal one. Pre-eclampsia in pregnancy might initiate the damage that results in later adult disease rather than it necessarily being dependent on a latent or common risk programmed in utero, often purported to be genetic (Lie et al., 1998). The G1 females in the Aberdeen cohort are currently aged between 47 and 52 years of age (as at 2002) so it is not yet possible to examine these associations within this generation. However it does have intergenerational information on hypertension in pregnancy obtained from perinatal records for the G0 grandmothers and the G1 mothers. It is therefore possible to determine whether there is an intergenerational association in pregnancy hypertension in this cohort. Further, using G1 maternal fetal growth and adult height, to determine whether any intergenerational association is mediated by size at birth or whether it, and possibly the risk of later adult hypertension, are linked through mechanisms other than reduced intrauterine growth.

10.2.2 Intergenerational continuities in hypertension in pregnancy

The extent to which the pregnancies of G1 females in adult life were affected by hypertension appeared to be directly related to the extent of hypertension complicating their own intrauterine development (*Table 10.6,* X^2=35.9 (4d.f.), p<0.001). Furthermore hypertension in G1 pregnancies tended to be more common in those G1 women who had reduced intrauterine growth themselves, although this trend was not statistically significant (*Table 10.7,* X^2=2.6 (4 d.f.), p=0.60). Logistic regression was used to estimate the risk of hypertension in pregnancy for G1 females whose own intrauterine development had been similarly affected. Robust standard errors were used to account for the repeated maternal information.

There continues to be much debate about whether pre-eclampsia and gestational hypertension without proteinuria are separate disease entities or part of a continuum of severity of the same disease process. For this reason two sets of results are presented, the first combines "other hypertension" with moderate to severe pre-eclampsia and defines it as "any hypertension" and the second considers pre-eclampsia alone, with "other hypertension" combined with the "no hypertension" category.

The risk of a G1 female having any hypertension (pre-eclampsia or "other hypertension") in her own pregnancy was increased 1.5 fold if her G0 mother had pre-eclampsia and by the same amount if her G0 mother had "other hypertension" during the G1 females own intrauterine development (*Table 10.8).* Her risk of developing pre-eclampsia increased 1.8 fold if her own mother's pregnancy was also complicated by moderate to severe pre-eclampsia and 1.6 fold if her G0 mother's pregnancy was complicated by "other hypertension" (*Table 10.9).* In the case of either categorisation of pregnancy hypertension the intergenerational association with G0 "other hypertension" remained significant, even after adjusting for known adult maternal risk factors for pre-eclampsia and adjusting for maternal size at birth (*Table 10.8).* However whilst the effect estimate remained almost the same with respect to the intergenerational risk of G1 maternal pre-eclampsia the confidence intervals were widened after adjustment for G1 adult maternal factors and maternal fetal growth. This may reflect the reduced power to find a significant effect with the small numbers of G0 and G1 mothers who fell into these categories, rather than the absence of effect.

The similarity in G1 maternal risk of either pre-eclampsia or hypertension in pregnancy, given hypertension affecting her own intrauterine development, suggests there may be a

common mechanism linking these two disease processes rather than the pathogenesis of each condition being distinct. The mechanism underlying transmission may well be genetic, or it may reflect a shared environment across two generations, or more probably some combination of the two. Further investigation of the underlying process requires more sophisticated biochemical data than this cohort has available. However it does not appear that the intergenerational association in gestational hypertension is mediated by the mothers own size at birth, despite the relationship between pre-eclampsia and reduced size at birth within a generation.

These maternal pregnancy-specific conditions are important determinants of size at birth for the individuals that they effect and for their families in terms of transmission within and across generations. However on a population basis severe maternal diseases such as pre-eclampsia affect only a small percentage of mothers (less than 5% in the moderate to severe categories which have the greatest impact on size at birth). Contrarily the intergenerational continuities in size at birth exist across the entire population range of birthweight, fetal growth and gestational age. Therefore it is likely that continuity in the other adult determinants of size at birth will be of greater importance than pregnancy-specific diseases with respect to intergenerational continuities in the whole population.

10.3 Continuities in the socioeconomic environment

The maternal factors that show continuity across generations, though often referred to as biological, are the result of a complex mix of genetic and environmental influences, the extent of each being difficult to unravel. One way of assessing the environmental influence is to consider the socioeconomic status of the family into which an infant is born. Social class is used as a proxy measure of the environment that exists at a certain period of time that is likely to influence the physical and emotional development of an infant. The extent of the continuity in socioeconomic environment between these two generations can be considered using measures of G0 and G1 paternal social class at the time of the G1 and G2 infant's birth respectively.

Social class measures in this cohort are based on occupational categories, as classified by the Registrar General. In Chapter 8 it was clear that the patterning of size at birth was similar with respect to either maternal or paternal occupational codes, but the paternal, being more complete, was chosen as the social class measure for these analyses. Within each generation there was a significant gradient in mean offspring size at birth according

to paternal social class at the time of the pregnancy, whereby infants born to fathers in the lowest social classes were smallest on average at birth (*Tables 8.1 and 8.3*).

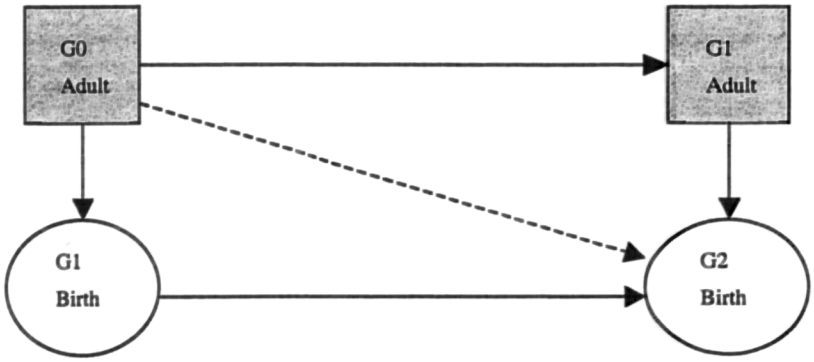
In an intergenerational context there was evidence of continuity between the social class of G1 females at their birth, as measured by the G0 paternal occupation, and in adulthood, as measured by the social class of their partners (*Table 10.10*, X^2= 265 (16d.f.), p<0.001). The occupational classes were regrouped as either "Non-manual" (grades I, II and IIINM) or "Manual"(grades IIIM, IV and V) and the "other" category was maintained to consider the continuity further. If a G1 female was born into a manual class she was more than twice as likely to reproduce with a partner who was also in a manual rather than a non-manual category (OR=2.5, 95% CI 2.2-2.7, p<0.001). Further the chance of a G1 woman in adult life being with a partner who was in a manual occupation increased in a graded fashion according to the "more manual" her own G0 father's occupation was (*Table 10.11*). Overall socioeconomic continuity between birth and adulthood was the norm with 1711 (61%) of the 2816 first generation mothers (excluding those in "other" social class categories) classified in the same manual or non-manual category at birth and in adulthood.

Therefore there were continuities in the social environment as well as in the maternal biological determinants of offspring size at birth. In particular the early social environment of the G1 females was associated with the social class of the partner she was with during her adult reproductive life.

10.4 Do these continuities in the biological and social adult determinants of size at birth help to understand the intergenerational continuities in size at birth?

The diagram below illustrates the nature of the associations that have been established for this cohort to date. The lower horizontal solid line represents the positive association in intergenerational measures of size at birth described in Chapter 9, and the upper horizontal line the intergenerational continuities in the adult determinants of offspring size discussed in this chapter. The vertical solid lines illustrate the within generation associations between adult parental characteristics and offspring size at birth described in Chapter 8. The diagonal dashed line represents the potential association that would follow from these associations if the continuity in the adult biological and social determinants of size at birth were sufficient to understand the intergenerational continuity in size at birth. If that were the case the associations between G0 adult characteristics and G2 size at birth would be

expected to be very similar to the associations between G1 adult characteristics and G2 size at birth.



To determine how far the continuities in maternal adult biological and social characteristics might explain the intergenerational continuity in size at birth multivariate regression was used. *Tables 10.12 and 10.13* summarise the results of these analyses in which the outcome is limited to fetal growth (SD scores) as the measure of size at birth. In all the adjusted analyses the outcome variable is G2 fetal growth conditional on G1 fetal growth (called **conditional G2 fetal growth** henceforth) as the aim here was to try to understand better the intergenerational continuity in these measures. Robust standard errors were calculated to take account of the repeated G1 and G0 maternal information in the intergenerational pairs. There was no evidence to suggest a departure from linearity in any of the univariate relationships of continuous parental characteristics with G2 size at birth and no evidence of any interaction between explanatory variables. *Table 10.12* presents the results of the analyses for the intergenerational effects on the conditional G2 fetal growth for all 6539 G2 infants in the *intergenerational dataset. Table 10.13* restricts the analyses to the subset of G2 infants (n=3665) for whom G1 maternal smoking information is available and repeats the same analyses on this subset. The format of both tables is however similar in that the first column presents the crude effects of each G0 and G1 parental characteristic on G2 fetal growth only (not conditional). The next columns present the results of the mutually adjusted effects separately for the G0 and G1 parental characteristics on the conditional G2 fetal growth. The right most column/s present the coefficients for the mutually adjusted effects of both G0 and G1 parental characteristics on conditional G2 fetal growth.

Firstly the crude effects of the G0 grandparental adult characteristics compared to the crude effects of the G1 parental adult characteristics on G2 fetal growth are considered (left most results columns in *Tables 10.12* and *10.13*). In general the adult characteristics

have similar effects on G2 fetal growth, regardless of whether the G0 grandmaternal or the G1 maternal characteristic is considered, providing evidence that continuity in adult determinants of size at birth across generations is partially responsible for the intergenerational continuity seen in offspring size at birth. However the direction and magnitude of crude effects of the two generations adult characteristics on G2 fetal growth are not completely uniform. In particular G0 grandmaternal parity has a crude negative association whereas G1 maternal parity has a crude positive association with G2 fetal growth. Further despite the intergenerational continuity demonstrated for maternal age at first delivery the effect of G0 grandmaternal age at delivery whilst positive is not as strong as G1 maternal age at delivery on G2 fetal growth.

10.4.1 G0 and G1 parental adult characteristics associated with conditional G2 fetal growth

Next the mutually adjusted effects of each generations adult characteristics on **conditional G2 fetal growth** were considered separately (centre columns of *Tables 10.12* and *10.13*). The graded effect of G0 grandparental social class was no longer evident on conditional G2 fetal growth after mutual adjustment for all G0 adult characteristics. However G0 grandmaternal height in adulthood and grandmaternal age at delivery both remained independently significantly associated with conditional G2 fetal growth after mutual adjustment. G0 grandmaternal parity remained significantly negatively associated with conditional G2 fetal growth with a doubling of effect in absolute terms.

Considering the more temporally proximate mutually adjusted effects of the G1 adult characteristics on conditional G2 fetal growth, G1 maternal adult height, age and parity all had positive associations with conditional G2 fetal growth, diminished slightly from their crude effects but remaining highly significant. The socioeconomic gradient in conditional G2 fetal growth according to G1 paternal occupation also remained significant after considering the mutual effects of other G1 adult characteristics (*Table 10.12*).

These associations with both G0 and G1 characteristics were apparent in both the G2 infants in the intergenerational dataset (n=6539) and in the subset for whom G1 smoking status was available (n=3665). The adjusted effects of the G1 maternal characteristics were largely unaltered after additionally adjusting for smoking status (*Table 10.13*). Most notably there was a reduction in the socioeconomic gradient with respect to G1 paternal social status but it remained significant. G1 maternal smoking in pregnancy was itself a

strong independent predictor of conditional G2 fetal growth independent of other G1 characteristics (*Table 10.13*).

In the mutually adjusted analyses for the effects of both G0 and G1 parental adult characteristics on conditional G2 fetal growth (far right columns of *Tables 10.12* and *10.13*) the G0 parental adult characteristics were largely unimportant in predicting conditional G2 fetal growth. This was with the exception of G0 grandmaternal parity which remained as strong a negative predictor of conditional G2 fetal growth as it was in the crude relationship with G2 fetal growth and grandmaternal age which remained significantly, positively associated with conditional G2 fetal growth in the intergenerational dataset (*Table 10.12*) but was no longer significant in the restricted subset (*Table 10.13*).

10.4.2 Intergenerational influences on continuity in offspring size at birth

Therefore overall the continuity in G0 and G1 parental characteristics appears to explain a part of the intergenerational continuity in offspring size at birth. Most of the effects of G0 parental adult characteristics on G2 fetal growth are probably exerted indirectly on G2 fetal growth through their direct influence on G1 fetal growth itself, hence their diminished effects in the mutually adjusted conditional model. The small residual significant effects of G0 characteristics should however be interpreted with caution given the multiple statistical testing carried out in these analyses and the measurement error in each of the characteristics, particularly in the assessment of the social environment that exists at any one time using a measure based on paternal occupation.

In the mutually adjusted model for conditional G2 fetal growth the G1 parental adult characteristics remained significant in determining conditional offspring growth. Therefore in addition to the continuity in adult characteristics, discontinuity across generations appears to have effects on G2 fetal growth independent of G1 fetal growth. Differences in attained adult height, social environment and adult reproductive characteristics across generations for G1 women with the same G1 fetal growth contributed significantly to differences in G2 fetal growth. G1 maternal smoking during pregnancy also reduced the size of a woman's offspring independently of the intergenerational association in fetal growth, although we have no information about G0 maternal smoking to check for possible continuities in behaviour as well as biological and social measurements.

There is further discontinuity of effect across generations as evidenced by the negative effect of G0 maternal parity and the positive effect of G1 parity on G2 fetal growth both in the crude and mutually adjusted conditional models. It is not immediately clear why there might be this differential effect across generations. It is possible that the negative effect of G0 parity on conditional G2 fetal growth represents a compensation for larger birth size but less growth to adulthood for the G1 female born to a higher parity G0 mother, with G1 parity held constant, but this is speculative.

One problem that these analyses highlight is the difficulty in unravelling the effects of intergenerational effects when intergenerational G0 and G1 measurements are highly correlated. A further problem is that the simplified diagram at the beginning of this section cannot hope to capture the complexity of the intergenerational relationships between all the variables. Some temporally distal variables appear to act directly on G2 fetal growth (e.g.G0 parity) and others probably represent steps on the causal pathway acting through their effects on G1 fetal growth (e.g. G0 height).

Interpreting repeated measures within and across generations can also be problematic. For some explanatory variables repeated measures do not always provide information about the nature of change in the intervening time between measurements. Adult biological measures are relatively straightforward to measure in that age, parity and height only increase monotonically between birth and adult reproductive life and relative measures may be compared directly across generations. By contrast, social class may change throughout a lifecourse and the change may not be monotonic, with inference about status between two time points made very difficult if interim measurements are not available.

Nevertheless a potential reason why there might be discontinuity in maternal biological measures across generations is because of discontinuity in the socioeconomic environment. The effect of such discontinuity is examined in this cohort.

10.5 G1 maternal adult characteristics according to social class at birth and in adult reproductive life

The maternal biological measures of height, age and parity at pregnancy which are influential for offspring size at birth are socially patterned themselves within each generation, according to concurrently measured paternal social class measures (Chapter 8). In addition to adult social class of the G1 mother, which is inferred from her partner's occupation, her G0 father's social class at the time of her own birth is also available and

may be considered to have been the dominant environmental influence on her early childhood development. The effect of change in social class from birth to adulthood will be considered with respect to maternal adult determinants of G2 size at birth. Broad categories of either manual or non-manual paternal social class will be considered to limit the comparison to four groups of women. The analyses will be restricted to 2816 of the first generation females for whom social class is graded either as manual (M) or non-manual (NM) and not as "other".

10.5.1 The effect of change in social class on adult biological characteristics

The maternal adult measures of height and age at first pregnancy are compared for four groups of G1 females. Two groups are women who were in the same social class in adult reproductive life and at birth (NM/NM and M/M) and the other two are those who changed class in the interim, the temporal order differing for each (NM/M and M/NM).

Table 10.14 summarises the mean maternal measures of attained adult height and age at first pregnancy for these four groups of women. Those who were in the most advantaged social class group at both time points (NM/NM) were the tallest adults and those in the least advantaged at both time points (M/M) were the shortest. Those women who had changed social class between childhood and adult reproductive life had intermediate values to these two extremes, with the taller of the mixed groups being the G1 women who were in non-manual social classes in adulthood rather than at birth. The differences in maternal adult height between each pair of the four groups were all significant at the $p<0.001$ level. Similarly with regard to age at first pregnancy the oldest primigravidae were women who were in non-manual classes at birth and in adult life whereas the youngest were in manual classes at both times (*Table 10.14).* Again those women who moved from manual to non-manual classes between birth and adult life had a later age at first delivery when compared to women who moved in the opposite direction (each pair of groups also had significantly different mean ages at first delivery, $p<0.001$). However overall the adult measure seemed the most important influence on these maternal characteristics.

Therefore a change in social class status between birth and adult reproductive life either caused or was driven by changed maternal height in comparison to the social class of origin and was associated with differences in reproductive behaviours in terms of age at first pregnancy. Illsley, who has written much about the social mobility of Aberdeen women, might suggest that within each broad social group there is wide biologic

variability in physical measures and educational achievement and that women who are "upwardly mobile" are more like the class to which they move to than the one from which they originated (Illsley, 1955). However it may not be possible to determine whether the change in biological measurements are cause or effect without further intermediate measures of size and information about the timing of status change.

10.5.2 Social class change and G2 fetal growth

Given the known effect of the adult maternal biological characteristics on offspring size at birth it might be expected that there would be differences in G2 offspring size at birth according to continuity or discontinuity of G1 socioeconomic status. There are only two time points at which social class is being considered here and if any change did occur it was not possible to determine when this might have been, nor for how long it endured. Nevertheless the measures of mean fetal growth for the four groups of **first-born G2 infants** shown in *Table 10.14* give preliminary insight into the importance of social class measured at different times in the course of a woman's life. The differences in mean fetal growth for these four groups of women suggest that it is not just social class at one point in a woman's development that is important in determining her offspring's size at birth but that changes in social environment over time may lead to different mean fetal growth of her offspring. Further the distribution of G2 size at birth according to social class change of the G1 mothers from birth to adult reproductive life *(Figure 10.1)* suggest that it is not only the mean size at birth that is affected but the entire distribution of G2 offspring size that is shifted according to the combination of the two G1 social class measures. Previously Baird demonstrated that the risk of giving birth to a low birth weight baby was related to childhood socioeconomic circumstances in Aberdeen women (Baird, 1974) and latterly Joffe confirmed this was also true for women in the National Child Development Survey (Joffe, 1989), however the evidence from this cohort suggests that the effects extend across the full range of fetal growth. Further, while traditionally maternal adult social class is regarded as being the important determinant of offspring size at birth it would appear that the earlier maternal childhood social environment also has some additional influence on offspring size.

10.6 Summary

Adult maternal characteristics of height and age at first pregnancy, which are determinants of size at birth, show intergenerational continuity across the entire population

of G1 and G2 births. These maternal adult determinants of offspring size at birth are highly socially patterned as are the measures of size at birth, and the continuity evident in the socioeconomic environment may begin to explain these intergenerational continuities in maternal adult characteristics. Further there is evidence in a subset of mothers in both generations that total family size shows intergenerational continuity. One potential contributory reason for this is the continuity that is seen in pregnancy specific conditions such as gestational hypertension.

The intergenerational continuities that are evident in the parental adult characteristics appear to partially explain the intergenerational continuities in offspring size at birth, but the biological mechanisms and the causal pathways that underlie these relationships remain to be fully elucidated, particularly in view of the anomalous intergenerational associations that are evident, for example, in the differential effect of grandmaternal and maternal parity on G2 fetal growth.

There is also evidence that socioeconomic discontinuity between generations is associated with differential G2 fetal growth. In particular changes in the maternal socioeconomic environment between birth and adult reproductive life are associated with differential mean offspring size at birth. The patterning of offspring size at birth appears to be influenced by social class at both time points and is not fully defined by one measurement at a singular time point.

Only two distinct periods have been considered thus far in the life course of the G1 female (her own fetal development and her adult reproductive status) and there may be other times in her development between birth and adult reproductive life that contribute significantly to her reproductive capacity. Therefore the next chapter moves from an intergenerational approach to consider a lifecourse approach to offspring size at birth.

Table 10.1 : **Frequency distribution of G1 maternal adult height according to G0 maternal adult height category**

G0 Maternal adult height category	G1 Maternal adult height category Frequency (%)				
	<150cm	**150-**	**160-**	**170+ cm**	**Total**
<150cm	40 (14.7)	191 (70.0)	42 (15.4)	0 (0.0)	273 (100)
150 -	91 (5.5)	933 (56.3)	604 (36.5)	28 (1.7)	1656 (100)
160 -	8 (0.7)	358 (29.3)	748 (61.1)	110 (9.0)	1224 (100)
170+ cm	0 (0.0)	11 (14.1)	39 (50.0)	28 (35.9)	78 (100)
Total	139 (4.3)	1493 (46.2)	1433 (44.4)	166 (5.1)	3231 (100)

Table 10.2 : **Mean G1 maternal adult height according to G0 maternal adult height category**

G0 Maternal adult height category	G1 Maternal adult height (cm)	
	Frequency	**Mean (standard deviation)**
<150cm	273	154.0 (4.9)
150 -	1656	157.8 (5.3)
160 -	1224	162.2 (5.5)
170+ cm	78	166.4 (6.4)
Total	3231	159.4 (6.1)

Table 10.3 : **Mean G1 maternal age at first pregnancy according to G0 maternal age category at first pregnancy (1012 pairs of primigravidae)**

G0 Maternal Age (years) at first Pregnancy	Frequency	G1 Maternal Age (years) at first pregnancy Mean (SD)
15-19	89	22.6 (5.2)
20-24	566	23.5 (4.7)
25-29	258	24.9 (5.0)
30-34	71	25.0 (5.2)
35+	28	25.6 (3.8)
Total	1012	23.9 (4.8)

Table 10.4 : **Mean G1 maternal age at first pregnancy according to G0 paternal age category at time of G0 maternal first pregnancy (1012 pairs of primigravidae)**

G0 Paternal Age (years) at first Pregnancy	Frequency	G1 Maternal Age (years) at first pregnancy Mean (SD)
15-19	31	21.5 (4.2)
20-24	385	22.9 (4.8)
25-29	403	24.3 (4.8)
30-34	132	25.3 (5.2)
35+	61	25.7 (4.7)
Total	1012	23.9 (4.8)

Table 10.5 : **Effect of G0 maternal and G0 paternal age on G1 maternal age at first pregnancy (n=1012 pairs of G0 and G1 maternal primigravidae)**

G0 Characteristic	G1 Maternal age at first pregnancy		
	Crude Regression coefficient (95% C.I.)	Adjusted for both ages Regression coefficient (95% C.I.)	Adjusted for both ages and G0 social class Regression coefficient (95% C.I.)
Maternal age (per 5 years)	0.89 (0.68 , 1.19)***	0.46 (0.02 , 0.91)NS	0.30 (-0.14 , 0.73)NS
Paternal age (per 5 years)	1.00 (0.81 , 1.28)***	0.91 (0.52 , 1.29)***	0.80 (0.41 , 1.12)***
Paternal Social Class	-1.18 (-1.43, -0.92)***	--	-1.19 (-1.53 , -0.89)***

***** Significant at p<0.001 level**

NS = non-significant

Table 10.6 : **Frequency distribution of hypertension in G1 pregnancy (1967-99) according to classification of hypertension in G0 pregnancy (1950-55)**

G0 Pregnancy	G1 Pregnancy Frequency (%)			
	No hypertension	Other hypertension	Pre-eclampsia	Total
No hypertension	4080 (75.9)	1160 (21.6)	136 (2.5)	5376 (100)
Other hypertension	639 (67.4)	272 (28.7)	37 (3.9)	948 (100)
Pre-eclampsia	147 (68.4)	59 (27.4)	9 (4.2)	215 (100)
Total	4866 (74.4)	1491 (22.8)	182 (2.8)	6539 (100)

Table 10.7 : **Frequency distribution of hypertension in G1 hypertension pregnancy (1967-99) according to G1 maternal size at birth category (1950-55)**

G1 Maternal size at birth	G1 Pregnancy Frequency (%)			
	No hypertension	Other hypertension	Pre-eclampsia	Total
SGA	475 (72.9)	153 (23.5)	23 (3.6)	651 (100)
AGA	3902 (74.5)	1194 (22.8)	139 (2.7)	5235 (100)
LGA	489 (74.9)	144 (22.1)	20 (3.0)	653 (100)
Total	4866 (74.4)	1491 (22.8)	182 (2.8)	6539 (100)

SGA = Small for gestational age (less than the 10^{th} centile of birthweight for gestational age)

AGA = Appropriate for gestational age (between the 10^{th} and 90^{th} centile of birthweight for gestational age)

LGA = Large for gestational age (greater than the 90^{th} centile of birthweight for gestational age)

Table 10.8 : **Odds ratio for any hypertension in G1 pregnancies (1967-99) according to classification of hypertension in G0 pregnancies (1950-55)**

	Any hypertension in G1 pregnancy OR (95% C.I.)		
G0 pregnancy	**Crude**	**Adjusted***	**Adjusted****
No hypertension (ref.)	1.0	1.0	1.0
Other hypertension	1.5 (1.3 , 1.8)	1.5 (1.3 , 1.8)	1.5 (1.3 , 1.8)
Pre-eclampsia	1.5 (1.1 , 1.9)	1.4 (1.1 , 2.0)	1.4 (1.1 , 1.9)

***Adjusted** for G1 maternal height, age and parity

****Adjusted** for G1 maternal height, age, parity and maternal fetal growth

Table 10.9: **Odds ratio for pre-eclampsia in G1 pregnancies (1967-99) according to classification of hypertension in the G0 pregnancies (1950-55)**

	Pre-eclampsia in G1 pregnancy OR (95% C.I.)		
G0 pregnancy	**Crude**	**Adjusted***	**Adjusted****
No hypertension	1.0	1.0	1.0
Other hypertension	1.6 (1.1 , 2.3)	1.6 (1.1 , 2.3)	1.6 (1.1 , 2.3)
Pre-eclampsia	1.8 (0.9 , 3.3)	1.6 (0.8 , 3.2)	1.6 (0.8 , 3.2)

***Adjusted** for G1 maternal height, age and parity

****Adjusted** for G1 maternal height, age, parity and maternal fetal growth

Table 10.10 : **Frequency distribution of G1 paternal social class (at the time of G2 birth) according to G0 paternal social class**

Grandpaternal (G0) social class category	Paternal (G1) social class category Frequency (%)					
	I&II	IIINM	IIIM	IV&V	Other	Total
I&II	140 (52.8)	28 (10.6)	39 (14.7)	35 (13.2)	23 (8.7)	265 (100)
IIINM	306 (25.9)	157 (13.3)	385 (32.5)	241 (20.4)	94 (7.9)	1183 (100)
IIIM	125 (19.2)	69 (10.6)	240 (36.9)	167 (25.6)	50 (7.7)	651 (100)
IV&V	124 (12.6)	87 (8.8)	376 (38.3)	297 (30.2)	99 (10.1)	983 (100)
Other	22 (14.7)	14 (9.5)	40 (26.8)	53 (35.6)	20 (13.4)	149 (100)
Total	717 (22.2)	355 (11.0)	1080 (33.4)	793 (24.5)	286 (8.9)	3231 (100)

Table 10.11 : **Odds ratio for G1 partner being in manual social class according to G0 manual paternal social class category(n=2945)***

G0 Paternal Social class	G1 partner in manual social class OR (95% CI)
I&II	0.20 (0.15 , 0.29)
IIINM	0.64 (0.52 , 0.79)
IIIM(reference)	1.00
IV&V	1.52 (1.21 , 1.91)
Other	1.23 (0.81 , 1.86)
	p-value (for trend) < 0.001

* G1 "other" paternal social class excluded as not possible to classify as manual or non-manual

Table 10.12 : **Intergenerational determinants of G2 fetal growth conditional on G1 fetal growth(n=6539)**

Intergenerational characteristics	Crude	Effects on Conditional G2 Fetal growth –Controlling for: G0 adult characteristics	G1 adult characteristics	G0 adult characteristics and G1 adult characteristics
	Coefficient (95% C.I.)	Coefficient (95% C.I.)	Coefficient (95% C.I.)	Coefficient (95% C.I.)
G0 Social Class I&II	0.0	0.0		0.0
IIINM	-0.15 (-0.25 , -0.06)	-0.04 (-0.13 , 0.05)		0.02 (-0.07 , 0.11)
IIIM	-0.12 (-0.22 , -0.01)	0.07 (-0.02 , 0.17)		0.13 (0.04 , 0.24)
IV&V	-0.23 (-0.32 , -0.13)	-0.01 (-0.11 , 0.08)		0.08 (-0.02 , 0.17)
Other	-0.30 (-0.44 , -0.16)	-0.08 (-0.22 , 0.06)		0.01 (-0.13 , 0.15)
p-value (trend)	p<0.001	p=0.13		p=0.09
G0 Height (per cm)	0.02 (0.01 , 0.03)***	0.01 (0.01 , 0.02)***		0.0 (0.01 , 0.01) NS
G0 Age Delivery (per 5 years)	0.03 (0.01 , 0.05)**	0.05 (0.03 , 0.08)***		0.03 (0.01 , 0.06)**
G0 Parity (per birth)	-0.04 (-0.06 , -0.02)***	-0.08 (-0.10 , -0.06)***		-0.06 (-0.08 , -0.03)***
G0 Pre-eclampsia (no/yes)	0.04 (-0.10 , 0.17)NS	0.11 (-0.02 , 0.24) NS		0.08 (-0.05 , 0.20) NS
G1 Social Class I&II	0.0		0.0	0.0
IIINM	-0.09 (-0.17 , 0.01)		-0.02 (-0.10 , 0.07)	-0.02 (-0.10 , 0.07)
IIIM	-0.19 (-0.25 , -0.12)		-0.07 (-0.14 , -0.01)	-0.08 (-0.14 , -0.01)
IV&V	-0.33 (-0.40 , -0.26)		-0.19 (-0.26 , -0.12)	-0.19 (-0.25 , -0.12)
Other	-0.14 (-0.23 , -0.04)		-0.13 (-0.22 , -0.04)	-0.11 (-0.21 , -0.02)
p-value (trend)	p<0.001		p<0.001	p<0.001
G1 Height (per cm)	0.04 (0.03 , 0.04)***		0.03 (0.02 , 0.04)***	0.03 (0.02 , 0.03)***
G1 Age at Delivery (per 5 years)	0 14 (0 12 , 0.16)***		0.06 (0.04 , 0.09)***	0.05 (0.03 , 0.08)***
G1 Parity (per birth)	0.14 (0.12 , 0.17)***		0.12 (0.09 , 0.15)***	0.12 (0.10 , 0.15)***
G1 Pre-eclampsia (no/yes)+	-0.19 (-0.33 , -0.04) *		-0.09 (-0.23 , 0.05) NS	-0.10 (-0.24 , 0.03) NS

NS = non-significant * significant at p<0.05 level ** significant at p<0.01 level ***significant at p<0.001 level

+ Treated as a binary variable none and "other" hypertension treated as no pre-eclampsia

Table 10.13 : **Intergenerational determinants of G2 fetal growth conditional on G1 fetal growth: restricted to subset with G1 smoking information(n=3665)**

			Effects on Conditional G2 fetal growth – Controlling for:			
Intergenerational characteristics		**Crude**	**G0 adult characteristics**	**G1 adult characteristics + Smoking**	**G0 adult characteristics and G1 adult characteristics**	**G0 adult characteristics and G1 adult characteristics + smoking**
		Coefficient (95% C.I.)	**Coefficient (95% C.I.)**	**Coefficient (95% C.I.)**	**Coefficient (95% C.I.)**	**Coefficient (95% C.I.)**
G0 Social Class	**I&II**	0.0	0.0		0.0	0.0
	IIINM	-0.18 (-0.34 , -0.04)	-0.06 (-0.21 , 0.08)		-0.02 (-0.16 , 0.12)	-0.03 (-0.17 , 0.11)
	IIIM	-0.19 (-0.35 , -0.04)	0.01 (-0.14 , 0.16)		0.07 (-0.08 , 0.22)	0.05 (-0.09 , 0.20)
	IV&V	-0.25 (-0.40 , -0.10)	-0.01 (-0.16 , 0.14)		0.06 (-0.09 , 0.21)	0.07 (-0.07 , 0.22)
	Other	-0.37 (-0.63 , -0.10)	-0.12 (-0.38 , 0.14)		-0.06 (-0.32 , 0.19)	0.02 (-0.22 , 0.27)
	p value (trend)	p<0.001	p–0.40		p–0.10	p=0.14
G0 Height (per 1 SD)		0.03 (0.02 , 0.03)***	0.02 (0.01 , 0.02)***		0.00 (-0.01, 0.01) NS	0.00 (-0.01 , 0.01) NS
G0 Age Delivery (per 5 years)		0.05 (0.02 , 0.08)**	0.07 (0.03 , 0.10)***		0.04 (0.01 , 0.08)**	0.03 (-0.01 , 0.05) NS
G0 Parity (per increase)		-0.04 (0.06 , -0.01)**	-0.08 (-0.11 , -0.05)***		-0.06 (-0.09 , -0.03)***	-0.04 (-0.07 , -0.01)*
G0 Pre-eclampsia (no/yes)		0.01 (-0.16 , 0.17)NS	0.06 (-0.10 , 0.22) NS		-0.01 (-0.17 , 0.15) NS	-0.01 (-0.16 , 0.15) NS
G1 Social Class	**I&II**	0.0		0.0	0.0	0.0
	IIINM	-0.08 (-0.20 , 0.04)		-0.01 (-0.12 , 0.10)	-0.01 (-0.12 , 0.11)	-0.01 (-0.13 , 0.10)
	IIIM	-0.20 (-0.28 , -0.11)		-0.04 (-0.13 , 0.03)	-0.09 (-0.17 , -0.01)	-0.05 (-0.14 , 0.03)
	IV&V	-0.36 (-0.46 , -0.27)		-0.13 (-0.22 , -0.04)	-0.22 (-0.32 , -0.13)	-0.14 (-0.23 , -0.04)
	Other	-0.14 (-0.30 , 0.03)		-0.01 (-0.17 , 0.14)	-0.09 (-0.25 , 0.06)	-0.01 (-0.17 , 0.14)
	p-value (trend)	p<0.001		p=0.02	p<0.001	p=0.01
G1 Height (per cm)		0.04 (0.03 , 0.04)***		0.03 (0.02 , 0.03)***	0.03 (0.02 , 0.03)***	0.03 (0.02 , 0.03)***
G1 Age at Delivery (per 5 years)		0.15 (0.12 , 0.18)***		0.04 (0.01 , 0.07)*	0.07 (0.04 , 0.10)***	0 04 (0.01 , 0.07)*
G1 Parity (per increase)		0.16 (0.12 , 0.19)***		0.14 (0.11 , 0.18)***	0.13 (0.10 , 0.17)***	0.14 (0.11 , 0 18)***
G1 Pre-eclampsia (no/yes)		0.22 (-0.38 , -0.06) **		-0.14 (-0.29 , 0.01) NS	-0.10 (-0.25 , 0.05) NS	-0.14 (-0.29 , 0.00) NS
G1 Smoking	**None (ref)**	0.0		0.0		0.0
	<10/day	-0.31 (-0.42 , -0.21)		-0.28 (-0.38 , -0.18)	—	-0.27 (-0.37 , -0.18)
	10-20perday	-0.46 (-0.54 , -0.40)		-0.41 (-0.48 , -0.33)		-0.40 (-0.48 , -0.33)
	>20 / day	-0.63 (-0.77 , -0.48)		-0.52 (-0.66 , -0.39)		-0.51 (-0.65 , -0.37)
	p-value (trend)	p<0.001		p<0.001		p<0.001

NS = non-significant * significant at p<0.05 level ** significant at the p<0.01 level *** significant at p<0.001 level

Table 10.14 : **G1 Maternal adult height, age at first pregnancy and first-born offspring fetal growth according to G1 social class at birth* and in adult reproductive life⁺ restricted to primigravidae (n=2537)**

G1 Social class Categories Birth/Adult	**M/M n=965**	**NM/M n=636**	**M/NM n=360**	**NM/NM n=576**
Maternal adult height (cm)				
Mean (SD)	158.3 (5.8)	159.3 (5.9)	159.9 (5.8)	161.1 (6.0)
Age at first pregnancy (years)				
Mean (SD)	21.9 (4.2)	23.0 (4.1)	24.2 (4.5)	25.8 (4.5)
Fetal growth of first born G2 offspring				
Mean (SD)	-0.27 (1.0)	-0.25 (0.9)	-0.11 (0.9)	-0.08 (0.9)

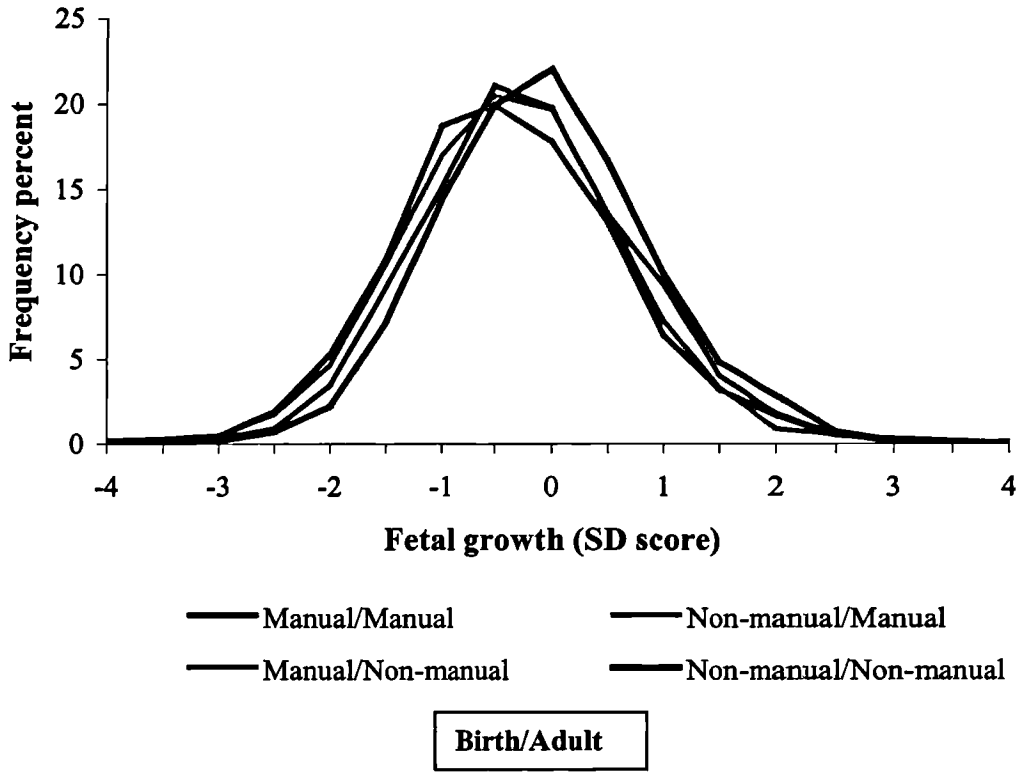
*** Defined by Father's social class at the time of birth** (Other not included)

⁺ Defined by Partner's social class at time of pregnancy (Other not included)

NM= Non-manual (Social classes I, II and IIINM)

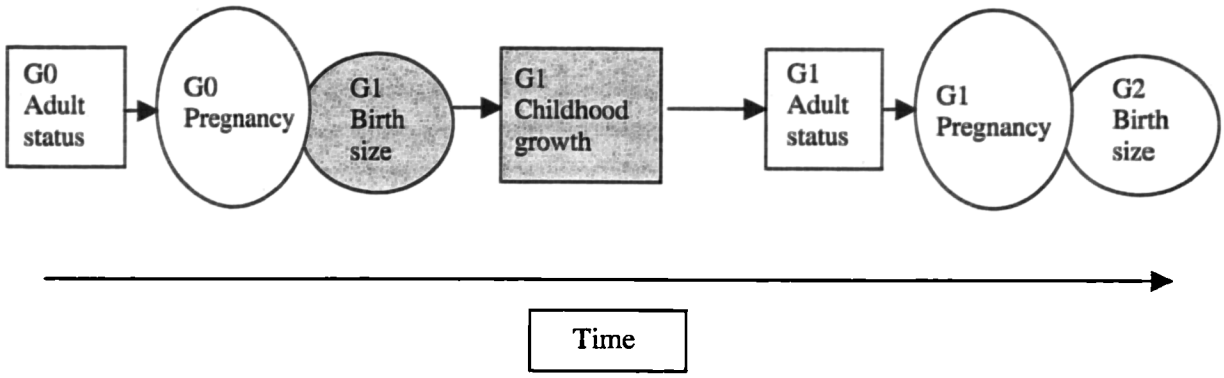
M = Manual (Social classes IIIM, IV and V)

Figure 10.1 : **Distribution of G2 fetal growth according to the combination of G1 maternal social class at birth and in adult reproductive life**



Chapter 11:

Maternal Childhood Growth –Towards a Lifecourse Approach



Consideration of the determinants of G2 size at birth have to date focussed on only two periods in a G1 woman's life, her intrauterine development and her adult life characteristics. Whilst maternal characteristics measured at both these times have been shown to have important influences on her offspring's fetal growth the potential influence of her development between birth and adult reproductive life has yet to be considered. This chapter moves from an intergenerational towards a life course approach to offspring size at birth by considering the impact of differential maternal childhood growth on the fetal growth of her offspring. Ideally, for a lifecourse approach, it would be preferable to examine the development of a woman between birth and her reproductive life at several different stages, however as is the case with almost all historically collected data, these stages are limited to the times at which developmental measurements were made. For this cohort there were repeated measures of childhood size and IQ test scores made between the ages of 4 and 11 years of age, of varying completeness. Therefore the determinants of childhood growth of the G1 reproducers up to the age of school entry (4 to 6 years of age) will be considered to illustrate a way of moving towards a lifecourse approach to the determinants of G2 offspring size at birth. In order to take a lifecourse approach to childhood growth the emphasis will be on an analysis of change in maternal size over time rather than a consideration of cross-sectional measurements of size.

11.1 Why consider size in childhood?

Much evidence exists for the importance of maternal size in adulthood, maternal pre-pregnancy weight and adult height in particular, as determinants of a woman's offspring size at birth. Historically the studies of Ounsted and Ounsted (Ounsted and Ounsted,

1968; Ounsted and Ounsted, 1973) linked maternal adult stature to reproductive outcome within a generation and latterly Emanuel found that maternal growth achieved before pregnancy in adulthood was one preconceptual factor which might affect reproductive outcome over more than one generation (Emanuel, 1993). However the focus has been largely on attained adult size and there is less evidence for the effect of maternal size in childhood being an influence on reproductive outcome. There is some indirect evidence from the 1958 British birth cohort study in which early age at menarche was noted to be a predictor of offspring size (Hennessy and Alberman, 1998a). However early age at menarche was used as a proxy for childhood growth in this study, having previously been found to be associated with weight at the age of 7 years and in turn with adult weight (Cooper et al., 1996) in the earlier 1946 British birth cohort. It was also included as a binary variable, whereas for this Aberdeen intergenerational cohort continuous measures of childhood height and weight are available.

11.2 Maternal childhood size of G1 reproducers

For the G1 cohort who were included in the original Child Development Study, measurements of height and weight in childhood were part of the routine health examination on entry to primary school in Scotland. For most children this occurred between the ages of 4 and 6 years (48-83 months inclusive) and analyses are restricted to this group for comparability between individuals. In 1963 the original study recorded the childhood measurements of height in inches and weight in pounds from the school health records for all the children in the study. These were converted to centimetres and kilograms respectively by the original researchers.

In *Chapter* 3 a basic description of the measures of childhood size was given for all core G1 females who were in the original Aberdeen Child Development study, aged 4 to 6 years at measurement with complete height and weight measures available. However in this chapter the group of females is restricted to the G1 females who are known to have reproduced because the intention is to understand better the effect of maternal lifecourse development on offspring size at birth. In *Chapter 6* the early life characteristics of the G1 females who were linked to deliveries were compared to those who were not linked. There was no evidence of differential intrauterine growth between the linked and unlinked females and, after adjusting for adult trace status in 2001, differences in childhood size were also not significantly associated with the odds of G1

adult reproduction. However the odds of a G1 female reproducing in adult life were found to be significantly associated with shorter G0 maternal height and lower G0 paternal social class.

Of the 3231 G1 female reproducers in the intergenerational dataset 3090 (95.6%) had complete weight and height measurements in childhood at the age of 4 to 6 years. The other 141 females were excluded either because of incomplete childhood size information (74/141, 52%) or because childhood measurements were taken after 83 months of age (67/141, 48%). This excluded group tended to be slightly smaller on average at birth than the 3090 with complete childhood measurements, but not significantly so. There was however no evidence of any differences in parental characteristics. In particular G0 maternal height and G0 paternal social class distributions were not significantly different between the included and excluded females. There was also no evidence of any difference in school IQ test performance between the included and excluded females at the age of seven years (mean IQ test scores were 109 vs.108 respectively, p=0.55).

Despite excluding G1 females who were not measured between the ages of 4 to 6 years, the range of age at measurement of the included group was nevertheless 36 months (mean age at measurement = 61 months, standard deviation = 3 months) during which time the G1 females may have been growing at different rates. Therefore in addition to measures of height (in cm), weight (in kg) and childhood Body Mass Index (BMI in kg/m^2), childhood measurements are represented as standard deviation (SD) scores of height and weight adjusted for age*.

The objective was to consider if differential G1 childhood growth (being change in size over time) might be related to differential G2 fetal growth of these G1 female's offspring, rather than to assess measures of size in childhood *per se*, which has previously been considered for populations of children in the United Kingdom and the United States (Davie et al., 1972; Baird, 1977; Tanner, 1978; Rona and Morris, 1982; Binkin et al., 1988; Roche, 1992). However to consider maternal childhood growth as part of the development of a G1 female over her lifecourse it was first necessary to

* Height for age and Weight for age SD scores were internally standardised normal variables calculated using the means and standard deviations of heights and weights for each 3 month age period between 48 and 83 months of age for all the core first generation females described in Chapter 3.

understand the earlier determinants of that growth, that is how her childhood size related to her G0 parental characteristics and her own G1 size at birth.

11.2.1 G1 childhood size according to G0 parental characteristics – univariate relationships

For the included 3090 G1 reproducers mean weight at 4 to 6 years of age was 18.5kg (SD = 2.3kg) and mean height at school entry was 107.1cm (SD = 5.3 cm). Mean BMI was 16.1 kg/m^2 (SD=1.4) and standardised mean weight and height for age scores were both –0.01, with standard deviations of 1.0. These were almost identical to all the mean childhood measures for the 4871 core first generation females with complete childhood data (*Section 3.5*).

Table 11.1 shows that the mean measures of size in childhood for the 3090 G1 females were strongly patterned by G0 parental adult biological and social characteristics. Childhood G1 weight was positively associated with G0 maternal height ($p<0.001$) and negatively associated with increasing maternal parity ($p<0.001$) and increasing family size ($p<0.001$). However childhood weight showed no clear relationship with G0 maternal age at delivery ($p=0.28$ for trend). These associations were seen for both absolute weight at 4-6 years and weight adjusted for age SD scores. Mean G1 height at school entry was also positively associated with G0 maternal adult height ($p<0.001$ for trend) and G0 maternal age at delivery ($p=0.03$ for trend), but was similarly negatively associated with maternal parity ($p<0.001$) and family size ($p<0.001$). These associations also existed for height adjusted for age SD scores (*Table 11.1*). Having been born to a G0 mother with any hypertension complicating her pregnancy was associated with increased absolute and age adjusted childhood weight and height at 4 to 6 years of age.

Mean size in childhood was also strongly patterned by G0 paternal social class ($p<0.001$ for trend). G1 females with fathers in Social class I were on average 2.4 kg heavier and 6.2 cm taller at school entry than females with fathers in Social class V. This was not the result of differences in age at measurement as the pattern was as strong for height for age and weight for age measures.

There was a tendency for G1 females with shorter G0 mothers to have a slightly greater BMI than those with taller mothers but otherwise BMI at this age was not clearly patterned by G0 parental characteristics in this cohort. In particular the relationship of G1 childhood BMI to G0 paternal social class tended towards being U-

shaped rather than linear, with the highest mean BMI in the most and the least socially advantaged groups of females (*Table 11.1*).

11.2.2 G1 childhood size according to G0 parental characteristics - multivariate relationships

The G0 parental characteristics that are associated with measures of childhood size are not independent (Chapter 8). Therefore multivariate regression was used to assess which G0 parental characteristics remained important influences on G1 childhood size after mutual adjustment for all the related characteristics. The outcome measures were weight and height adjusted for age rather than absolute values because of the 36 month range of age of the females at measurement. It should be noted however that there was no change in the significance of the predictor variables if absolute height and weight measures were used (results not shown). Standardised weight and height for age scores were preferred to parallel the fetal growth scores (birthweight adjusted for gestational age) used to characterise size at birth. Childhood BMI measures were not used further as outcome measures largely because debate continues in the literature about the usefulness of the Quetelet index (BMI = weight (kg)/ height $(m)^2$) as a measure of weight for height in childhood. In a study using measurements from the 1958 British Child Development Study it was shown that BMI was not independent of height at different ages in childhood, undermining the key rationale for using such a measure (Freeman et al., 1995b). Further for the same population it was noted that whilst childhood height at seven years was highly predictive of adult height (correlation of 0.7) the correlation of childhood BMI at the same age with adult BMI was much weaker (Power et al., 1997b). The Fels longitudinal growth study from Ohio studied serial changes in body "fatness" during childhood and adolescence from 2 to 18 years (Siervogel et al., 1991). It was noted that the minimum mean value of BMI in childhood occurred between the ages of 4 and 6 years for this American population, with a minimum value of approximately $15kg/m^2$ in females at the age of 6 years. Prior to 6 years of age mean BMI tended to be decreasing from a highpoint in late infancy and subsequently increased until after puberty. Therefore the BMI measurements in this group of Aberdeen females have probably occurred at or near to a turning point in terms of increase or decrease in magnitude. They are also not independent of height measured at the same age for these females, but rather are negatively correlated with a correlation coefficient of $r = -0.18$ ($p<0.001$). Therefore whilst it would be useful to include an

outcome measure of weight for height, in the absence of agreement about the usefulness of the Quetelet, or any other weight/height^n (n>0) index for this age group, measures of standardised height for age and weight for age only were used.

G0 maternal height, age, parity and family size were entered as continuous measures but G0 paternal social class was categorical and maternal hypertension in pregnancy was considered as a binary variable (no hypertension versus any hypertension). Paternal social class was grouped into fewer groups than those in *Table 11.1* to increase the numbers of females particularly in the highest category which was the reference group in the regression analyses. There was no evidence to suggest a departure from linearity in the univariate relationship between any of the parental characteristics and childhood height and weight for age measurements, nor was there any evidence of interaction between the related variables. The crude relationships of childhood weight and height for age in *Tables 11.2* and *11.3* with each of the G0 parental characteristics confirm the associations shown for the categorical breakdown of these variables in *Table 11.1.* In the mutually adjusted analyses the G0 parental characteristics that remained important predictors of weight for age and height for age were very similar, which might be expected given the high correlation between weight and height at school entry for this cohort ($r= 0.70$, $p<0.001$). All the parental social and biological variables remained significant predictors of childhood weight for age after mutual adjustment for the effects of each. The same is true for height for age, with the exception of maternal pregnancy hypertension which just failed to reach statistical significance ($p=0.07$). In general G1 females born to older, taller G0 mothers were taller and heavier for their age at school entry than females born to shorter, younger women. Females born as a result of pregnancies that were complicated by hypertension tended to be heavier and taller in childhood than their peers. However females born to mothers of high parity tended to be smaller in childhood, as did those born into large families regardless of birth order. The gradient seen in childhood size with respect to G0 paternal social class was partly explained by the differences in other maternal variables but it nevertheless remained a significant predictor after mutual adjustment, with children in less advantaged families being smaller for their age, in terms of weight and height, at school entry than their more advantaged peers.

11.2.3 Comparison of G0 parental influences on measures of G1 size at birth and G1 size in childhood

G1 fetal growth and G1 childhood weight for age and height for age were all significantly associated with G0 parental adult characteristics. The direction of these parental associations with G1 childhood size were the same as with G1 size at birth for G0 maternal height and age at delivery and G0 paternal social class but in the opposite direction for increasing G0 maternal parity. This probably reflects the two different implications of increased maternal parity for different stages of early development. Perinatally parity indicates the extent of maternal constraint likely to be exerted on fetal growth in utero, with constraint getting less and mean fetal growth tending to increase with increasing parity. However postnatally increasing parity indicates that the child was of higher birth order, i.e. potentially had several older siblings, which, as the negative association between childhood size and family size suggests, seems to have a limiting effect on postnatal size.

What is not yet clear after comparing the G0 patterning of cross-sectional measures of G1 size at birth and size in childhood is whether the patterning of childhood size is entirely mediated through the G0 patterning of size at birth or whether the G0 parental characteristics have an influence on postnatal growth through pathways other than via size at birth.

11.3 The concept of childhood growth (change in childhood size)

Rather than just considering and comparing the determinants of two cross-sectional measures of early maternal size the change in size between birth and school entry, or growth as it more appropriately termed, is the focus of this section. Childhood growth is important as a predictor of a child's general well-being and childhood measurements are used widely throughout infant, pre-school and school health assessments to detect, in particular, children who are considered to be at risk of growth-failure (or failure-to-thrive). Standardised population growth charts have been the usual method used to monitor the growth of an individual and to track changes in size over time. Until those developed by Cole et al (Freeman et al., 1995a) they have usually been derived from sets of cross-sectional measurements, rather than measurements obtained longitudinally. The underlying assumption in using growth charts is that a child should largely track along one centile of growth to be considered to be growing "normally". However if the aim is to measure longitudinal growth for individuals then repeatedly comparing them

to cross-sectional standardised measures is not the most appropriate way to consider temporal change. The aim for these G1 females is to use the information on size at birth and size at school entry to capture a measure of change in size over time that compares their childhood growth with their peers according to their relative size at birth.

One particular aspect of change in size over time that will be examined in this cohort is the concept of "catch-up" growth. This term has commonly been applied when the longitudinal growth pattern of an individual leads to crossing upwards of centiles on "growth" charts. Historically "catch-up" growth was defined by Tanner in 1978 as "the rapid growth following the end of a period of growth restriction for whatever reason" (Tanner, 1978), but attributed usually to the recovery phase following the temporary fall-off in growth due to the effects of disease or ill-health. Since that time "catch-up" growth has generally been thought of as very much a biological, genetically driven phenomenon (Tanner, 1981), the tempo of which is set by intrauterine development. In a recent paper "catch-up" growth was stated to be "a property of human growth whereby children return to their genetic trajectory after a period of growth arrest or delay, and that pronounced "catch-up" growth is often seen after severe intrauterine growth retardation" (Ong et al., 2000). "Catch-up" growth has recently taken on renewed significance as it appears to modify the adult health risks associated with reduced intrauterine growth. It has been suggested that infants who are born smallest but who show accelerated postnatal growth (that is "catch-up") are at greatest risk of cardiovascular disease as adults (Eriksson et al., 1999). Many studies that have previously examined the predictors of "catch-up" have been largely concerned with "at risk" groups of infants, low birthweight, small for gestational age and preterm in particular (Hack et al., 1996), rather than with predictors for a whole population. They have also tended to concentrate on biological predictors of "catch-up" growth, including size at birth (Ong et al., 2000). While social factors are acknowledged to influence size in childhood (Rona et al., 1978) there have been few attempts to determine whether groups of infants whose parents share different socioeconomic characteristics grow differently in childhood (dos Santos Silva et al., 2002). Therefore the biological and social determinants of childhood growth (change in size between birth and school entry), including "catch-up" growth, will be considered for G1 females.

11.3.1 Change in G1 size between birth and school entry relative to size at birth

Consideration of the change between size at birth and size at school entry was restricted to considering change in weight to maintain a consistency in the measurement type at both time points, as only birth weight and not birth length was available for these G1 females. The greatest change in childhood size is known to occur in the first 2 years of life, with the correlation in size from 2 years to later childhood and adulthood being approximately 0.7 (Rona and Morris, 1982). Intermediate measurements between birth and school entry were not available for these G1 females, but the change in measurements between birth and school entry should have encapsulated this early period of rapid and individually variable change.

Using weight for age scores at both time points allowed direct comparison of the two scores independent of age at measurement (gestational age at delivery or age at 4 to 6 years) and removed the problem of increasing variance of measurements over time since both scores were internally standardised (Cole, 1995). Each absolute weight for age SD score represented the relative deviation from the internal population mean for either a G1 female born the same gestational age, or a child measured at the same age, together with a positive or negative sign to denote whether the deviation was above or below the mean.

G1 maternal size at school entry was positively associated with maternal size at birth with a Pearson correlation coefficient equal to 0.31 ($p<0.001$). The relationship existed across the full range of size at birth and size in childhood (*Table 11.4*) with the quintile of G1 size in childhood being positively associated with the quintile of G1 size at birth ($X^2 = 323$ (16 d.f.), $p<0.001$).

To consider this relationship further and to determine in particular how "catch-up" growth in childhood might be related to size at birth G1 females were grouped according to tenths of fetal growth. The mean size (in normalised SD age adjusted scores) of each of these groups at birth and at 4 to 6 years was compared diagrammatically (*Figure 11.1*). Comparing the average slope of their trajectories, G1 females who were smallest for gestational age at birth tended to show the greatest average "catch-up" growth by school entry, whereas those females who were largest for gestational age tended to show the greatest average "catch-down" growth.

Numerically "catch-up" growth has been defined using the difference in SD scores over time, and the usual change required for "catch-up" is a positive difference of

greater than 0.67 SD (equivalent to crossing at least one centile on traditional childhood growth charts) (Ong et al., 2000). Applying this numerical definition of "catch-up" growth to the change in SD scores between birth and 4 to 6 years for all 3090 G1 females, 799 (26%) showed significant "catch-up" growth over that time period. However among females who were born small for gestational age (in the lowest ten percent of birthweight for any gestational age) 201/287 (70%) showed "catch-up" growth by school entry. Logistic regression predicted that G1 females who were born small for gestational age were over eight times more likely to show "catch-up" growth then G1 females who were not small for gestational age at delivery (OR=8.6, 95% CI 6.6 – 11.3). Similarly if "catch-down" is defined as a change downwards in SD scores between birth and 4 to 6 years of more than 0.67, then for the 3090 G1 females, 887 (29%) showed "catch-down" growth by school entry. In females who were born large for gestational age (in the greatest ten percent of birthweight for any gestational age) 257/345 (74%) showed "catch-down" growth by school entry. Logistic regression predicted that G1 females who were born large for gestational age were almost ten times more likely to "catch-down" than females who were not large for gestational age (OR=9.8, 95% C.I. 7.6 – 12.7).

However "catch-up" growth is not universal in small for gestational age infants and indeed it also occurs in G1 females who are not classified as small for gestational age at birth. Therefore considering which G1 females are likely to "catch-up" and which are not according to G0 parental characteristics may offer further insight into the determinants of childhood growth, other than size at birth alone.

11.3.2 Change in G1 size between birth and school entry according to G0 parental characteristics – univariate relationships

To consider the G0 parental determinants of differential childhood growth for these G1 females diagrams similar to *Figure11.1* were used. However, instead of dividing the females according to tenths of fetal growth the initial point for each "growth trajectory" was the mean size at birth of G1 infants in each category of the G0 parental adult characteristic under consideration. The size at school entry was the mean weight for age of the same group of infants at 4 to 6 years of age. These diagrams are shown in *Figures 11.2(i)-(vi)* according to the G0 characteristics of adult height, maternal age at delivery, parity, hypertension in pregnancy, paternal social class at the time of the G1 females' birth and G1 family size in 1962. The slope of the trajectories indicates whether each

group of G1 females "caught-up" (positive slope) or "caught down"(negative slope) on average over the period between birth and school entry. The straight line joining the points indicates the average slope of the change, rather than implying that the growth has been constant and linear, which is almost certainly not the case.

(i) Maternal adult height (Figure 11.2(i))

There was a positive gradient in G1 size at birth according to G0 maternal adult height as previously demonstrated (*Chapter 8*). This positive gradient in size according to maternal height was still present at school entry. However unlike the trajectories grouped by size at birth (*Figure 11.1*) there was no evidence of regression to the mean over time with repeated measurements of females grouped according to categories of G0 maternal height. On average the G1 females born to taller G0 mothers were larger at birth and tended to become relatively larger by 4 to 6 years of age, with G1 females born to shorter G0 mothers becoming relatively smaller. Attained size in childhood is often regarded as an indicator of true genetic potential after maternal constraint during intrauterine development. However the divergence of the extreme groups, given that both measures are standardised, suggests that the postnatal growth trajectory may not simply represent a return to a genetically determined course after the release of maternal intrauterine restraint.

(ii) Maternal age (Figure 11.2(ii))

Mean G1 size at birth increased as G0 maternal age increased, as previously described in *Chapter 8*. However by school entry the differences in size with respect to maternal age at delivery had disappeared. The G1 females born to the youngest G0 mothers (aged <25 at delivery) had shown the greatest "catch-up" growth (positive shift in mean size) in the preschool years, whereas those born to mothers aged over 30 years at delivery had shown considerable "catch-down" growth (negative shift in size at school entry). This was probably due in part to the association between increasing maternal parity and increasing maternal age. The youngest G0 mothers were likely to be primiparous, whereas in the 1950s G0 mothers delivering infants over the age of 30 were more likely to be multiparous.

(iii) Maternal parity (Figure 11.2(iii))

Mean G1 size at birth tended to increase with increasing G0 parity. However at school entry the ranking of mean childhood size according to maternal parity was entirely the opposite of the ranking of the same groups of infants at birth. The higher the G0 parity the smaller the G1 female was likely to be on average relative to the whole cohort at school entry. This confirmed the observation in section 11.2.3, whereby increased parity was noted to have a positive effect on fetal size but a negative effect on postnatal size. This figure however highlights the extent of the change in relative size and the grading of the effect for each stepwise increase in parity. This change in size in childhood according to maternal parity may well have contributed to the changes seen in childhood growth with respect to maternal age considered in (*ii*) above.

(iv) Maternal hypertension in pregnancy (Figure 11.2(iv))

G1 infants born to G0 mothers who either had no hypertension during pregnancy, or "other hypertension" tended to be of average size at birth for this group of infants, whereas G1 females whose mothers had moderate to severe pre-eclampsia during their pregnancies tended to have reduced mean fetal growth. By school entry the mean size of the group unaffected by pregnancy hypertension tended to remain approximately the same, whereas the groups whose G0 mothers had any hypertension had shown considerable postnatal "catch-up" growth, the more severe the pregnancy hypertension the greater the relative positive change. This probably does more closely represent a release of maternal constraint and a return to a genetic potential as described by Tanner. However interestingly according to the latest studies addressing the fetal origins hypothesis it does predispose the group of G1 females who were born to G0 mothers with hypertension in pregnancy to increased risks of hypertension themselves in later adult life, because of reduced intrauterine and accelerated postnatal growth. This finding also concurs with the intergenerational continuities in maternal pregnancy hypertension observed in Chapter 10, since these women may in turn be at high risk of hypertension in their own pregnancies.

(v) Paternal social class (Figure 11.2(v))

Mean G1 size at birth is patterned according to G0 paternal social class at birth, as previously demonstrated for this cohort (Chapter 8). However by school entry the difference between the average size of the G1 females according to their early social

environment had increased, with G1 females in higher social classes tending to "catch-up" and those in lower social classes tending to "catch-down", with the amount of "catch-up or down" being relative to their social class ranking. This divergence of trajectories suggests that there may be social class patterning of childhood size in addition to the patterning of size at birth.

(vi) Family size in 1962 (Figure 11.2(vi))

Size at birth according to family size in 1962 showed a rather mixed picture. Certainly for families with only one child in 1962 mean fetal growth was the least, and for those with more than six children fetal growth was the greatest, however between these two extremes the mean fetal growth showed little or no relationship with family size. This might have been predicted given that family size in 1962 was measured some 7-12 years after the birth of the G1 females and was therefore acting more as a postnatal influence than a prenatal one. However if there was still only one child in 1962 it was almost certainly the first born G1 female, who was likely to be small because her mother was primiparous. Similarly if there were a large number of children in 1962 then the G0 mother was more likely to have been multiparous in 1950-55 and therefore the G1 female was likely to have been larger at birth. However by school entry family size had a clear effect on childhood size with children in the largest families being least likely to "catch-up" and children in the smallest families being most likely to "catch-up" regardless of their parity.

11.4 Change in size between birth and school entry – calculating a measure of change over time

In order to model the combined effect of these parental characteristics on change in childhood size the outcome of interest is the change in size, rather than the maternal size at either point. Change in size may be calculated for each individual by considering their attained size at school entry conditional on their size at birth (both adjusted for age and standardised). This conditional measure essentially captures the information about the individual trajectories of childhood growth which combine to provide the average trajectories shown diagrammatically in *Figure 11.2* for each group of G1 infants. The change measures are estimated as the residuals after regressing maternal weight for age on maternal birthweight for gestational age, shown diagrammatically in *Figure 11.3*. These measures are called "childhood growth" as distinct from "fetal growth" and have

the advantage of being independent of measures of fetal growth. The two variables, fetal growth and childhood growth together define the growth trajectory in childhood of each G1 female. The childhood growth variable represents the deviation from the population average growth at 4-6 years for any individual G1 female, relative to all other G1 female infants who had the same fetal growth.

The overall mean of this childhood growth measure is 0.0 and the standard deviation is 0.9. It is treated as a continuous measure and is normally distributed. The subset of G1 females who have reproduced are slightly more homogeneous than all core first generation G1 females, on whom the standardised size measures are based (Chapter 3). This concurs with earlier discussions that suggested that females who had the greatest growth in childhood were less likely to reproduce as adults (explained almost entirely by selective migration of these females) and the non-significant trend towards those infants born preterm, and likely to have grown less well in childhood, also being less likely to reproduce (Chapter 6).

11.4.1 Change in G1 size between birth and school entry according to G0 parental characteristics – multivariate relationships

The effects of the G0 adult parental characteristics on childhood growth are not independent, as suggested for the biological characteristics of maternal age and maternal parity (with respect to the discussion regarding *Figure 11.2*). In addition G0 paternal social class is associated with G1 family size in 1962, with larger families being associated with lower paternal social class ($r=0.22$, $p<0.001$). Therefore linear regression was used to mutually adjust for these G0 parental variables. The outcome variable was childhood growth as defined above. There was no evidence of departure from linearity or interaction between the explanatory variables. Maternal height, age, parity and family size were treated as continuous variables, but paternal social class was categorical and maternal hypertension in pregnancy was a binary variable (none versus any hypertension).

The results of the regression analyses are shown in *Table 11.5*. The crude analyses confirm the univariate relationships shown in *Figure 11.2*. In particular lower G0 paternal social class has a negative effect on childhood growth, in addition to its previously demonstrated negative effect on size at birth. In the mutually adjusted regression analysis (*Table 11.5*) it appears that a proportion of this negative effect of lower paternal social class on childhood growth acts via socially patterned differences in

G0 maternal height, parity, age and family size. Nevertheless G0 paternal social class exerts a small but significant effect on childhood growth even after adjusting for these other parental characteristics. Therefore childhood growth, including "catch-up" growth, appears to be a socially patterned phenomenon as well as a biological one. Infants born to fathers in lower social classes are likely to be smaller at birth than those born to more advantaged families. In addition they are likely to grow less well and show less "catch-up" growth in childhood and therefore be relatively smaller by school entry than their more socially advantaged peers.

11.5 The effect of differential G1 maternal childhood growth on G2 fetal size at birth

The socioeconomic environment present during a female's childhood seems to be acting at more than one critical point to alter maternal size, acting instead over time to alter a female's childhood growth trajectory which might eventually alter her final adult size and potentially therefore affect her own offspring's fetal growth. This was examined for the 6369 G2 infants who were the offspring of the 3090 G1 female reproducers with complete growth information (*Intergenerational and lifecourse dataset*, Chapter 5). The 170/6539 (2.6%) G2 infants included in the intergenerational analyses but for whom G1 maternal childhood size measures were incomplete did not differ significantly from the included infants with respect to any measures of G2 fetal growth or G1 adult characteristics. For the 6369 included intergenerational pairs of mother and offspring, G2 mean size at birth was positively associated with the quintile of G1 maternal childhood growth (*Table 11.6*, $p<0.001$ for linear trend). Further differential maternal childhood growth was associated with differential G2 fetal growth, shown in *Figure 11.4*, not just in terms of shifting the mean size at birth but in shifting the distribution stepwise towards a higher range of G2 fetal growth for each increasing quintile of G1 maternal childhood growth. The effect on the distribution was not as pronounced as the effect with respect to quintiles of G1 fetal growth (*Figure 9.2*). However childhood growth measures are a measure of postnatal growth that is independent of fetal growth, therefore this suggests that childhood growth has an effect on G2 size at birth that is additional to the effect of fetal growth.

11.6 Summary

Childhood growth has recently emerged as a potential modifier of the association between reduced growth in utero and later adult disease whereby those infants who are small for gestational age but who show significant postnatal "catch-up" growth are potentially at greatest later risk. However over two-thirds of all small for gestational infants show postnatal "catch-up" growth, as defined by centile crossing or a change in SD scores of greater than 0.67 and "catch-up" is not confined to this relatively growth restricted group. If only "at risk" groups of infants defined by categories of reduced size at birth are considered in a study of postnatal growth, then relative to a normal population they might be expected to "catch-up". Hence this information adds little to the a priori information regarding their reduced intrauterine growth status.

However, while the chance of postnatal "catch-up" is associated with reduced intrauterine growth, on a population basis "catch-up" growth is socially patterned and is most common in children born early into small families whose mothers are tall and whose fathers are in high status occupations. Infants who are the same size at birth (in terms of fetal growth scores) with mothers of the same height, age and parity will show differences in their rates of childhood growth according to their childhood socioeconomic environment and their family size. Postnatal catch-up growth is therefore not purely a biological phenomenon that is driven by relative under- or over-growth in utero. Growth in childhood also has long-term implications over a woman's lifecourse in that differential, socially patterned maternal childhood growth leads to differential offspring size at birth, independent of G1 fetal growth.

The challenge is to untangle the determinants of G2 size at birth to try to establish which are the most important times for maternal development so as to know better where to intervene to improve the adult health of G2 offspring by maximising their intrauterine growth. This is the challenge for the next chapter in which the intergenerational and life course determinants of G2 size at birth will be considered together.

Table 11.1 : **Mean and standard deviation G1 childhood size according to categorical G0 parental characteristics (n=3090)**

G0 Parental Characteristic	Frequency	G1 Maternal Childhood size Mean (SD)				
		Weight (kg)	Height (cm)	BMI (kg/m^2)	Weight-for-age SD score	Height-for-age (SD score)
TOTAL	3090	18.5 (2.3)	107.1 (5.3)	16.1 (1.4)	-0.01 (1.0)	-0.01 (1.0)
Maternal height categories (cm)						
<150	263	17.5 (2.0)	103.7 (5.0)	16.2 (1.5)	-0.46 (0.8)	-0.66 (1.0)
150-	1588	18.2 (2.1)	106.0 (4.8)	16.2 (1.5)	-0.16 (0.9)	-0.22 (0.9)
160-	1164	19.1 (2.3)	108.9 (5.1)	16.1 (1.4)	0.23 (1.0)	0.35 (0.9)
170+	75	20.5 (2.7)	112.5 (5.2)	16.1 (1.2)	0.81 (1.1)	1.00 (0.9)
p-value (for linear trend)*		p<0.001	p<0.001	p=0.03*	p<0.001	p<0.001
Maternal Age at delivery (years)						
15-19	118	18.4 (2.0)	106.2 (5.9)	16.3 (1.6)	-0.04 (0.9)	-0.15 (1.1)
20-24	1044	18.5 (2.3)	106.8 (5.3)	16.2 (1.5)	-0.04 (1.0)	-0.07 (1.0)
25-29	983	18.6 (2.3)	107.2 (5.4)	16.1 (1.5)	0.0 (1.0)	0.01 (1.0)
30-34	601	18.5 (2.3)	107.2 (5.2)	16.1 (1.5)	0.0 (1.0)	0.01 (1.0)
35-39	273	18.5 (2.1)	107.4 (4.8)	16.0 (1.1)	-0.02 (0.9)	0.07 (0.9)
40+	71	18.8 (2.9)	107.3 (6.6)	16.3 (1.5)	0.13 (1.2)	0.08 (1.1)
p-value (for linear trend)*		p=0.32	p=0.02	p=0.14*	p=0.28	p<0.001
Maternal Parity						
0	1063	18.9 (2.4)	108.0 (5.2)	16.2 (1.4)	0.15 (1.0)	0.17 (1.0)
1	922	18.5 (2.2)	107.1 (5.2)	16.1 (1.5)	-0.03 (1.0)	0.0 (1.0)
2	546	18.4 (2.2)	107.1 (5.0)	16.0 (1.3)	-0.06 (0.90	-0.02 (0.9)
3	285	18.0 (2.2)	105.5 (5.8)	16.2 (1.7)	-0.23 (1.0)	-0.32 (1.1)
4+	274	17.9 (2.0)	104.9 (5.0)	16.3 (1.4)	-0.28 (0.9)	-0.43 (0.9)
p-value (for linear trend)*		p<0.001	p<0.001	p=0.70*	p<0.001	p<0.001
Maternal hypertension in pregnancy						
None	2545	18.4 (2.3)	106.9 (5.3)	16.1 (1.5)	-0.05 (1.0)	-0.05 (1.0)
Other hyp.#	444	19.0 (2.2)	108.0 (5.3)	16.3 (1.3)	0.17 (1.0)	0.14 (1.0)
Pre-eclampsia	101	18.6 (2.2)	107.8 (5.2)	16.0 (1.1)	0.05 (1.0)	0.16 (0.9)
p-value (for linear trend)*		p<0.001	p<0.001	p=0.07*	p<0.001	p<0.001

G0 Parental Characteristic	Frequency	G1 Maternal Childhood size Mean (SD)				
		Weight (kg)	Height (cm)	BMI (kg/m^2)	Weight-for-age SD score	Height-for-age (SD score)
Paternal social class						
I	37	20.4 (3.3)	111.6 (5.2)	16.3 (1.5)	0.72 (1.3)	0.79 (0.9)
II	193	19.5 (2.5)	109.4 (6.0)	16.3 (1.5)	0.39 (1.0)	0.44 (1.1)
IIINM	1141	18.6 (2.2)	107.7 (5.2)	16.0 (1.4)	0.03 (1.0)	0.11 (0.9)
IIIM	632	18.4 (2.2)	106.9 (5.3)	16.1 (1.4)	-0.07 (0.9)	-0.04 (1.0)
IV	449	18.5 (2.2)	106.5 (4.9)	16.2 (1.5)	-0.04 (1.0)	-0.12 (0.9)
V	503	18.0 (2.1)	105.4 (5.0)	16.2 (1.5)	-0.22 (0.9)	-0.35 (0.9)
Other**	135	18.4 (2.3)	106.1 (5.7)	16.4 (1.4)	-0.06 (0.9)	-0.22 (1.1)
p-value (for linear trend)*		p<0.001	p<0.001	p=0.07*	p<0.001	p<0.001
Childhood family size (in 1962)						
1	286	19.2 (2.5)	108.6 (5.1)	16.3 (1.6)	0.28 (1.1)	0.27 (0.9)
2	990	18.9 (2.4)	108.1 (5.4)	16.1 (1.5)	0.14 (1.0)	0.20 (1.0)
3	794	18.5 (2.2)	107.1 (5.1)	16.1 (1.3)	-0.05 (0.9)	-0.02 (0.9)
4	525	18.2 (2.1)	106.2 (5.0)	16.1 (1.4)	-0.14 (0.9)	-0.16 (0.9)
5	272	17.9 (2.0)	105.0 (4.9)	16.2 (1.5)	-0.29 (0.9)	-0.42 (0.9)
6	123	18.1 (2.1)	105.5 (4.4)	16.2 (1.3)	-0.21 (0.9)	-0.33 (0.8)
7 or more	100	17.7 (1.9)	104.1 (5.6)	16.3 (1.4)	-0.40 (0.8)	-0.59 (1.0)
p-value (for linear trend)*		p<0.001	p<0.001	p=0.55*	p<0.001	p<0.001

* **p-value** refers to test for heterogeneity for mean BMI, not linear trend as for all other measures

** **Other** refers to father unemployed, disabled or single mother

Other hyp. refers to mild pre-eclampsia or other hypertension (as previously defined in Chapter 10)

Table 11.2 : **Effects of G0 parental adult characteristics on G1 childhood weight for age at 4-6years (n=3090)**

G0 Parental characteristic	G1 childhood weight for age (4-6 yrs) Regression coefficient (95% Confidence interval)	
	Crude	Mutually Adjusted
Maternal Height (per cm)	0.05 (0.04 , 0.06)***	0.05 (0.04 , 0.05)***
Maternal Parity (per birth)	-0.11 (-0.14 , -0.08)***	-0.06 (-0.10 , -0.02)***
Maternal Age (per 5 years)	0.02 (-0.01, 0.05) NS	0.04 (0.01 , 0.08)*
Maternal Hypertension # (no/any)	0.19 (0.10 , 0.28)***	0.11 (0.02 , 0.20)*
Paternal Social Class		
I&II (reference)	0.0	0.0
IIINM	-0.42 (-0.55 , -0.30)	-0.28 (-0.41 , -0.15)
IIIM	-0.52 (-0.66 , -0.37)	-0.31 (-0.45 , -0.17)
IV&V	-0.58 (-0.72 , -0.44)	-0.33 (-0.46 , -0.16)
Other	-0.50 (-0.70 , -0.30)	-0.25 (-0.44 , -0.05)
p-value (linear trend)	p<0.001	p<0.001
Family Size (per child)	-0.12 (-0.14 , -0.09)***	-0.07 (-0.10 , -0.04)***

 # Occurring in G0 pregnancy – categorised as none or any which refers to "other hypertension" or pre-eclampsia

*** Significant at p<0.05 level**

***** Significant at p<0.001 level**

NS = not significant

Table 11.3 : **Effects of G0 parental adult characteristics on G1 childhood height for age at 4-6years (n=3090)**

G0 Parental characteristic	G1 childhood height for age (4-6 years) Regression coefficient (95% Confidence interval)	
	Crude	Mutually Adjusted
Maternal Height (per cm)	0.07 (0.06 , 0.08)***	0.07 (0.06 , 0.07)***
Maternal Parity (per birth)	-0.14 (-0.17 , -0.12)***	-0.08 (-0.12 , -0.05)***
Maternal Age (per 5 years)	0.04 (0.01 , 0.07)*	0.08 (0.05 , 0.11)***
Maternal Hypertension # (no/any)	0.19 (0.09 , 0.28)***	0.06 (-0.01 , 0.15) NS
Paternal Social Class		
I&II (reference)	0.0	0.0
IIINM	-0.39 (-0.52 , -0.25)	-0.19 (-0.32 , -0.07)
IIIM	-0.54 (-0.68 , -0.39)	-0.24 (-0.37 , -0.11)
IV&V	-0.73 (-0.87 , -0.60)	-0.33 (-0.46 , -0.20)
Other	-0.72 (-0.92 , -0.51)	-0.35 (-0.54 , -0.17)
p-value (linear trend)	p<0.001	p<0.001
Family Size (per child)	-0.16 (-0.18 , -0.14)***	-0.05 (-0.07 , -0.03)***

Occurring in G0 pregnancy – categorised as none or any which refers to "other hypertension" or pre-eclampsia

*** Significant at p<0.05 level**

***** Significant at p<0.001 level**

NS = not significant

Table 11.4 : **Frequency distribution of G1 childhood size according to G1 size at birth quintiles (n=3090)**

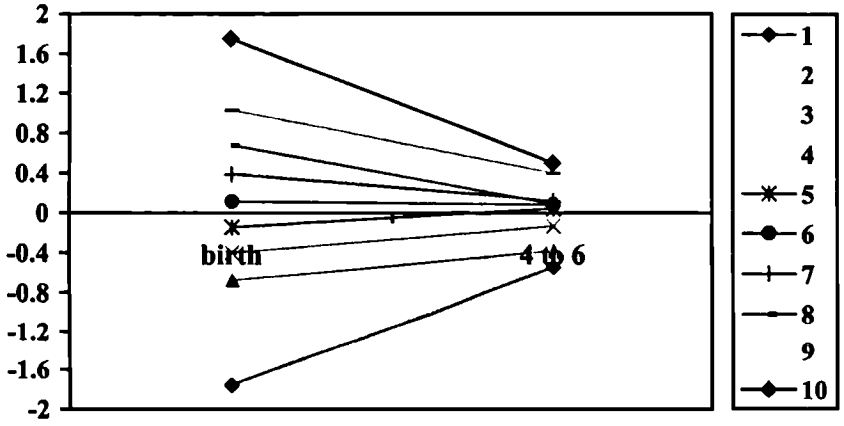
G1 Maternal fetal growth* quintiles	G1 Childhood size at school entry – weight for age Frequency (%)					
	1	2	3	4	5	Total
1	218 (33.2)	164 (25.0)	128 (19.5)	84 (12.8)	63 (9.6)	657 (100)
2	165 (26.7)	129 (20.9)	131 (21.2)	112 (18.2)	80 (13.0)	617 (100)
3	115 (18.3)	109 (17.4)	121 (19.3)	156 (24.9)	126 (20.1)	627 (100)
4	89 (14.7)	109 (18.1)	123 (20.4)	135 (22.4)	148 (24.5)	604 (100)
5	38 (6.5)	79 (13.5)	112 (19.2)	154 (26.3)	202 (34.5)	585 (100)
Total	625 (20.2)	590 (19.1)	615 (19.9)	641 (20.7)	619 (20.0)	3090 (100)

* **Fetal growth** is the standardised birthweight for gestational age score, the main outcome measure of size at birth

For all Figures 11.1 and 11.2:

- The vertical axis represents the SD score (birth and 4-6 years)
- The left-hand point represents the fetal growth SD score
- The right-hand point represents the weight for age SD score (4-6)

Figure 11.1 : **Change in G1 maternal weight for age between birth and 4-6 years according to deciles of G1 maternal fetal growth (1=least, 10=greatest)**

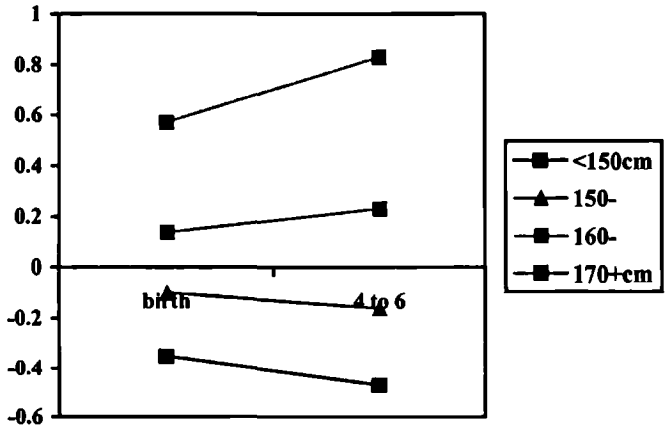


NB: The lowest tenth is equivalent to SGA (small for gestational age) females and the highest tenth is equivalent to LGA (large for gestational age) females

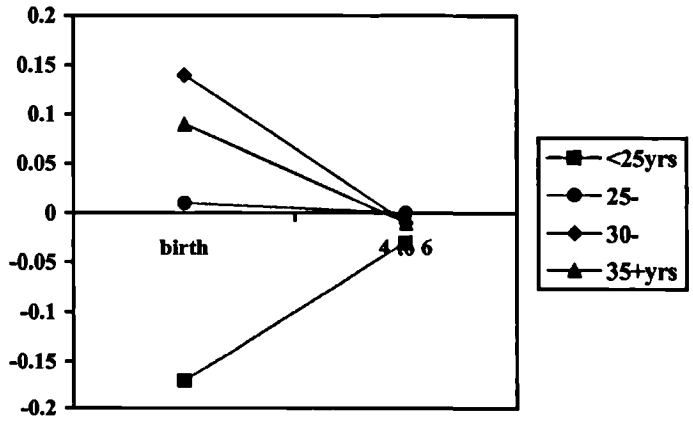
Figure 11.2 : **Changes in G1 maternal weight for age SD scores between birth and 4-6 years according to G0 parental characteristics**

Figures 11.2 (i)-(vi) illustrate the mean change in G1 size between birth and school entry according to categorical G0 parental adult characteristics. The two mean measures for each category are joined with a straight line to illustrate the direction of the change rather than to capture the nature of the change over time, which is almost certainly not linear.

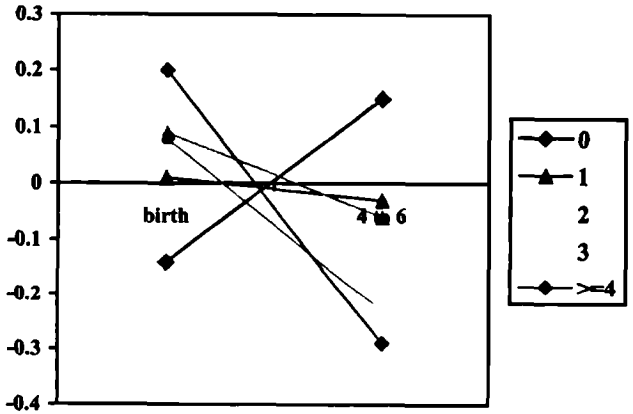
(i) According to G0 Maternal Height



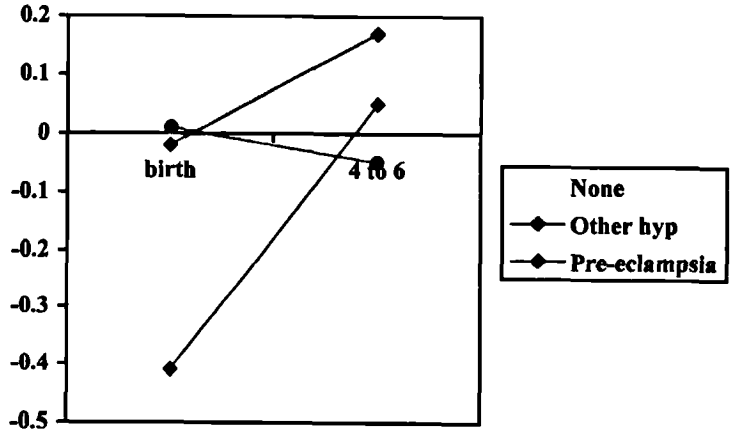
(ii) According to G0 Maternal Age



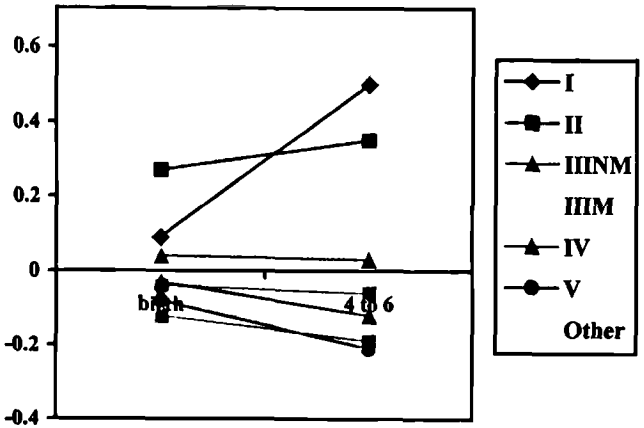
(iii) According to G0 Maternal Adult Parity



(iv) According to G0 Hypertension in Pregnancy



(v) According to G0 Paternal social class



(vi) According to G0 Family size in 1962

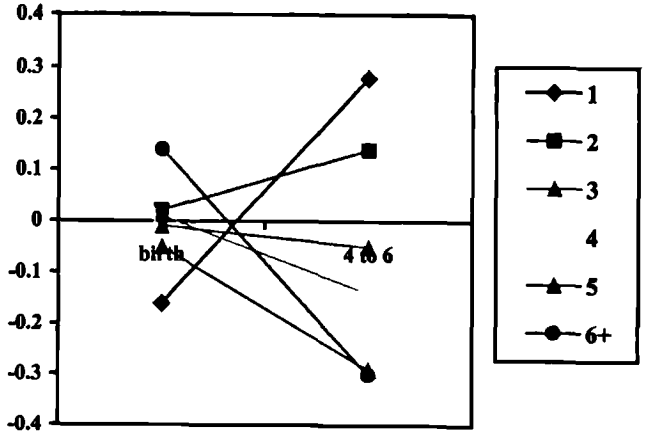
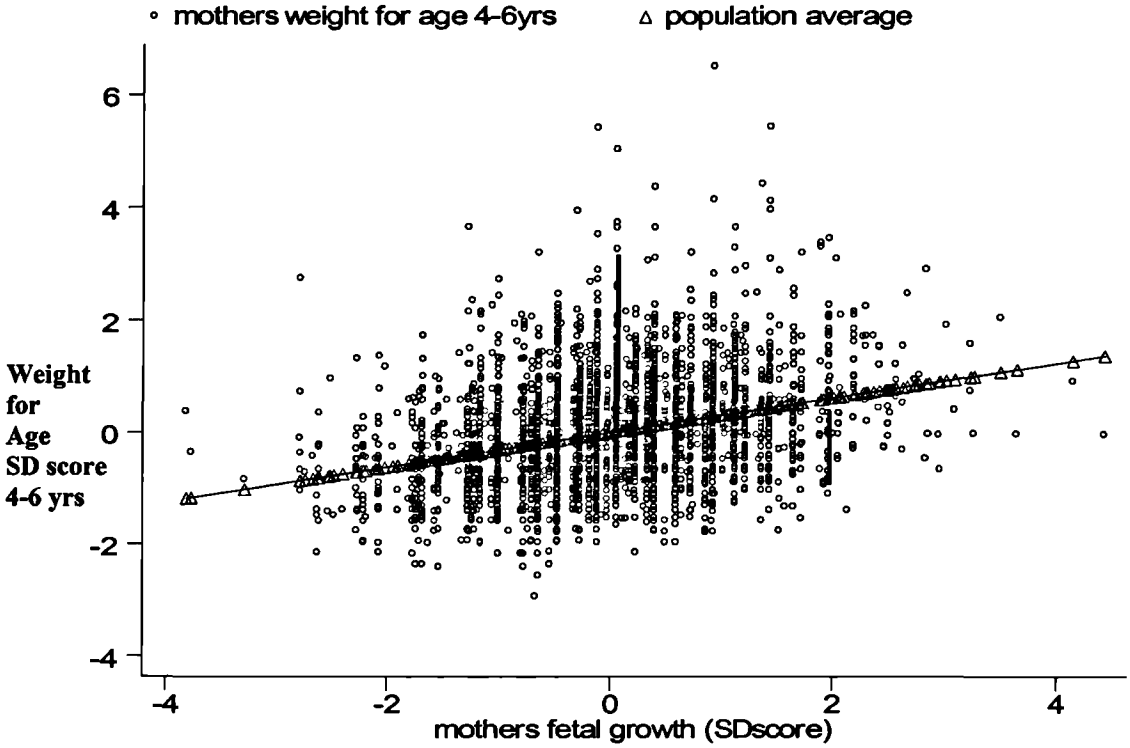


Figure 11.3 : **"Childhood growth" – illustrating the derivation of the temporal change variable**



Note: The red lines indicate a measure of "childhood growth", which has two components.

The **absolute magnitude** defines the distance that the individual childhood size is from the population average for all children at school entry who had the same fetal growth measure.

The **sign** denotes whether there has been "catch-up" or "catch-down" over time with respect to the population average growth

Table 11.5 : **Effects of G0 parental adult characteristics on G1 "childhood growth" (n=3090)**

Parental (G0) predictor variable	G1 childhood growth Regression coefficient (95% Confidence interval)	
	Crude	Mutually Adjusted
Maternal Height (per cm)	0.04 (0.03 , 0.05)**	0.04 (0.03 , 0.04)**
Maternal Age (per 5 years)	-0.01 (-0.04 , 0.02) NS	0.04 (0.01 , 0.07)*
Maternal Parity (per birth)	-0.13 (-0.16 , -0.11)**	-0.09 (-0.12 , -0.05)**
Maternal Hypertension # (no/any)	0.22 (0.14 , 0.31)**	0.12 (0.04 , 0.20)*
Paternal Social Class		
I&II (reference)	0.0	0.0
IIINM	-0.35 (-0.48 , -0.22)	-0.21 (-0.32, -0.10)
IIIM	-0.40 (-0.54 , -0.26)	-0.23 (-0.36 , -0.09)
IV&V	-0.48 (-0.61 , -0.35)	-0.25 (-0.38 , -0.09)
Other	-0.35 (-0.55 , -0.15)	-0.14 (-0.33 , 0.05)
p-value (heterogeneity)	p<0.001	p=0.002
Family Size in 1962	-0.12 (-0.14 , -0.10)**	-0.06 (-0.09 , -0.04)**

Occurring in G1 pregnancy – categorised as none or any which refers to "other hypertension" or pre-eclampsia

* Significant at p<0.05 level

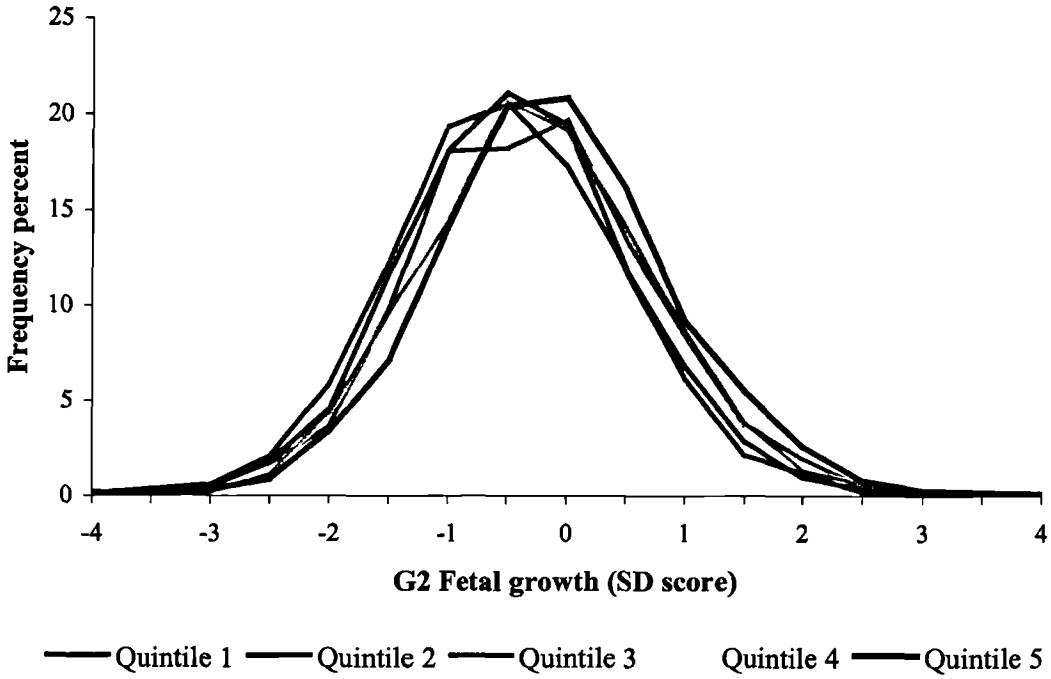
** Significant at p<0.01 level

NS = not significant

Table 11.6 : **Mean fetal growth of G2 offspring according to quintile of G1 maternal childhood growth (n=6369 intergenerational pairs)**

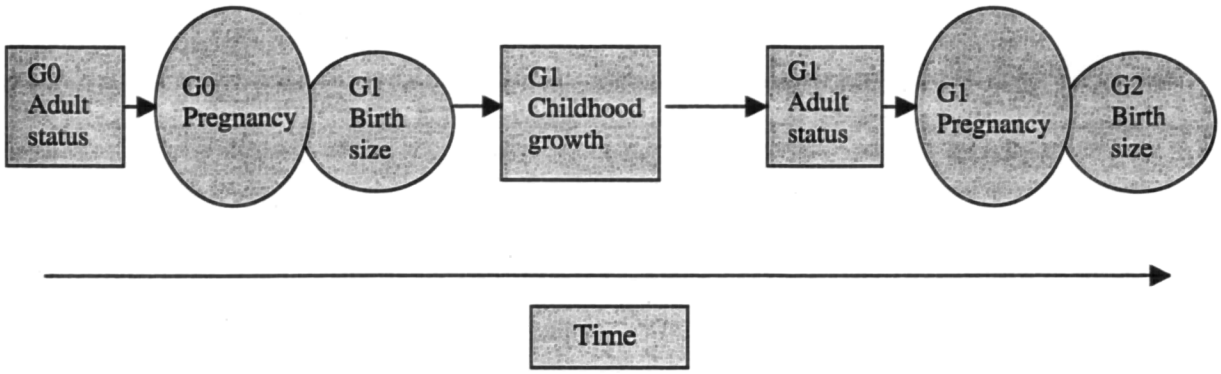
G1 Maternal Childhood growth quintiles	G2 Fetal growth (SD score)	
	Frequency	Mean (standard deviation)
1	1278	-0.24 (1.0)
2	1266	-0.16 (1.0)
3	1297	-0.03 (1.0)
4	1256	0.01 (1.0)
5	1272	0.13 (1.0)
Total	6369	-0.06 (1.0)

Figure 11.4 : **Distribution of G2 fetal growth according to quintile of G1 maternal childhood growth (n=6369 pairs)**



Chapter 12:

Intergenerational and Lifecourse Approach to the Determinants of Size at Birth



The aim of this chapter is to consider the determinants of G2 offspring size at birth taking both an intergenerational and a lifecourse approach. The analyses are intended to be illustrative rather than exhaustive as the approach is restricted to the measurements made historically and those available from record linkage for this intergenerational cohort. In the preceding chapters the following relationships have been established between different time periods in a woman's lifecourse and her offspring's size at birth:

- Within each generation offspring size at birth is patterned according to differences in adult biological and social characteristics. In particular there is a socioeconomic gradient evident in offspring size at birth that is not fully explainable in terms of adult maternal characteristics of height, age, parity and hypertension in pregnancy, nor by health-related behaviours such as smoking in pregnancy.
- Measures of size at birth show intergenerational continuity, with offspring fetal growth being significantly associated with maternal fetal growth. This continuity partly reflects the intergenerational continuity in adult characteristics that influence size at birth within generations.
- Changes in social class between birth and adult reproductive life are associated with differences in offspring fetal growth which are not fully accounted for by a single cross-sectional measure of social status at one point in a woman's lifecourse.
- Differential maternal growth in childhood has a differential effect on the size at birth of her offspring. Further maternal childhood growth is socially patterned in addition to being influenced by maternal under- or over-growth in utero.

These periods in a woman's development that have been shown to influence her offspring size at birth are not independent. They represent "snap-shots" of the lifecourse development of the G1 women and whilst the measurements made at each point are themselves distinct, they represent slices of a continuum of growth and development between intrauterine life and adult reproductive life.

One problem in attempting to unravel the effects of these different time periods is that cross-sectional measurements made during a woman's lifecourse are often highly correlated, making interpretation complex. Therefore rather than concentrating on the effects of measurements made at discrete time points on offspring size at birth, the aim is to attempt to capture aspects of temporal change in a woman's development and consider how these might affect her offspring's fetal growth. To more clearly determine the relative importance of periods in a lifecourse which influence offspring size at birth statistically independent variables which measure change over time, such as "childhood growth" derived in *Chapter 11*, will be utilised. The nature of the socioeconomic gradient seen in size at birth will also be reconsidered in a lifecourse and intergenerational context.

12.1 Adding the temporal dimension to lifecourse measurements

Measures of G1 maternal size are used from three points in her lifecourse to illustrate a lifecourse approach to developing variables that capture change in size over time and can be used in multivariate regression analyses to determine the independent effects of each. This is not to imply that maternal growth is the only biological maternal variable that might be environmentally modified over a lifecourse, or for which these changes may have implications for her later reproductive outcomes. However maternal growth is an important determinant of offspring size as was discussed in Chapter 11 and it has the advantage of being relatively straightforward to measure, which has been done at convenient times for this Aberdeen intergenerational cohort. Ideally it would be useful to have more than three measurements, but the approach used here could be extended to contend with greater than three age-defined cross-sectional measurements. Importantly the measures of size for the G1 females are at crucial times in her lifecourse development. Size at birth is the starting point for a woman's measurable lifecourse growth outside the intrauterine environment. Size at 4 to 6 years summarises total pre-school development and includes the immediate postnatal period and the first 24 months

of growth in which the greatest relative change in size occurs in any lifecourse. Further it is before the pre-pubertal growth spurt, when children mature at different rates. Height in adulthood is largely fixed throughout a woman's reproductive years and together with current weight has repeatedly been shown to be an extremely important determinant of fetal growth.

To derive variables that capture change between each of these measures each size measure is internally standardised according to age at measurement, which eliminates any increase in the variance of scores over time. The later size variable, in a temporal sense, is regressed on the earlier measure to consider conditional change in size over time. The magnitude and direction of the deviation from the population average for any individual, given their size at the original time point, defines the independent growth variable.

12.1.1 Change in G1 maternal weight for age between birth and school entry

In Chapter 11 "childhood growth" was derived (as described above) as a measure of an individual female's deviation from the population average growth for all infants who had the same fetal growth score at birth. This variable, which is statistically independent of size at birth, is both socially patterned according to G0 paternal social class (*Table 12.1 and Table 11.5*) and significantly associated with G2 offspring size at birth (*Figure 11.4*).

12.1.2 Change in G1 maternal height between school entry and adult reproduction

A similar measure may be calculated to capture change over time in height between school entry and adult life. Using standardised height for age scores at school entry and adult maternal height which had also been standardised to the first generation population mean, a measure of "height change" was calculated which estimated the conditional change in height between the age of 4 to 6 years and adult reproductive life. This variable was derived in a similar manner to "childhood growth", so that an individual female's "height change" represents the deviation from the population average for adult height of all females of the same height for age in childhood. This variable is also largely statistically independent of earlier measures of maternal size. It is normally distributed and is treated as a continuous variable. The overall mean of the "height change" is –0.01 and the standard deviation is 0.9. Once again the subset of G1

reproducers is a slightly more homogeneous, and marginally shorter group of females, than the all first generation females (Chapter 6).

Height for age was used as the starting point to derive this second change variable whereas weight for age was used as the final point for the first (childhood growth). However at 4 to 6 years of age these two age-standardised variables are highly correlated, in particular for these G1 females ($r=0.70$, $p<0.001$), and therefore one may be regarded of as a proxy for the other. Ideally the same intermediate measure should be used, but for this cohort length is unavailable at birth and maternal weight is unavailable either before or during each pregnancy.

This derived "height change" between childhood and adulthood is also socially patterned according to G0 paternal social class during the G1 female's childhood (*Table 12.2*, $p<0.001$ for trend) and is significantly positively associated with mean G2 fetal growth (*Table 12.3*, $p<0.001$ for trend).

12.1.3 The effect of G1 maternal lifecourse growth on G2 fetal growth

The three variables: fetal growth, childhood growth, and height change, characterise an individual G1 female's growth from birth to adult reproductive age, relative to her peers. The three are largely mutually statistically independent (*Table 12.4*), particularly in comparison to the highly correlated standardised cross-sectional measures of maternal size at birth, weight and height in childhood, and adult height (*Table 12.5*). Interestingly there is a small positive correlation that remains between fetal growth and height change that might reflect genetic potential, in that larger infants at birth are likely to be born to taller mothers and become taller adults themselves. It may also be due in part to the use of the highly correlated but not identical measures of height for age and weight for age in childhood as proxy measures for each other.

Multivariate regression was used to consider the effect of these maternal growth variables on G2 fetal growth (*Table 12.6*). The three measures were calculated to be largely statistically independent, therefore the mutually adjusted regression coefficients were changed little from the crude coefficients for the derived growth variables. This is in contrast to the change in the coefficients of the repeated cross-sectional measures of size at different time points in the mutually adjusted model which are highly correlated (*Table 12.7*). An advantage of using the statistically independent variables is that it is possible to ascertain better the relative contribution of each broad time period and in particular the effect of change in G1 maternal size between birth, early childhood and

adulthood on G2 offspring size at birth. In the regression analyses using the cross-sectional life course variables while it is clear that G1 maternal size is important, interpreting the meaning of the coefficients for the highly correlated variables in the adjusted model gives limited further insight into the relative importance of the temporal dimension to maternal growth. The independent variables highlight the importance of G1 fetal growth, both its direct and indirect effects on G2 fetal growth, and further suggest that the early development of the mother has a greater influence on her offspring's size at birth than her growth to adulthood, although this later growth also remains a significant independent influence on G2 offspring size.

12.2 Intergenerational measures of social class

In Chapter 10 continuity in social class across generations was considered for this intergenerational cohort, and it was noted that it was more likely that a G1 female would remain within the broad categories of either manual or non-manual throughout her life than change classification (according to her G0 father's and her G1 partner's occupational classifications). Changes in social class between early life and adulthood though were associated with changes in G1 maternal adult characteristics and first born G2 offspring size (*Figure 10.1*), compared to measures in G1 females who had been in the same broad social class categories in both childhood and early adult life. It is possible to look more closely at this distribution of G2 size at birth using finer gradations of social class at both time points, and extending the analysis to all G2 offspring, rather than restricting to first-born infants.

12.2.1 G2 mean size at birth according to G1 maternal early childhood and maternal adult social class

G0 paternal social class measured at the time of the G1 female's birth is referred to as the G1 maternal early childhood social class, as this is the proxy measure for the social environment which was most likely to have prevailed during the G1 female's intrauterine development, her immediate postnatal and her early childhood development. The proxy measure for maternal adult social class is her G1 partner's occupational social class, shown in Chapter 8 to be related to G2 size at birth in the same way that the less complete adult G1 maternal markers of status were (maternal completed education and pre-marital occupation).

Rather than grouping social class at both time points into the two broad categories of manual or non-manual, five categories of social class are used here (I & II, IIINM (non-manual), IIIM (manual), IV & V, and "other"). The "other" category is meaningful as a group of lesser relative social status than the preceding four with respect to G1 maternal early social class but represents a mixed group for the class in adulthood (as previously discussed).

Mean G2 fetal growth is tabulated according to the combination of G1 maternal early childhood and maternal adult social class in *Table 12.8.* Using these finer gradations of social class, confirms that the relationship between G2 offspring size at birth and G1 maternal social class is not one-dimensional. Instead both early and adult maternal measurements of G1 social class appear to influence G2 fetal growth. Excluding women who were in the "other" category at either time point, G2 infants born to G1 females who were in the lowest social class category (IV & V) in both early childhood and adult life had the least mean fetal growth. For G1 females who were in the lowest social class category at only one time point, there appeared to be some compensatory effect on G2 fetal growth for the time spent in the more advantaged social group, particularly if the higher measure was in adult life. By contrast those women who were in non-manual classes in early childhood and adult life had G2 infants with the greatest mean fetal growth (shaded area, *Table 12.8*). The pattern was less distinct for the combination of advantaged groups but having been in Social class I & II in particular at either time point seemed to confer an advantage in terms of G2 offspring growth.

Multivariate regression was used to consider further the mutual effect of both early maternal childhood and maternal adult social class on G2 fetal growth. The results are presented in *Table 12.9.* In the crude analyses it was apparent that G2 fetal growth showed a significant gradient with respect to both maternal early childhood (G0 paternal) and maternal adult (G1 paternal) social class of approximately the same magnitude. Mutual adjustment tended to diminish the effect of maternal early childhood social class, but greater childhood social disadvantage nevertheless remained a significant negative predictor of G2 offspring growth. The effect of maternal adult social class was only slightly reduced after controlling for the early life measure, confirming that the two measures do appear to exert their own influences on offspring size, rather than one merely acting as a proxy for the other. There was however no evidence of interaction between these two social class measure ($p=0.15$ in test for interaction), rather they appeared to be acting in an additive fashion.

12.2.2 Towards a better understanding of the social class gradient in offspring size at birth

Social class is a proxy measure for the environment an individual is exposed to but it is a construct that remains difficult to correlate fully with biological measurements. Categories of social class are broad and the individuals within them are not homogeneous with respect to individual characteristics. Nevertheless graded social class categories often define graded health outcomes, among them the mean size at birth of offspring born collectively to individuals in different social groups. For both generations in this intergenerational cohort there is a gradient that exists in mean size at birth of offspring according to paternal social class at the time of the infants' birth. This gradient is reduced, but not fully explained, by taking account of differences in socially patterned adult maternal characteristics (height, age and parity) and behaviours, such as smoking. It is likely that there are other unmeasured individual characteristics that might explain more of this gradient, however it is also possible that the social class measure, which is concurrent to the pregnancy, is either not the most appropriate one or not sufficient on it's own, to explain the differences in offspring size at birth. In addition to maternal adult social class, maternal early childhood social class (as measured by her G0 paternal social class) has also been shown to influence the mean size at birth of her offspring. However the effect of social class may not be limited to these two specific periods of time. The derived independent measures of maternal growth between birth and adult reproductive life were each patterned according to maternal early childhood social class. Further each of these measures of maternal growth were also associated with G2 fetal growth. Maternal early social class may therefore be a proxy measure for a childhood environment that acts to continually alter trajectories of change between two points, rather than acting at one point to set a trajectory throughout life. The next section will explore the possibility that G1 maternal early social class might affect G2 size at birth through its differential effect on G1 maternal growth throughout her lifecourse.

12.2.3 G1 maternal lifecourse growth and intergenerational social class effects on G2 fetal growth

Multivariate regression was used to consider the joint effects of G1 early childhood and adult maternal social class together with measures of G1 maternal lifecourse growth

on G2 fetal growth. The crude and adjusted regression coefficients are shown in *Table 12.10*. A comparison of that model to the one that previously only considered the two measures of G1 social class (*Table 12.9*), supports the contention that that the early social class environment of the mother has its effect on G2 offspring fetal growth by influencing G1 maternal growth throughout her development from in-utero to adult reproductive life. The early social environment of the G1 female, measured by G0 paternal social class at the time of her birth, no longer has any significant effect on G2 fetal growth after the effect of measures of differential growth throughout a mother's lifecourse, which are socially patterned, are allowed for (*Table 12.10*). However greater G1 maternal adult social disadvantage, measured by her G1 partner's social class, continues to have a significant negative effect on G2 fetal growth, although diminished slightly in comparison to when it was only adjusted for early maternal social class (*Table 12.9*). Hence it appears that the maternal early social patterning of G2 size at birth can be understood in terms of the environmental modification of trajectories of maternal growth throughout her lifecourse which ultimately determine the adult characteristics which are known to influence offspring size at birth.

12.3 Lifecourse and intergenerational determinants of G2 fetal growth

Throughout the preceding chapters adult maternal characteristics and behaviours within and across generations have been shown to be associated with G2 offspring size at birth in addition to the influence of measures of maternal growth and paternal social class. Hence in this final section the aim is to combine all the intergenerational and lifecourse influences that have been demonstrated to be important in earlier analyses into a final model that considers the intergenerational and lifecourse determinants of G2 offspring size at birth for this cohort. As outlined earlier this is intended to be illustrative of this type of approach being limited, as is the case for all such studies, to the lifecourse and intergenerational variables that are available.

12.3.1 Acknowledging the temporal dimension in lifecourse and intergenerational analyses

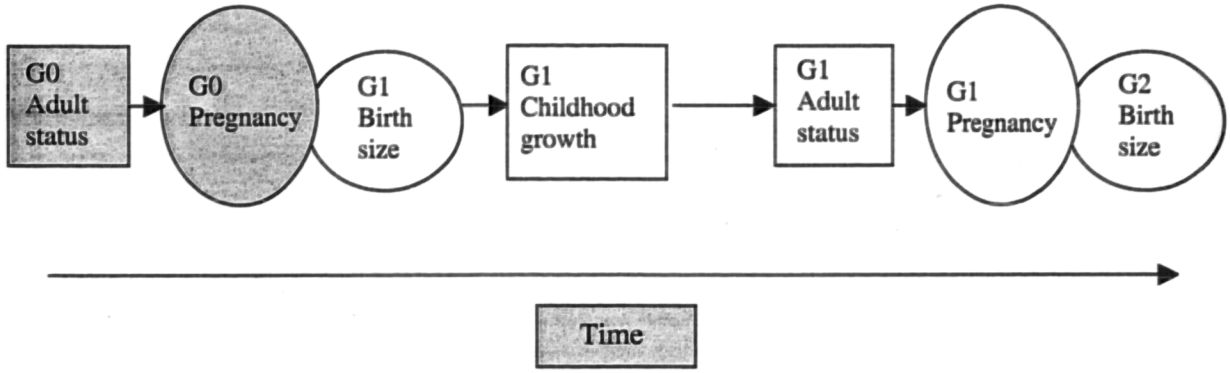
It is possible to carry out a multivariate regression analysis that considers the influence of all the intergenerational and lifecourse data by entering all the potential explanatory variables simultaneously into a model with G2 fetal growth as the outcome. However given that there is a temporal order to these variables it seems appropriate to

conserve this order and to enter the potential explanatory variables in a way which reflects their probable temporal order of influence. This allows a consideration of the effect of each group of contemporaneous variables, as either acting independently of or acting as a step on the pathway between the more temporally distal variables and G2 fetal growth after mutual adjustment for successive groups at each addition.

The outcome variable for the multivariate regression was G2 fetal growth and explanatory variables were treated as continuous, except for social class and maternal smoking which were categorical and hypertension in pregnancy which was entered as a binary variable (none or other versus pre-eclampsia). All measures of size and growth were entered as standardised variables to allow comparison of their relative effects. There was no evidence of any departure from linearity in any univariate relationships between variables and G2 size at birth and no evidence of any statistical interaction between related explanatory variables. Robust standard errors were calculated to allow for the repeated maternal information.

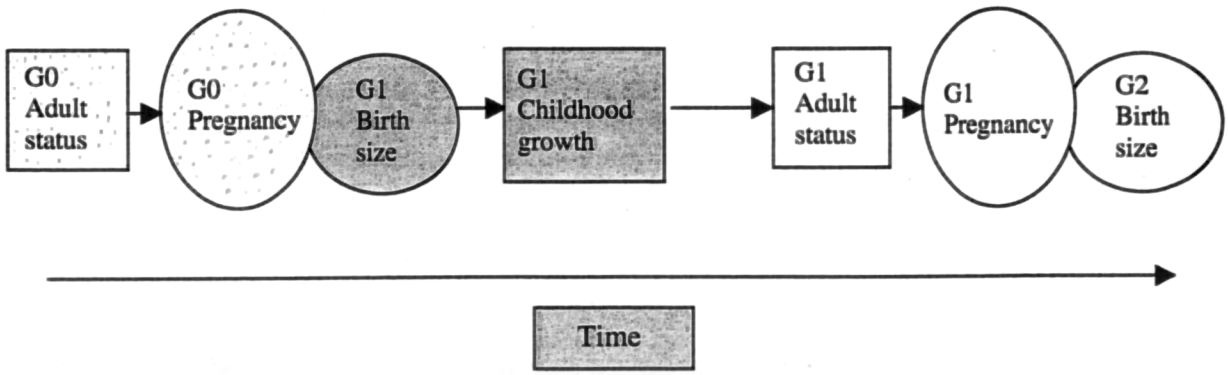
Tables 12.11 and 12.12 display the results of the multivariate analyses. *Table 12.11* presents the regression coefficients for the effect of each of the parental intergenerational and lifecourse characteristics on G2 fetal growth for all 6369 G2 infants in the *intergenerational and lifecourse dataset. Table 12.12* presents the same analyses for the G2 infants restricted to the subset with G1 maternal smoking information available (n=3602). In addition it presents adjusted analyses including G1 maternal smoking as one of the G1 parental explanatory variables. In both tables the temporal ordering of the explanatory variables is reflected in the way in which they are grouped and entered together into the regression analyses. G0 paternal characteristics are considered initially, followed by G1 maternal intrauterine and early childhood growth measures and lastly G1 adult characteristics. The G1 adult and pregnancy specific characteristics are entered into the regression model together but described separately in the text. The effect of the addition of each successive group is discussed below. Each group is highlighted on the diagram that has been presented at the beginning of each chapter from Chapter 7 onwards to indicate which has been most recently added (shaded) and which are already included (speckled).

(i) G0 Adult characteristics



The most temporally removed influences on G2 size at birth available for this intergenerational cohort were the G0 adult social and biological characteristics (grandparental with respect to the G2 infants). In considering their crude influence on G2 fetal growth the directions of the significant associations with G2 fetal growth were consistent with their influences on G1 fetal growth (*Table 8.2*), except for maternal parity which had an opposite negative effect on G2 fetal growth as G0 maternal parity increased. The presence of pre-eclampsia in a G0 pregnancy was significantly associated with G1 fetal growth but it was not significantly associated with G2 fetal growth. Contrarily whilst G0 maternal age at delivery was not a significant influence on G1 fetal growth after adjusting for G0 parity, it was weakly associated with G2 size (per 5 year age increase) after mutual adjustment for other G0 characteristics (*Table 12.11).*

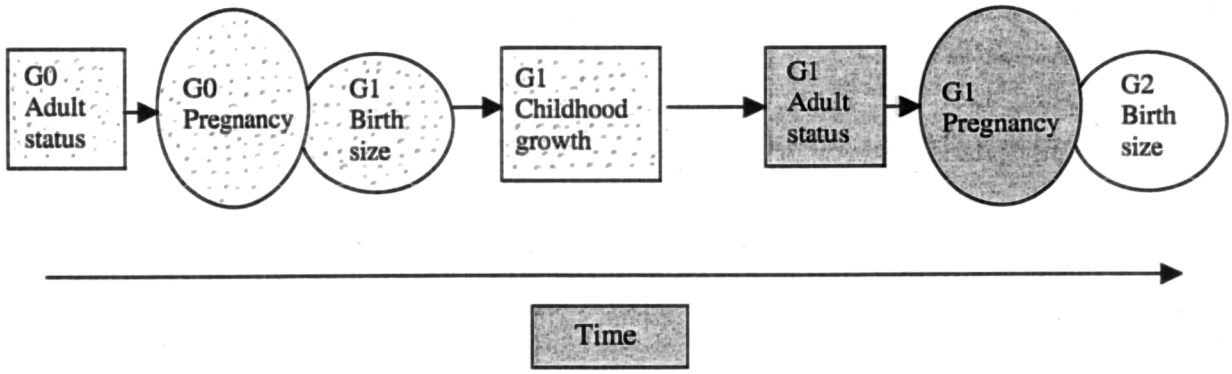
(ii) Early G1 maternal growth and family size



Measures of early G1 maternal growth (fetal and childhood growth) were entered in the second step of the multivariate regression. As was suggested in *Table 12.10* G0 parental social class (or G1 early social environment) appeared to have its major effect

on G2 fetal growth through its influence on G1 early growth. G1 females who themselves had the greatest fetal growth and the greatest childhood growth tended to have the largest G2 infants. G1 family size was also entered at this point because it is descriptive of the childhood postnatal environment and was previously shown to have a negative influence on G1 maternal childhood growth in addition to G0 maternal parity (Chapter11). However it was not a significant influence on G2 fetal growth after adjusting for maternal early growth and G0 maternal parity. G0 social class was also no longer a significant influence on G2 fetal growth after considering G1 early growth. G0 parity though continued to have a negative effect and G0 age at delivery a positive effect on G2 size at birth. G0 maternal height continued to have a positive, but less substantial effect, due probably to the positive association between G0 maternal height and G1 size at birth and size in childhood.

(iii) G1 Adult characteristics



Thirdly the adult characteristics of the G1 mother and her partner, including the final component of her lifecourse growth (height change from childhood to adulthood) were added to the regression model. At this point G0 maternal adult height became non-significant, probably now fully accounted for by its influence on the G1 females attained adult height. Both grandmaternal (G0) and maternal (G1) age at delivery remained positive influences on G2 fetal growth, after controlling one for the other. By contrast grandmaternal (G0) parity and maternal parity (G1) at delivery, while remaining significant, were associated in opposite directions with G2 fetal growth. Maternal adult (G1 paternal) social class had a significant effect on G2 fetal growth with infants born to mothers with partners in lower social classes being smaller at birth on average than those born to more advantaged parents. The effect of the maternal early childhood social environment remained non-significant after the addition of the G1 adult characteristics.

(iv) Maternal pregnancy-specific characteristics

G1 pregnancy specific characteristics were entered into the regression analyses together with the G1 adult characteristics. G1 maternal pre-eclampsia in pregnancy was not a significant predictor of G2 fetal growth after allowing for the earlier G0 characteristics and G1 growth and development. The model which included smoking status was restricted to 3602 intergenerational pairs for whom information on G1 smoking in pregnancy was available. However the regression coefficients for all explanatory variables remained largely unchanged from those in the larger group (n=6369) when the analyses excluding the smoking categories were applied to the subset for whom smoking information was available (*Table 12.12*).

Maternal smoking in pregnancy was an important independent predictor of reduced G2 fetal growth. There was a dose-response effect on G2 fetal growth, with the more cigarettes smoked per day by the G1 mother the more reduced the G2 fetal growth. In numerical terms the effect of smoking 10 cigarettes per day in pregnancy was approximately equivalent to the loss of one standard deviation of a mother's own fetal growth on average.

12.4 An illustration of a lifecourse and intergenerational approach to determinants of G2 offspring size at birth - "A temporal map"

The regression coefficients and the joint effects of these G0 and G1 determinants of G2 fetal growth over time may be represented graphically using a technique that is largely illustrative and an adjunct to the regression analyses themselves rather than a stand alone description. This is displayed in *Figure 12.1* and has been named a "temporal map" because it allows the effect of each explanatory variable on the outcome variable of G2 fetal growth and the effect relative to other explanatory variables to be tracked over time. The variables are entered into the model using the same temporal ordering as was used for *Table 12.11* and *Table 12.12* but are entered either singularly or in small groups. Only the two extreme social class categories are displayed to ease clutter (social classes I & II compared to IV & V) and all size and growth measures are entered as standardised variables for comparative purposes. The explanatory variables are assigned a number between 1 and 12 to represent the temporal order in which they are added to the regression model. Variables entered together share the same number.

Figure 12.1 illustrates the initial differential effect of grandparental (G0) social class on G2 fetal growth, but demonstrates that as measures of G1 maternal lifecourse growth are entered the effect of maternal early social class (G0 social class) becomes negligible and non-significant. However the measures of G1 maternal growth remain important predictors of G2 fetal growth acting largely independently of any later G1 adult social or biological influences. G1 maternal adult social class similarly exerts an initial differential effect on G2 size at birth that is only partially explained by other G1 adult characteristics. Extrapolating beyond the G2 perinatal period it might be expected to act in a similar manner to G0 social class on G1 development, therefore continuing to influence G2 development into childhood and beyond before loosing its importance in a similar manner to the maternal early social class measure.

It is also apparent from *Figure 12.1* that the influence of some variables is largely independent of the influence of others. Grandmaternal (G0) parity, for example, has an almost constant negative association with G2 fetal growth that is not fully explained by later G1 development. Perhaps of greater importance is the intergenerational effect of G1 fetal growth on G2 fetal growth that is consistent over time and does not diminish with changes in G1 adult characteristics.

12.5 Discussion

It has previously been established for this cohort that G2 fetal growth is influenced by biological and social parental characteristics measured at different points over a lifecourse, in particular by maternal intrauterine growth, and maternal size in childhood and adulthood, and paternal social status in adult life. However a lifecourse approach to the determinants of G2 fetal growth requires an approach that considers not only associations with measurements made at different times in the lifecourse but one which also attempts to capture the temporal dimension in which these measures develop. Often when historical cohort data are used to examine lifecourse effects the retrospective measurements that are available have not been made at the most critical or sensitive times in developmental terms according to the outcome of interest. However if repeated cross-sectional measures are available they provide proxy markers for the change in a variable between consecutive measurement points. Considering the change in a variable over time may be more meaningful, in terms of summarising development, than the discrete cross-sectional measurements alone.

The aim has therefore been to illustrate such an approach by deriving independent variables that capture the nature of the trajectory of change in G1 maternal size between birth and adult reproductive life. These change variables were then used in multivariate regression analyses considering the determinants of G2 offspring size at birth rather than entering repeated, highly correlated measures of G1 maternal size. The statistical independence of the change variables over each time period allowed deductions about the importance of these different time periods to be made in the face of an otherwise complex analysis.

Using this approach, it appears that the social class gradient that is commonly seen in offspring size at birth, but which is not explainable by adult characteristics alone, may be better understood in the light of intergenerational continuities in social class, between maternal early (G0 paternal social class) and adult life (G1 paternal social class) in particular. The maternal early social environment not only influences maternal size at birth, but also alters the trajectory of her postnatal growth throughout childhood to adult reproductive life, to in turn influence the size at birth of her offspring. A lifecourse approach suggests that the socioeconomic inequalities seen in offspring size at birth may be mediated by differential maternal growth across her lifecourse, particularly by her growth in early life. The socioeconomic environment appears to be acting throughout a woman's life course to alter her development, that is as part of the causal pathway rather than simply acting as a confounder of any relationship between biological measurements. However there remains an additional unexplained effect of current paternal social class on G2 fetal growth. It seems likely that this is capturing aspects of the G1 adult female's biology and behaviour that are not already measured by her height, age, parity, pregnancy specific conditions and her smoking behaviour. These might be related to her level of education and her health-related behaviours, including her nutritional status, but this is speculative. To have an effect on fetal growth social and biological influences must be mediated through biochemical pathways and there remains much to be learnt about the underlying mechanisms that influence fetal development.

In contrast to the differential lifecourse effect of early maternal social class on G2 fetal growth, which is eliminated as maternal lifecourse growth is accounted for, maternal intrauterine (G1 fetal) growth appears to have an important intergenerational effect on G2 fetal growth that is not diminished or altered by later G1 adult maternal or paternal characteristics. Using independent variables to capture maternal growth

highlights the importance that the maternal intrauterine environment has on her own reproductive capacities, both directly and via the indirect and often less easily measured effect due to the influence of her fetal growth on her later adult size.

Beyond the lifecourse development of the G1 mother herself, some grandpaternal (G0) characteristics are still significantly associated with G2 fetal growth even after accounting for their contribution to maternal (G1) fetal and subsequent growth. While G0 and G1 maternal age and maternal height acted in the same direction on G1 fetal and G2 fetal growth, G0 and G1 maternal parity acted in opposite directions on G2 fetal growth. G0 maternal parity had a positive proximal influence on G1 fetal growth but the more distal effect on G2 fetal growth was negative. In Chapter 10 the suggestion was made that the G0 and G1 parity measures might be acting in balance, so that if the G0 pregnancy was of a higher parity than the G1 pregnancy then the negative effect of the earlier measure compensated for the larger size of the mother herself at birth (i.e. G1 fetal growth). However the fact that G0 parity has a negative effect on G2 fetal growth before adjusting for G1 parity, and that it persists almost unaltered after adjusting for G1 parity, suggests that this may not be the entire explanation. It is perhaps more likely that G0 parity is acting as a proxy measure for the G1 postnatal environment. It is highly correlated with G1 family size, which has been shown to have a limiting effect on maternal postnatal growth, and by restricting maternal final adult size may therefore restrict the size at birth of the G2 offspring. G1 family size is not a significant independent predictor of G2 fetal growth in the adjusted model with G0 parity already included.

While abstract variables, such as social class, might be predicted to have differential effects on outcomes depending on what they are a proxy for, it is unusual to consider that a biological variable such as parity, which is straightforward to measure, might have such a differential effect on fetal growth. Depending on the time at which it is measured in a lifecourse, it may be acting as a proxy for different parental characteristics, either biological or social, and therefore have different implications for growth across different generations.

Acknowledging the temporal dimension is an important feature of a lifecourse approach to any outcome. Understanding when and through what mechanisms variables have their greatest effect and by what later variables they might be modified will be of key importance for public health interventions hoping to improve the health of mothers and their infants.

12.6 Summary

This chapter has illustrated a lifecourse and intergenerational approach to the determinants of offspring fetal growth. While the Aberdeen intergenerational cohort is well suited to this type of analysis it does lack information that would have made it even more useful. In particular it would have been extremely valuable to have had measures of G0 and G1 maternal adult weight, preferably pre-pregnancy weight, so that adult BMI, which is known to have a positive effect on fetal growth, could have been considered in addition to attained height as part of a mother's lifecourse growth. Additionally further G1 maternal measures of size in childhood, particularly in infancy, might have been useful to untangle further the effect of early childhood growth. Despite repeated measures of G1 size in later childhood for a subset of the original Child Development Study only three measures of G1 maternal size were complete enough to be used for all females in these analyses. For both G1 and G2 infants birth length would have allowed ponderal indices to be calculated in addition to birthweight for gestational age, which may have offered a supplementary way of assessing intrauterine development. Information on G0 maternal smoking during pregnancy would have been useful to explore the intergenerational relationships between behaviours that influence offspring size at birth. Further there was little information regarding paternal biological characteristics, which may have provided some additional explanation for gradients seen in size at birth, particularly perhaps with respect to the gradient according to paternal social class at the time of the infant's birth.

Aside from these limitations the analyses do however provide evidence that it is the early life growth of the G1 mother that is most influential in determining her G2 offspring size at birth, and that this growth is largely influenced by her early childhood social environment. The idea that childhood is an important time for adult health is not new in epidemiology, in fact it was the prevailing model of health in the early part of the 20th century (Kuh and Davey Smith, 1993). With respect to reproductive potential in particular, it was a view that was expressed almost 50 years ago by Baird with respect to Aberdeen women after his consideration of the effects of both biological and social conditions in early life (Baird, 1949). However appropriate intergenerational data to investigate these health models, with quality biological and social information across several generations, have been limited until recently (Power, 1992; Wadsworth and Kuh, 1997; Golding et al., 2001). As these data become available the analytical

challenge remains to consider fully the complex interactions between the lifecourse measures and importantly to include the temporal dimension. As stated in a recent editorial on pursuing a life course approach to adult disease by Kuh and Ben-Shlomo "The lifecourse approach is paradoxical in that it is intuitively obvious ... but empirically complex" (Ben-Shlomo and Kuh, 2002).

Table 12.1 : **Mean G1 maternal childhood growth according to G0 social class (maternal early childhood social class) (n=3090)**

G0 Paternal social class	Frequency	G1 Childhood growth Mean (SD)
I&II	230	0.37 (1.0)
IIINM	1141	0.02 (0.9)
IIIM	632	-0.03 (0.9)
IV&V	952	-0.11 (0.9)
Other	135	0.02 (0.9)
TOTAL	3090	0.0 (0.9)

Table 12.2 : **Mean conditional change in G1 maternal height (height change) according to G0 paternal social class (maternal early childhood social class) (n=3090)**

G0 Paternal social class	Frequency	G1 Height change Mean (SD)
I&II	230	0.07 (0.9)
IIINM	1141	-0.01 (0.8)
IIIM	632	-0.01 (0.9)
IV&V	952	-0.04 (0.8)
Other	135	-0.10 (0.9)
TOTAL	3090	-0.01 (0.9)

Table 12.3 : **Mean G2 fetal growth according to G1 quintiles of "height change" (n=6369)**

G1 height change* quintiles	Frequency	G2 Fetal growth Mean (SD)
1	1279	-0.27 (0.9)
2	1280	-0.13 (1.0)
3	1277	-0.03 (1.0)
4	1264	0.0 (1.0)
5	1269	0.13 (1.0)
TOTAL	6369	-0.06 (1.0)

* **Height change** = standardised measure of change in height for age between 4-6 years and adulthood

Table 12.4 : **Measures of correlation between lifecourse G1 maternal change in size (growth) variables (n=3090)**

	Fetal growth	Childhood growth	Height change
Fetal growth	1.000	0.0040	0.1644
Childhood growth		1.000	0.0029
Height change			1.000

Table 12.5 : **Measures of correlation between cross-sectional G1 maternal size variables (n=3090)**

	Fetal growth	Weight for age 4-6yrs	Height for age 4-6yrs	Adult height*
Fetal growth	1.000	0.3224	0.2667	0.3035
Weight for age 4-6yrs		1.000	0.6989	0.5071
Height for age 4-6 yrs			1.000	0.6611
Adult height*				1.000

* **Adult height** = internally standardised SD score

Table 12.6 : **Effects of lifecourse measures of G1 maternal growth on G2 fetal growth (n=6369)**

G1 Maternal growth	G2 Fetal growth		
	Crude Coefficient (95% C.I.)	Mutually adjusted for early maternal growth Coefficient (95% C.I.)	Mutually adjusted for early and later growth Coefficient (95% C.I.)
G1 Fetal growth (per 1 SD)	0.23 (0.20 , 0.26)***	0.23 (0.20 , 0.25)***	0.22 (0.19 , 0.24)***
G1 Childhood growth (per 1 SD)	0.15 (0.12 , 0.18)***	0.15 (0.12 , 0.17)***	0.15 (0.12 , 0.17)***
G1Height change (per 1 SD)	0.17 (0.14 , 0.20)***	—	0.12 (0.09 , 0.15)***

*** Significant at p<0.001 level

Table 12.7 : **Effects of cross-sectional G1 maternal size measures on G2 fetal growth (n=6369)**

G1 Maternal growth	G2 Fetal growth		
	Crude Coefficient (95% C.I.)	Mutually adjusted for early maternal size Coefficient (95% C.I.)	Mutually adjusted for early and adult size Coefficient (95% C.I.)
G1 Fetal growth	0.23 (0.21 , 0.26)***	0.18 (0.16 , 0.20)***	0.16 (0.14 , 0.19)***
G1 Weight for age 4-6yrs	0.21 (0.19 , 0.23)***	0.06 (0.03 , 0.10)***	0.06 (0.02 , 0.09)*
G1 Height for age 4-6yrs	0.22 (0.19 , 0.24)***	0.12 (0.09 , 0.16)***	0.04 (0.01 , 0.08)*
G1 Adult height +	0.24 (0.21 , 0.26)***	—	0.13 (0.10 , 0.16)***

+ Internally standardised score

* Significant at p<0.05 level

*** Significant at p<0.001 level

Table 12.8 : **Mean G2 fetal growth according to G1 maternal social class in early childhood and in adult life**

Mean (SD) G2 fetal growth						
G1 Maternal childhood social class*	**G1 Maternal adult social class****					
	I&II	**IIINM**	**IIIM**	**IV&V**	**Other**	**TOTAL**
I&II	0.13 (0.9)	0.17 (1.0)	0.09 (0.9)	-0.11 (1.1)	0.32 (0.9)	0.11 (1.0)
IIINM	0.18 (0.9)	0.11 (1.0)	-0.12 (1.1)	-0.15 (1.0)	-0.02(1.0)	-0.05 (1.0)
IIIM	0.10 (1.0)	0.01 (0.9)	-0.07 (1.0)	-0.18 (0.9)	-0.12 (1.0)	-0.01 (1.0)
IV&V	0.06 (1.0)	-0.05 (0.9)	-0.07 (1.0)	-0.30 (1.0)	-0.14 (1.0)	-0.12 (1.0)
Other	0.03 (1.0)	-0.11 (1.1)	-0.12 (0.9)	-0.33 (0.9)	-0.47 (1.1)	-0.20 (1.0)
TOTAL	0.11 (1.0)	0.02 (0.9)	-0.08 (1.0)	-0.22 (1.0)	-0.03 (1.0)	-0.06 (1.0)

***Maternal childhood social class** uses G0 paternal social class as proxy

**** Maternal adult social class** uses G1 paternal social class as proxy

Table 12.9 : **Effects of G1 maternal social class in early childhood and in adult life on G2 fetal growth (n=6369)**

G1 measures of Social class and Maternal growth	G2 Fetal growth	
	Crude Regression coefficients (95% C.I.)	**Mutually Adjusted Regression coefficients (95% C.I.)**
G0 Paternal Social Class[+]		
I&II (reference)	0.0	0.0
IIINM	-0.15 (-0.25 , -0.06)	-0.09 (-0.19 , 0.00)
IIIM	-0.10 (-0.20 , -0.01)	-0.03 (-0.13 , 0.07)
IV&V	-0.22 (-0.31 , -0.12)	-0.12 (-0.22 , -0.02)
Other	-0.32 (-0.46 , -0.17)	-0.22 (-0.37 , -0.07)
p-value (linear trend)	p<0.001	p=0.01
G1 Paternal Social Class[++]		
I&II (reference)	0.0	0.0
IIINM	-0.08 (-0.17 , 0.01)	-0.07 (-0.16 , 0.01)
IIIM	-0.18 (-0.25 , -0.12)	-0.16 (-0.23 , -0.10)
IV&V	-0.32 (-0.39 , -0.25)	-0.30 (-0.37 , -0.23)
Other	-0.13 (-0.23 , -0.03)	-0.11 (-0.21 , -0.01)
p-value (linear trend)	p<0.001	p<0.001

[+] Proxy for G1 maternal early childhood social class

[++] Proxy for G1 adult social class

Table 12.10 : **Effects of G1 maternal lifecourse growth and social class on G2 fetal growth (n=6369)**

G1 measures of Social class and Maternal growth	G2 Fetal growth	
	Crude Regression coefficients	Mutually Adjusted Regression coefficients
G0 Paternal Social Class[+]		
I&II (reference)	0.0	0.0
IIINM	-0.15 (-0.25 , -0.06)	0.01 (-0.08 , 0.11)
IIIM	-0.10 (-0.20 , -0.01)	0.12 (0.03 , 0.23)
IV&V	-0.22 (-0.31 , -0.12)	0.02 (-0.07 , 0.13)
Other	-0.32 (-0.46 , -0.17)	-0.05 (-0.20 , 0.09)
p-value (linear trend)	p<0.001	p=0.79
G1 Fetal growth (per 1 SD)	0.23 (0.20 , 0.26)***	0.21 (0.19 , 0.23)***
G1 Childhood growth (per 1 SD)	0.15 (0.12 , 0.18)***	0.14 (0.12 , 0.17)***
G1Height change (per 1 SD)	0.17 (0.14 , 0.20)***	0.12 (0.09 , 0.15)***
G1 Paternal Social Class[++]		
I&II (reference)	0.0	0.0
IIINM	-0.08 (-0.17 , 0.01)	-0.04 (-0.13 , 0.05)
IIIM	-0.18 (-0.25 , -0.12)	-0.13 (-0.19 , -0.06)
IV&V	-0.32 (-0.39 , -0.25)	-0.24 (-0.31 , -0.17)
Other	-0.13 (-0.23 , -0.03)	-0.11 (-0.20 , -0.01)
p-value (linear trend)	p<0.001	p<0.001

[+] Proxy for G1 maternal early childhood social class

[++] Proxy for G1 adult social class

***** Significant at p<0.001 level**

Table 12.11 : **Life course and intergenerational determinants of G2 fetal growth (n=6369)**

G2 Fetal growth				
Intergenerational and lifecourse Characteristics	**Crude Coefficient (95% C.I.)**	**G0 adult characteristics Coefficient (95% C.I.)**	**G0 adult characteristics and early G1 growth Coefficient (95% C.I.)**	**G0 adult characteristics, G1 growth and G1 adult characteristics Coefficient (95% C.I.)**
G0 Social Class I&II	0.0	0.0	0.0	0.0
IIINM	-0.15 (-0.25 , -0.06)	-0.07 (-0.17 , -0.02)	-0.01 (-0.11 , 0.10)	0.02 (-0.08 , 0.12)
IIIM	-0.10 (-0.20 , -0.01)	-0.02 (-0.14 , 0.12)	0.11 (0.0 , 0.23)	0.13 (0.02 , 0.25)
IV&V	-0.22 (-0.31 , -0.12)	-0.08 (-0.18 , -0.01)	0.03 (-0.08 , 0.13)	0.06 (-0.05 , 0.17)
Other	-0.32 (-0.46 , -0.17)	-0.19 (-0.37 , -0.01)	-0.08 (-0.25 , -0.10)	-0.05 (-0.22 , 0.13)
p value (trend)	p<0.001	p=0.03	NS	NS
G0 Height (per 1 SD)	0.14 (0.11 , 0.16)***	0.13 (0.10 , 0.16)***	0.05 (0.02 , 0.08)*	0.03 (-0.01 , 0.06) NS
G0 Age Delivery (per 5 years)	0.03 (0.0 , 0.06)*	0.05 (0.02 , 0.09)*	0.04 (0.01 , 0.08)*	0.03 (0.01 , 0.06)*
G0 Parity (per birth)	-0.04 (-0.06 , -0.02)***	-0.06 (-0.09 , -0.03)***	-0.05 (-0.09 , -0.03)*	-0.05 (-0.09 , -0.03)*
G0 Pre-eclampsia (no/yes)	0.03 (0.13 , 0.20)NS	0.03 (-0.13 , 0.20) NS	0.09 (-0.06 , 0.25)NS	0.08 (0.07 , 0.23)NS
G1 Fetal growth (per 1 SD)	0.23 (0.20 , 0.26)***		0.23 (0.20 , 0.26)***	0.22 (0.19 , 0.25)***
G1 Family size (per child)	-0.05 (-0.07 , -0.03)***		-0.01 (-0.04 , 0.01)NS	-0.02 (0.04 , 0.01)NS
G1 Childhood growth (per 1 SD)	0.15 (0.12 , 0.18)***		0.12 (0.09, 0.15)***	0.12 (0.09 , 0.16)***
G1 Height change (per 1 SD)	0.17 (0.14 , 0.20)***			0.10 (0.06 , 0.13)***
G1 Social Class I&II	0.0			0.0
IIINM	-0.08 (-0.17 , 0.01)			-0.01 (0.11 , 0 08)
IIIM	-0.18 (-0.25 , -0.12)			-0.09 (-0 16 , -0 01)
IV&V	-0.32 (-0.39 , -0.25)			-0.20 (-0.28 , -0.11)
Other	-0.13 (-0.23 , -0.03)			-0.11 (-0.21 , -0.01)
p-value (trend)	p<0.001			p=0.008
G1 Age Delivery (per 5 years)	0.13 (0.11 , 0.16)***			0 05 (0.02 , 0.08)*
G1 Parity (per birth)	0.14 (0.12 , 0.17)***			0.13 (0.09 , 0.16)***
G1 Pre-eclampsia (no/yes)	-0.17 (-0.32 , -0.06)*			-0.09 (-0.24 , 0.06)NS

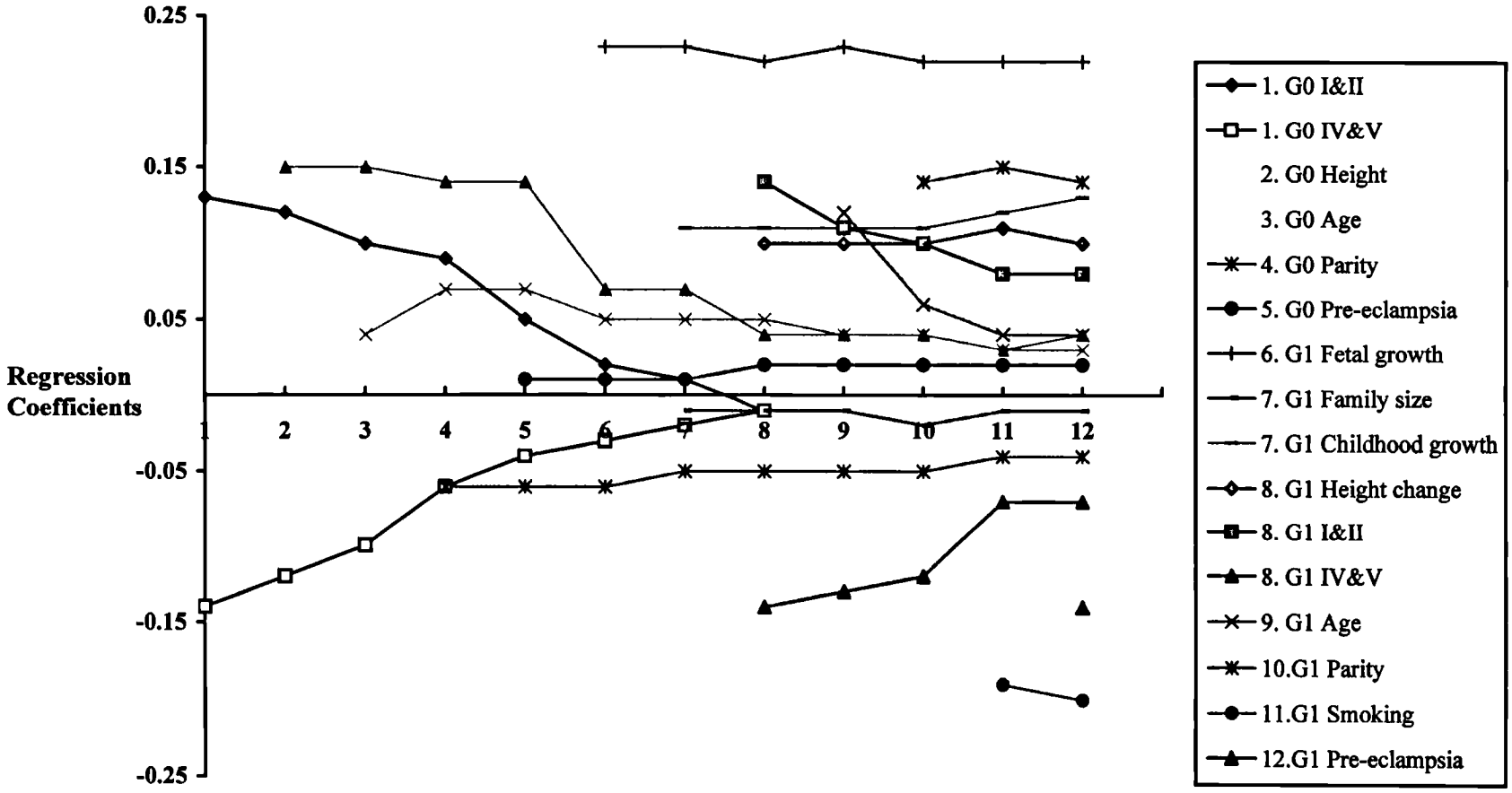
NS = non-significant * significant at p<0.05 level * significant at p<0.001 level**

Table 12.12 : **Life course and intergenerational determinants of G2 fetal growth : restricted to subset with G1 smoking information (n=3602)**

G2 Fetal growth						
Intergenerational and lifecourse predictors		**Crude** Coefficient (95% C.I.)	**G0 adult characteristics** Coefficient (95% C.I.)	**G0 adult characteristics and early G1 growth** Coefficient (95% C.I.)	**G0 adult characteristics, G1 growth and G1 adult characteristics** Coefficient (95% C.I.)	**G0 adult characteristics, G1 growth G1 adult characteristics + smoking** Coefficient (95% C.I.)
G0 Social Class	**I&II**	0.0	0.0	0.0	0 0	0 0
	IIINM	0.19 (0.34 , -0.04)	-0.10 (-0.28 , -0.05)	-0.04 (-0.19 , 0.12)	-0.01 (-0.16 , 0.15)	-0.01 (0.17 , 0.13)
	IIIM	-0.19 (-0.34 , -0.03)	-0.09 (-0.27 , 0.09)	0.04 (-0.13 , 0.21)	0.09 (-0.08 , 0.25)	0.07 (-0.10 , 0.25)
	IV&V	-0.24 (-0.39 , -0.09)	-0.11 (-0.28 , 0.06)	0.02 (-0.14 , 0.18)	0.08 (-0.09 , 0.24)	0.09 (-0.07 , 0.25)
	Other	-0.38 (-0.66 , -0.11)	-0.25 (-0.55 , 0.05)	-0.14 (-0.45 , 0.17)	-0.09 (-0.37 , 0.18)	-0.01 (0.30 , 0.29)
	p-value (trend)	p<0.001	p=0.02	NS	NS	NS
G0 Height (per 1 SD)		0.15 (0.12 , 0.18)***	0.14 (0.10 , 0.18)***	0.07 (0.34 , 0.11)*	0.04 (0.0 , 0.08)*	0.04 (0.0 – 0.08)*
G0 Age Delivery (per 5 years)		0.04 (0.01 , 0.08)*	0.07 (0.03 , 0.11)***	0.05 (0.01 , 0.09)*	0.05 (0.01 , 0.10)*	0.03 (-0.01 , 0.07) NS
G0 Parity (per birth)		-0 04 (-0.07 , -0 01)***	-0.06 (-0.09 , -0.01)*	-0.05 (-0.09 , -0.02)*	-0.06 (0.10 , -0.02)***	-0.04 (-0 08 , -0 01)*
G0 Pre-eclampsia (no/yes)		0 01 (-0.15 , 0.18) NS	0.01 (-0.18 , 0.20) NS	0.06 (-0.12 , 0.24)	0 02 (0.15 , 0.18)NS	0 02 (0.16 , 0.19) NS
G1 Fetal growth (per 1 SD)		0.25 (0.22 , 0.28)***		0.23 (0.19 , 0.27)***	0.23 (0. 18 , 0.26)***	0.22 (0.18 , 0.26)***
G1 Family size (per child)		-0.05 (0.07 , -0.03)***		-0.01 (-0.05 , 0.02) NS	-0.01 (-0.05 , 0.02)NS	-0 01 (-0.04 , 0.03)NS
G1 Childhood growth (per 1 SD)		0.15 (0.11 , 0.18)***		0.11 (0.07 , 0.14)***	0.11 (0.08 , 0.16)***	0.13 (0 09 , 0.17)***
G1 Height change (per 1 SD)		0.18 (0.14 , 0.22)***			0.10 (0.05 , 0.16)***	0.10 (0 05 , 0.16)***
G0 Social Class	**I&II**	0.0			0.0	0 0
	IIINM	-0.09 (-0.21 , 0.03)			-0.01 (-0.15 , 0.10)	-0.02 (-0.15 , 0.10)
	IIIM	-0.21 (-0.29 , -0.12)			-0.11 (-0.20 , -0.01)	-0.08 (-0.18 , 0.02)
	IV&V	-0.37 (-0.46 , -0.27)			-0.24 (-0.35 , -0.13)	-0.15 (0.25 , -0.05)
	Other	-0.15 (-0.32 , 0.02)			-0.09 (-0.27 , -0.05)	-0.02 (-0.18 , 0.15)
	p-value (trend)	p<0.001			p<0.001	p=0.02
G1 Age Delivery (per 5 years)		0.15 (0.12 , 0.18)***			0.07 (0.02 , 0.10)***	0 04 (0.01 , 0.08)*
G1 Parity (per birth)		0.16 (0.12 , 0.17)***			0.13 (0.10 , 0.18)***	0.14 (0.10 , 0.18)***
G1 Pre-eclampsia (no/yes)		-0.20 (-0.36 , -0.04)*			-0.10 (-0.29 , 0.07)NS	-0.14 (-0.31 , 0.03) NS
G1 Smoking	**none (ref)**	0.0			—	0 0
	<10/day	-0.31 (-0.42 , -0.21)				-0.27 (-0.38 , -0.16)
	10-20 per day	-0.46 (-0.54 , -0.40)				-0.42 (-0.50 , -0.33)
	>20 / day	-0.63 (-0.77 , -0.48)				-0 52 (-0.69 , -0.35)
	p value (trend)	p<0 001				p<0.001

NS = non-significant * significant at p<0.05 level * significant at p<0.001 level**

Figure 12.1 : **A "temporal map" of the intergenerational and lifecourse determinants of G2 fetal growth**



Note: The **numbering 1-12** by each explanatory variable refers to the temporal order in which variables are entered into the model

Chapter 13:
Concluding Remarks

Offspring size at birth is the result of a complex interplay of biological and social variables acting over several generations. It is a measure of the outcome of a pregnancy that occurs during the mid-point of the average woman's lifecourse, as well as being an important measurement for the offspring in its own right.

Much current epidemiological research tends to focus on measures of size at birth as initial explanatory variables in the pathway between early life and later adult health outcomes. Size at birth is undoubtedly a convenient place to start measuring development over a lifecourse, being a readily available measure and one that is made at the same time for almost all individuals. However beginning at this point to explain later adult health largely ignores the intergenerational influences and the maternal lifecourse development that has shaped the measures of offspring size. Similarly the preoccupation in perinatal epidemiology with attempting to understand the determinants of offspring size at birth according to adult parental characteristics occurring concurrently to a pregnancy also tends to ignore the earlier life influences on the parental adult characteristics themselves.

13.1 What has this study added?

The Aberdeen intergenerational cohort used in these analyses has some unique features. The first generation females were drawn from the population of all primary school children in Aberdeen in 1962 who were born in Aberdeen between 1950 and 1955. The linkage to the second generation was not limited to one delivery per first generation woman, nor to Aberdeen deliveries, nor to a restrictive time period. Instead the obstetric records of all second generation singleton live births that occurred to first generation females in Scotland throughout their reproductive years were sought. This created a more complete intergenerational dataset than many previous intergenerational studies, particularly in the United Kingdom, which was further enriched by the lifecourse data obtained from the original Aberdeen Child Development Study.

Using this Aberdeen intergenerational cohort this study has attempted to extend the approach of other studies which have considered the determinants of size at birth but which have limited their study to either the largely biological or social dimension or confined their investigations to within a generation, or to the immediate perinatal environment of pregnancy across generations. In particular it has taken an integrated

lifecourse and intergenerational approach to offspring size at birth; it has considered measures of birthweight adjusted for gestational age across the full range of population values; it has attempted to add the temporal dimension to multivariate regression analyses and to extend this temporal dimension to measures of socioeconomic status over the lifecourse. These particular aspects are described in more detail below.

13.1.1 An intergenerational and lifecourse approach to offspring size at birth

This study illustrates how both maternal intrauterine and lifecourse development are important and may complement each other to explain the determinants of offspring size at birth. The combined approach has been an illustrative rather than an exhaustive attempt to reconcile the two models of fetal origins and lifecourse approaches to health outcomes, which have not always been seen as complementary. However the analyses have demonstrated that influences on offspring size at birth in this cohort are both intergenerational, in terms of the independent strong effect of maternal fetal growth on the fetal growth of her own offspring and the result of her trajectory of lifecourse development, as illustrated by the effect of her maternal growth. There is some evidence that there may be additional distal effects that persist beyond a generation, for example the negative effect of grandmaternal parity, and other more proximal effects, particularly with respect to maternal adult behaviours such as smoking. Overall it is apparent that the maternal determinants of fetal development are not limited to one period of maternal lifecourse development.

13.1.2 A consideration of fetal growth measures across the range of population parameters

In the Aberdeen intergenerational cohort measures of absolute birthweight and fetal growth were available across the full population range of gestational age, unlike many earlier studies that were either limited to term deliveries or had only categorical information about gestation at delivery. It has therefore been possible to confirm the existence of a positive intergenerational association in length of gestation as well as in absolute birthweight and fetal growth for this cohort. This suggests that intergenerational associations in size at birth are not only the result of similar growth rates in utero as previously speculated but are also due to similar lengths of gestation.

13.1.3 A consideration of the temporal dimension in the analyses

Standard epidemiological methods and traditional perinatal epidemiological approaches are not always sufficient to explore a lifecourse approach to health outcomes, specifically because of the highly correlated nature of lifecourse variables and the fact that they often lie on common causal pathways. Further, standard multivariate regression models tend to lose touch with the temporal ordering of the data, effectively considering all explanatory variables as though they were acting contemporaneously. Appropriate lifecourse analyses should consider the temporal dimension, rather than just applying standard methods to data collected at discrete points over a lifecourse.

In an attempt to capture the temporal dimension for the Aberdeen intergenerational cohort and to minimise the use of highly correlated variables in regression analyses, statistically independent variables were derived to summarise the trajectory of change in maternal size measurement between discrete time points. This allowed the effect of each derived variable and the time period it represented to be assessed independently in the multivariate regression analyses.

As is the case with all historical data, analyses were limited to consider the early maternal and grandparental measures that were made by the original researchers at particular time-points. Similarly the perinatal variables obtained from the record linkages were constrained by those recorded in routine data collection. However utilising cross-sectional measures to determine change between discrete time points aimed to make maximal use of the available lifecourse data.

13.1.3 Exploring the social dimension of influence on maternal and offspring measures

Efforts to understand the causal pathways that might link intrauterine development with later adult health by elucidating the underlying biochemical mechanisms that may lead to the associations has meant that much of the perinatal research focus has tended to be largely biological and to an extent has ignored the social perspective. These analyses have attempted to consider the combined effects of the social and the biological environment, rather than separating them in a false dichotomy. The two are intimately connected throughout the lifecourse development of a mother and her offspring. Social class does not only act at one point in a life course and set a trajectory that remains unaltered over time. Using the example of maternal early growth for this

cohort, it is clear that parental social class influenced maternal size at birth which in turn was related to her childhood growth. However her childhood social class had a further effect on her trajectory of postnatal development independent of the effect mediated by fetal growth. Therefore it would have been insufficient in these analyses to account for even the early lifetime influence of social class by adjusting for socioeconomic status using only one cross-sectional measure as is often done in epidemiological studies with a biological focus. Similarly summary measures of lifetime socioeconomic status, whilst useful for estimating the effects of cumulative disadvantage, nevertheless flatten the temporal dimension so that it is not clear which period of disadvantage has the maximal effect.

The gradient that is present in size at birth with respect to parental adult social class concurrent with the time of pregnancy has received much attention in the political arena of late. These analyses suggest that it is not so much the socioeconomic environment concurrent to the pregnancy that has a direct influence on offspring size at birth, but instead the cumulative effects of the early socioeconomic environment of a mother during her own intrauterine development and her childhood that are of greatest importance. Taking a lifecourse and intergenerational approach to the socioeconomic inequalities seen in offspring size at birth aids in our understanding of their generation. The effect of social class tends not to be immediate but a delayed effect of earlier maternal disadvantage. The socioeconomic differentials are perpetuated across generations because their tends to be continuity of the socioeconomic environment across generations and hence continuity in the socially patterned maternal adult determinants of offspring size at birth. Therefore so long as inequalities exist in the social environment, social inequalities will continue to exist in size at birth.

13.2 Moving forward

There remain important questions to be answered regarding the determinants of offspring size at birth. Most importantly the biological mechanisms that underlie these lifecourse and intergenerational associations remain elusive, as does the quantification of the genetic versus the environmental influences.

Standard multivariate regression modelling was used to facilitate the understanding of the effect of each explanatory lifecourse and intergenerational determinant of offspring size at birth but it may be useful in the future to apply more complex statistical

models to this data and compare the effect estimates to those obtained using more traditional methods.

The data also offers opportunities to consider further the optimum timing for interventions aimed at improving maternal and infant health, and those aiming in particular to reduce the socioeconomic inequalities that are currently perpetuated across generations in offspring size at birth. These possibilities are elaborated below:

13.2.1 Further analyses

Studies are beginning to use more complex methods to try to unravel the effects of highly correlated lifecourse variables (dos Santos Silva et al., 2002). These have occasionally proved to be a deceptively simple solution as they can be difficult to apply and interpret. The advantage of the standard regression techniques used in these analyses is the clarity with which the coefficients can be interpreted. However as the underlying mechanisms and pathways of effect are better understood there may be good reason to apply more complex methods with appropriate *a priori* assumptions in place (Gillman, 2002) and in particular to compare the results of the standard and more complex analyses.

The type of population analysis applied using this cohort can help to direct research attention to the periods in the lifecourse with the greatest influence on later adult outcomes, whether those be reproductive or other health outcomes. However population data that deals with gross measures cannot hope to capture the intricate biochemical processes that must inevitably mediate all growth, from intrauterine development to adulthood. Nor can the complexity of fetal development be fully captured with one measure of offspring size at birth, even if it is adjusted for gestational age. Understanding the many pathways that lead to the same measures of size at birth and maturity at delivery remains a challenge (Harding, 2001).

However to concentrate only on understanding the biochemistry of pregnancy or the immediate prenatal environment in an attempt to improve fetal growth is to ignore the evidence that suggests that it is the mother's own intrauterine development that has a large effect on her own reproductive potential, independent of her growth to adulthood, her behaviours and her pregnancy course. Within a population, rather than within at-risk sub-groups, this may have more to do with the social structure of society than the intimate functions of maternal and fetal hormonal networks.

13.2.2 Untangling the effect of genes and the environment

This study has been unable to contribute to the ongoing concerns regarding the differentiation of genetic and environmental effects on offspring size at birth. The perpetuation of adult biological characteristics that influence size at birth across generations is often referred to as an example of genetic continuity. However there are fundamental difficulties in determining the extent of genetic and environmental factors influence on shared intergenerational characteristics. The reality is that the environmental conditions shared across generations within a family are more alike than for individuals in separate families within a generation so untangling what is genetic and what is epigenetic or environmental is difficult. Further the effects of genes and the environment are not mutually exclusive. A particular genotype may not be reflected in the phenotype of an individual unless the appropriate environmental conditions exist, both at the cellular level and external to the individual. In an intergenerational context what is genetic for the mother, may be environmental for the fetus (Gillman, 2002), as the maternal genome provides the basis for the environmental milieu in which the fetus develops and in which fetal genes are expressed. Studies with more sophisticated biological measurements are required to untangle these complex effects.

13.2.3 Platform for further study of women's health

The established intergenerational dataset is poised to prospectively consider the intergenerational and lifecourse influences on women's later adult health, importantly incorporating aspects of her reproductive history. Pregnancy occurs at the mid-point in a woman's lifecourse, and the physiological stress it produces in the mother may unmask the potential for her later adult disease. To date there are studies that have separately examined early life influences on later reproductive health and others that have examined the impact of reproductive health on later adult health outcomes, particularly breast and ovarian cancers and cardiovascular disease (Rich-Edwards, 2002). However as yet no large study of women's health in the United Kingdom has had sufficient data on intergenerational and lifecourse measures of health, including full reproductive histories, and the potential to collect data on later adult health outcomes, particularly cancer and cardiovascular disease. This intergenerational study offers the chance to consider the interplay of the intergenerational, early and later life influences, including the impact of her reproductive history, on women's health in later adult life.

13.2.4 Interventions to improve population health

The results of the analyses carried out using the Aberdeen intergenerational cohort suggest that interventions aimed at improving offspring size at birth and therefore infant and adult health on a population scale require intergenerational and lifecourse considerations rather than just a short term focus on the immediate pre-pregnancy and pregnancy period. However these need not be mutually exclusive. Proximate interventions aimed at reducing rates of maternal smoking in pregnancy have been shown to be beneficial, as have nutritional supplementation in previously undernourished women, and folic acid supplementation for the prevention of neural tube defects. However on a population level many of the interventions that may be required to improve infant and adult health across the whole range of birth size may be social rather than biological. They are also likely to be long-term solutions, requiring at least one generation's development between fetal life and adult reproductive life before any change is seen, rather than "quick-fixes" as Emanuel has so appropriately stated:

> "Because of the intergenerational phenomenon, it is clear that improvement in a populations reproductive outcomes will not be fully addressed simply by the provision of health services. Such improvement is probably partly dependent on the long-term complex processes of improvement in fetal and child health, which accentuates the urgency to address these issues in a more comprehensive way. Short term goals are not enough." (Emanuel et al., 1992)

A lifecourse and intergenerational approach to offspring size at birth challenges our ideas about the *origins* of reproductive health as much as it does the *origins* of adult health, whether in terms of fetal, childhood or adult risk factors. Size at birth is a convenient measure from which to begin tracking an individual's development over their lifecourse and a measure which is associated with later health. However it is a proxy marker not only for an individuals fetal development but also for the lifecourse development of the mother from her own fetal development to her adult reproductive status, which in turn is a marker of the lifecourse development of her grandmother before her. Size at birth is but one cross-sectional measurement on the continuum of intergenerational, lifecourse development. In the gender adapted words of Wordsworth – truly "the child is the *mother* of the *woman*".

(William Wordsworth, 1770 – 1850)

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