Influences on growth: a study of two generations based on the 1958 British Birth Cohort

A thesis presented for the degree
of Doctor of Philosophy
University of London

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2003

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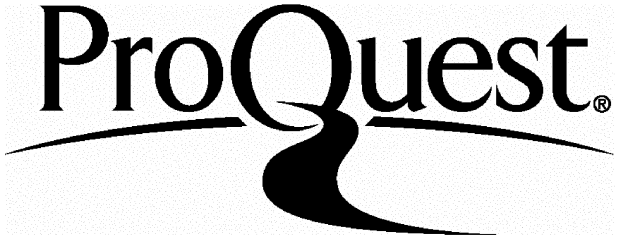

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Abstract

Height is a well-established health indicator, which is determined by genetic and early environmental factors. This thesis investigates (i) contributions of a wide range of early environmental factors on growth at each life stage; (ii) whether the strength of the associations has changed between two generations; and (iii) whether social inequalities in height have narrowed. The study is based on the 1958 British Birth Cohort, all born between 3rd-9th March 1958, followed up at 7, 11, 16, 23, 33, and 41y, and their offspring.

Fetal and childhood influences on growth of cohort members were examined using information on height at all ages simultaneously. Multivariate response models were used to explore these effects on growth trajectories, because these models take into account the fact that measurements on the same individual are correlated and also allow the comparison of the strength of associations across ages. Multilevel models were applied to compare the early life influences on childhood height between two generations taking account of correlations between cohort members and their offspring, and offspring themselves within families.

Early life factors, including maternal smoking during pregnancy, social class, family size, household crowding, and parental divorce, had stronger effects on childhood height than on adult height. This suggests that children whose growth is adversely affected by unfavourable early conditions may catch up later. Childhood height is therefore a better indicator of early life circumstances than final adult height. However, the impact of some influences has changed over time, with some factors (i.e. maternal smoking, breastfeeding, maternal age at childbirth, social class, number of younger siblings, crowding, maternal education, and parental divorce) showing a decline in importance in a younger generation. Increases in height across generations, i.e. the secular trend, were due to a greater height gain in manual social class. This resulted in a narrowing of inequalities in height in more recently born British children.

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Acknowledgements

First I would like to thank my supervisors, Professor Chris Power and Professor Tim Cole for their support, guidance, inspiration, and encouragement throughout the development of this thesis. I much appreciated the stimulating discussions with Huiqi Pan, Mario Cortina-Borja, Min Yang, and Alice McLeod and helpful suggestions from Orly Manor. I would also like to thank Deborah Ridout for reading and commenting on sections of this thesis. Finally, I would like to thank my family for being patient, supportive and understanding, especially during the months of writing-up.

The data was made available from Centre for Longitudinal Studies, Institute of Education, National Child Development Study Composite File including selected Perinatal Data and sweeps one to five [computer file]. National Birthday Trust Fund, National Children's Bureau, City University Social Statistics Research Unit [original data producers]. Colchester Essex: The Data Archive [distributor], 1994. SN:3148.

Chapter 1

Introduction

1.1 Life-course studies of adult health

In the past, studies investigating potential risk factors of adult disease have concentrated on adult risk factors. More recently, evidence has suggested that social, biological, or psychological exposures operating across the life-course, rather than just exposures in later life, are important in relation to health outcomes.

The timing of exposure may be critical. There are vulnerable periods, particularly during early development, where an insult results in permanent and irreversible damage to future health [1]. Factors operating during fetal development and early childhood may have long-lasting influences on later health. It has been recognized that retarded fetal growth, as an indicator of prenatal exposure, is associated with cardiovascular disease, high blood pressure, and diabetes [2-4]. A study of Scottish men born in the 1920s suggests that some adult diseases were affected by socio-economic conditions in childhood; men who came from manual social class origins had increased risk of mortality from stroke and stomach cancer [5]. Although exposures in "critical periods" may be important, they may influence disease risk with additional exposures from later life or later effect modification. The idea of later effect modification is that the effect of early exposure manifests itself in the presence of a later life "stressor", so that the critical period may only be critical for

individuals who also experience the later risk factor. The association between fetal development and some adult diseases may be influenced by early growth, acting as a pathway factor or a modifier, or confounded by socio-economic conditions. For example, being relatively small at birth but with improved catch-up growth in childhood has been associated with raised adult blood pressure [2] and coronary heart disease [3;6;7]. Deprivation in childhood, with an additive influence of adult circumstances, also influences risk of mortality from coronary heart disease and respiratory disease in adulthood [5]. Although childhood origins of cardiovascular disease may be important, risks may still be modified substantially in adult life; for example, current socio-economic disadvantage has a strong influence on important risk factors such as physical inactivity, metabolic and haemostatic profile, and smoking [8].

Social, biological and psychological exposures at different life stages may accumulate gradually throughout the life-course, which as a result, could increase the risk of adult morbidity and mortality. These factors may influence health independently, cumulatively, or interactively, with or without pathway factors [9]. For example, the excess risk of cardiovascular disease accumulates through life as a result of adverse socio-economic circumstances, starting in childhood [8]. There are different models for accumulation of risks; exposures throughout the life-course may affect health independently, and more commonly, cluster together, or even accumulate over time where one adverse exposure leads to another as "chains of risks", with sequential relationships or interactions between risk factors.

1.1.1 Adult height and disease

Height is one of several factors that has been taken to represent early life exposures and investigated in relation to adult health. Selected studies of associations between adult stature and risks for various diseases are summarized in Table A1.1 (Appendix 1). There is a large literature showing the associations of height with a variety of adverse health outcomes in adulthood. Shorter adult stature is a well-established predictor of cardio-respiratory disease later in life, among men and women [10-16]. Inverse relationships have also been found between adult stature and increased all-cause mortality [10;12;15], stroke [10;15-21] and stomach cancer [15]. However, increasing stature is not always beneficial for health outcomes. For example, mortality from cancers unrelated to smoking, with the exception of stomach cancer, tends to be related to tallness [10;15;22-24]. Hip fracture is also linked to tall stature [25].

Unlike most health outcomes or adiposity measures, height changes little once final adult height is achieved, at least in early adulthood, though from late middle age there is a trend of increasing "shrinkage" [11]. In general, adult height is unlikely to be a causal factor for adult disease. The stature-disease association may well reflect the long-term consequences of early life exposures that operate at different stages during fetal development and childhood, or even in previous generations.

1.1.2 Fetal, infant, and childhood exposures and adult health

Height is an indicator of early environment. While many studies of stature-disease relationships focus on final adult height, growth in childhood may also be important in

relation to adult disease as childhood height is more sensitive to early environment than final adult height.

Nystrom Peck and Vagero [12] reported only a slight reduction in the height-mortality association after controlling for adult social class, suggesting that the connection between height and mortality is established at a young age. Impaired postnatal growth has been found to be associated with increased blood pressure [26-29], cardiovascular disease [30], and poor cognitive function [31]. The risk of hip fracture in adult life was also greater for those with poor height gain in childhood, independent of maternal height and socio-economic status [32]. Whereas the risk of having a stroke was increased by accelerated growth in height during childhood [33].

Early life circumstances, both before birth and during childhood, have a life-long health impact. It has been suggested that some adult diseases are affected by socio-economic conditions in childhood, rather than the continuity of disadvantage throughout life [5]. Leg length, which is a component of height and sensitive to early environment [34], has been found to be inversely associated with risk of cardiovascular mortality and insulin resistance among adults and positively associated with risk of cancer in later life [30;35].

Poor growth in childhood resulting from adversity in early life may underlie the relationship between adverse early exposure and cardiovascular diseases and respiratory diseases [5;14;15;23;36;37]. Conversely, it has also been argued that the increasing risk of cancer may be related to a high calorie intake during the growth period [37]. This evidence has implicated improved socio-economic environment, nutrition and growth in childhood as influences on health in later life.

Figure 1.1 Direct and indirect effects of early exposures on adult disease

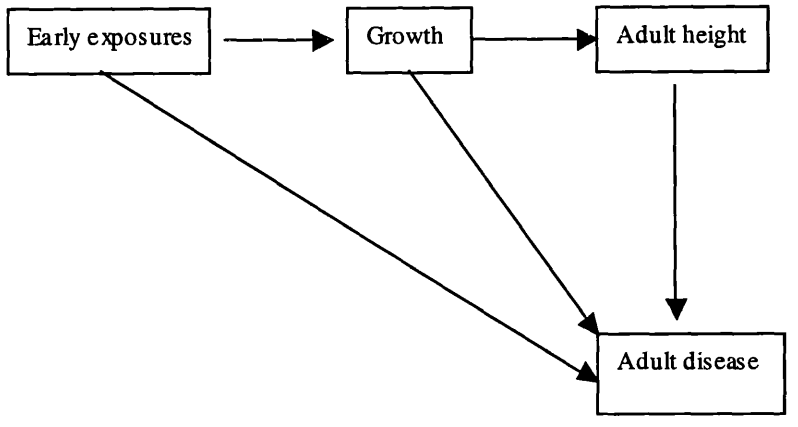


Figure 1.1 shows the pathways through which childhood exposures might affect adult disease. Children living in adverse early life conditions have poorer growth, which in turn may lead to shorter stature in adulthood. Reduced adult height is linked to adult mortality and morbidity. Since adult height remains unchanged once achieved, the stature-disease relationship is possibly explained by the impact of childhood growth on adult diseases. It is also known that poor early environment has a direct impact on adult disease, independent of childhood growth. For example, fetal environment is found to be associated with cardiovascular disease risk factors, independently of height growth in childhood [29]. The association between early exposure and later disease may also be modified by later growth. Thus early exposures can have either a direct impact on adult health, or an indirect effect, through childhood growth and adult height. Early life circumstances not only influence growth, but also are key determinants of later health [5]. There is a range of prenatal and

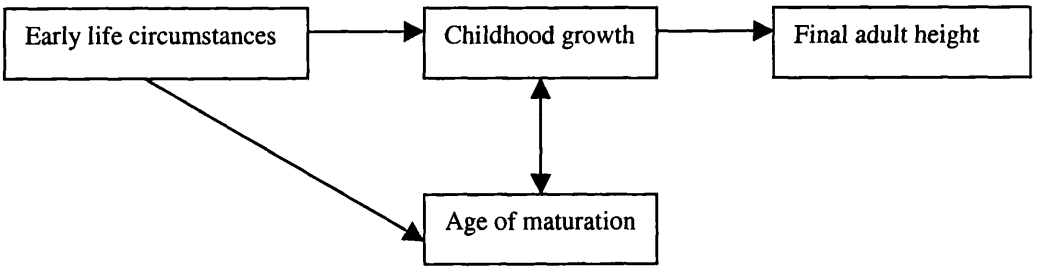
childhood factors representing early exposures that have been found to be associated with height. Birthweight is a marker for nutrition and environment in utero [38]. Parental social class and education are indicators of some socially patterned exposures during fetal development, infancy, and childhood. Household tenure or crowding, and family size (birth order and number of younger siblings) are markers of exposures to infection as well as socio-economic conditions. Household crowding is also associated with sleep disturbance and stress. It is known that growth retardation at any stage of development may contribute to short adult stature [39]. But neither the early exposures nor the critical period when growth is affected are well characterized. One way of further investigating stature-disease associations is to study the relationships between early life factors and height at different stages to identify the age when these factors start to operate and are the strongest, in order to determine the "critical period" for these early life exposures in relation to adult diseases.

1.2 Height

Height at a given age and the tempo of growth (maturation) are partly genetic and partly environmental [40]. As illustrated in Figure 1.2, factors that have an impact on height start to act in childhood. Their impact on final achieved height can be mitigated by catch-up growth and the extension of the growth period as some factors also influence the age of maturation. For example, children living in unfavourable conditions in early life tend to be shorter in pre-pubertal years, mature later, continue to grow for a longer period, and are not necessarily short as adults [41]. We would expect therefore, childhood height to be a better indicator of socio-economic circumstances in early life than adult height. Growth of children and youth has been recommended by the World Health Organization as one of the

best indices of health and nutritional status of a population [42]. Secular trends in height and changes in the early life influences on height are therefore important in relation to trends in health status and socio-economic conditions in the population.

Figure 1.2 Direct and indirect relationships between early life circumstances and adult height



1.2.1 Phases of growth

Adult height is influenced by fetal development (indexed by birthweight) and growth during infancy, childhood, and adolescence (puberty). Pregnancy is the start and an important part of human growth due to the high growth velocity during fetal life. Fetal growth is influenced by maternal factors such as parity, maternal age, maternal smoking, and maternal height [43].

Growth during *infancy* is characterised by rapid growth, with the velocity as high as 28 cm in boys and 26 cm in girls in the first year of life, during which body length increases by about 50% [44;45].

Childhood growth begins during the second year of life. Children grow an average of 12-13 cm or so in the second year [45]. The growth velocity then declines slowly until the start of puberty, with the rate falling to about 4 cm per year [44].

Puberty is the final phase of growth. During this period, the growth velocity accelerates dramatically, reaching a maximum of about 12 cm per year [44]. The adolescent growth spurt typically begins around the ages of 10 or 11 in girls and with a peak velocity at about age 12, gaining a total of about 16 cm during the spurt. In boys the growth spurt begins at age 12 or 13, reaches a peak at about 14 years, and gains about 20 cm during the final growth spurt [45]. The timing of the onset of puberty varies and is regulated by genetic and environmental factors [46-48]. The growth spurt is followed by a rapid slowing of growth: girls reach 98% of their final height by ages 16 to 17 years, whereas boys reach the same stage between 17 and 18 years [45]. However, there is wide variation around the mean age at which adult height is attained.

Up to the time of the growth spurt, there is little difference in mean height between boys and girls. Since the growth spurt begins earlier in females, at about 11 years girls are taller than boys. By the age of 14 years, boys have overtaken girls in height and remain taller thereafter [45].

Human growth is usually displayed as a growth curve divided into several different growth phases. The velocity is not constant at different stages. The cut-off points and the number of phases depend on the purpose of the study [49]. There are several non-linear models to describe the whole growth process, from birth to adulthood. Amongst the most frequently used models are infancy-childhood-puberty (ICP) growth model [50-53], triple logistic model [54], and Jolicoeur-Pontier-Pernin-Sempé (JPPS) growth model [55;56], all indicating three phases of growth. These models are used to monitor or assess growth of children and they all require frequent height measures throughout the growth period.

1.2.2 Factors influencing height

A large number of studies have shown that height depends on a number of interacting factors, such as genetics, health, emotional well-being, and social environment in childhood. Selected studies concerning the influences of genetic and socio-environmental factors on height are summarised in Table A1.2 (Appendix 1).

Maternal and paternal heights are indicators of the genetic potential of a child and have been found to have strong influences on offspring's height, as shown in Table A1.2 [57-60]. Parental height also represents their own childhood environment [57;58;61;62]. Mid-parental height in particular is widely used to assess growth of children within the normal range of height [63]. *Age of the mother* at childbirth has been found to be associated with the height of the child in several studies, with children of younger mothers tending to be shorter than others, independent of other social environmental factors, although the difference is small [57;61].

Fetal growth is sensitive to environment. Factors affecting birth size include size of parents, length of pregnancy, maternal illness (e.g. high blood pressure can lead to lower birthweight, while diabetes can contribute to higher birthweight), maternal nutrition and life style during pregnancy (i.e. smoking, drinking, and some drugs can all have a significant negative effect on offspring birthweight), and birth order (later-borns are on average heavier than first-borns). Therefore *birthweight* is the outcome of both genetic and social environmental influences. As shown in Table A1.2, the strong effect of birthweight on postnatal growth and final height has been found in many studies. Infants with lower birthweight are more likely to remain shorter throughout childhood, especially those who are intrauterine growth retarded rather than premature [64]. Conversely, infants with higher birthweight are likely to remain taller.

Factors that result in reduced birthweight may also have a long lasting influence on growth [57;58;61;62;65]. For example, the impact of *maternal smoking* during pregnancy on fetal growth is well accepted [66;67]. It has also been suggested that throughout childhood and even in early adulthood, the growth attained by children of mothers who smoked is less than that of children of non-smoker mothers [68-70], although the evidence regarding the long-term influence of smoking on human growth is inconsistent as some studies also show that maternal smoking has little effect on height [70;71]. How maternal smoking interferes with growth of children is relatively unexplored, with some studies suggesting that smoking has a causal effect on growth retardation in childhood, while others indicate that the effect of smoking on height is attributable to socio-economic circumstances, which are potentially major confounders. It remains unclear whether the deficits observed in childhood are extensions of the growth retardation experienced during fetal growth or whether they occur independently of fetal growth retardation.

Breastfeeding has been shown to provide not only nutritional essentials during infancy [72-76], but also some protection against infection [77], which is known to affect growth, especially in developing countries [78]. Yet, there are also studies showing that there is no relationship between breastfeeding and height even during infancy, especially among babies whose alternative feeding is infant formula [79]. Long-term effects of breastfeeding on growth are less consistent, with some studies showing a significant impact of breastfeeding on growth in height [34;80;81] and others finding no evidence of a relationship [60;82;83]. It is possible that the impact of breastfeeding has changed over time. Thus a study of a recent sample will help our understanding of the benefit of breastfeeding on growth in height in the current society.

Adverse social circumstances in early life are related to slow growth and short adult stature [41]. As illustrated in Table A1.2, *family size* has been associated with height of children in a number of studies, with children from larger families tending to be shorter than children from smaller families, although those from larger families are heavier at birth [57;61]. There is also evidence that family size influences height partly through its influence on the tempo of growth [84]. Family size is sometimes divided into two variables: *birth order* and *number of younger siblings*, both of which are negatively associated with height in childhood [57] and adulthood (Table A1.2) [85]. There is also evidence to suggest that the effect of number of younger siblings on height is attributable to socio-economic conditions [60].

It has long been recognized that *social class of origin*, most frequently defined as father's social position, is associated with stature both in childhood [57] and adulthood [86;87]. Children from higher social classes tend to be taller than those from lower classes, with social gradients in height still existing in many populations. As demonstrated in Table A1.2, there

is evidence to suggest that social differences have become smaller in several countries (e.g. Sweden [88] and Norway [89]). In a study of parents and children of the 1946 and the 1958 cohorts, social class differences in height have diminished gradually in boys [87]. There is little evidence on current trends in height inequalities in Britain.

Maternal education has been associated with height of children, although results are not consistent, with some studies showing a difference in height between children of mothers with higher and lower education [60], and others showing no evidence of a relationship (Table A1.2). Such inconsistencies may be due to the broad groups used in the comparison [90].

Associations between *housing conditions* and physical development have also been observed in many studies. In Britain, children from owner-occupier households are significantly taller on average than those living in council rented accommodation, even after allowing for social class, family size, household crowding, amenities, and region [84]. Children living in over-crowded conditions are shorter on average than those living in uncrowded conditions [60]. *Family income* is also found to be associated with height, with children from families receiving benefits tending to be shorter on average than those who are not [84]. Poverty has been associated with the development of children [91].

In addition, it is now suspected that adverse psychosocial circumstances and family environment can retard children's physical development. Children with *enuresis*, a marker of emotional disturbance, are significantly shorter than other children even after adjusting for parental height and social environmental factors (Table A1.2) [92]. *Family distress* (caused for example by parental death) is associated with early puberty, which is in turn associated with shorter final stature in girls [93]. Similarly, measures of *family conflict* are

associated with slow growth in childhood, independently of social class, crowding, sex, and predetermined height [94]. *Abuse and neglect* are associated with short stature and limb disproportion in children [95]. Child abuse, which may take the form of emotional or physical abuse can limit growth and cause serious physiological problems for the rest of the child's life. Wales et al (1992) suggested that a combination of emotional and environmental factors, possibly with chronic sleep disturbance, act through the hypothalamus to decrease nocturnal growth hormone release [95].

Childhood illness may also decrease the rate of growth, although results are not consistent. Several studies show associations between height and respiratory symptoms and illness such as wheeze, bronchitis and asthma [92;96;97], but others show no significant difference in height between asthmatic and non-asthmatic children after allowing for social class and sex [98]. Common illness in childhood do not appear to affect height either in the short or the long-term, but chronic illness may do so [92]. The long-term effect of childhood illness has not yet been determined.

There are also *regional* and *seasonal* differences in height. For example, Scottish children are shorter than English children on average [58;99]. Children from Southern England are taller than those from the North [58]. Seasonality in growth has been found in both developing and developed countries. Growth rates tend to be faster in spring and summer than autumn and winter, although this rate change can be very small [45;100]. The mechanisms of seasonal variation are still unclear, and may differ between developing and developed countries [41].

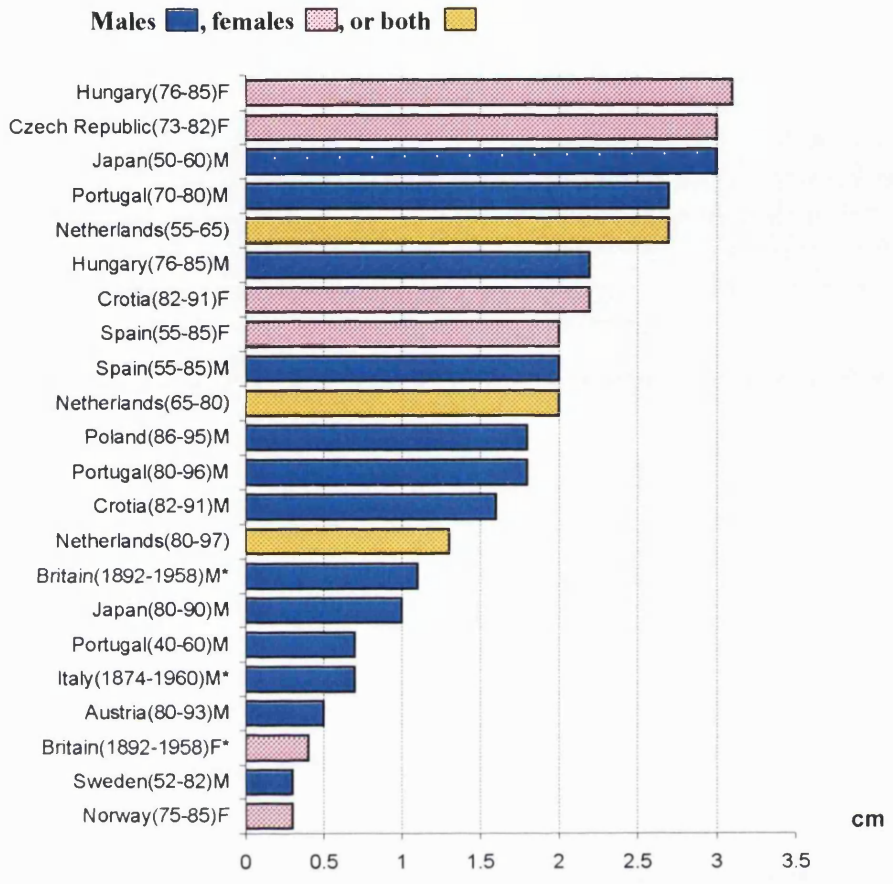
1.3 Secular trends in height

Secular trends in height are continuing in many populations and are attributable predominantly to an increase in leg length rather than trunk length [101;102]. Although the mechanisms underlying secular trends in growth are not fully understood, environmental factors are believed to be major causes.

1.3.1 Adult height

Table A1.3 (Appendix 1) provides a summary of secular trends in childhood and adult height (cm per decade) in selected countries. Results on adult height are also illustrated in Figure 1.3. Secular trends in adult height have varied from 0.3 cm to 3.1 cm per decade, depending on the population and the period of observation [103]. For example, the secular trend in Japan was very high between 1950 and 1960 (3 cm per decade) and is now at 1 cm [104]. In the Netherlands, the rate of secular increase declined gradually from 2.7 cm per decade between 1955 and 1965 to 1.3 cm per decade between 1980 and 1997, for men and women (Figure 1.3) [105]. The secular trend has not stopped in any of the countries listed, although it is small in some countries. The smallest increase in adult height was observed in Norway and Sweden (0.3 cm/decade) [106;107]. However, the trends of increasing height tend to be greater among short groups. As shown in Figure 1.3, an increase up to 2.7 cm per decade was observed among Portuguese men born between 1952 and 1962.

Figure 1.3 Secular increase per decade (period of study) in adult height in selected countries



* year of birth
Source: compilation of data from studies summarised in Table A1.3

In Britain, the mean trend for a sample born over the period from 1892 to 1958 (parents and offspring in the 1946 and 1958 British birth cohorts) was 1.1 cm per decade for men and 0.4 cm for women [87].

1.3.2 Childhood height

Most of the adult trend has occurred in early childhood [89]. Little or no secular trend was found in birthweight [108-110], although there is some indication of a trend towards heavier

births [110] and increasing low birthweights [110;111]. The secular increase in height is due predominantly to an increase in leg length, which is the most rapidly growing part of the body during early childhood when the impact of the environment is at its greatest [101;102]. Secular changes in height have occurred simultaneously with secular changes in tempo of growth, with menarcheal age falling steeply [112]. Thus height trends tend to be greater in childhood than in adulthood and adult height is reached at an earlier age [102]. The secular change in childhood height is therefore due at least in part to a secular change leading to earlier maturation, although there is evidence showing that menarcheal age has stabilized in some populations [103].

Secular trends of increasing height in children have been observed in many countries as shown in Table A1.3 [113;114]. Increases in childhood height were seen in Dutch children aged 6-18 years during the 1980s. For example, an increase equivalent to 2.6 cm for boys and 1.4 cm for girls was evident at age 17 years (Table A1.3) [115]. In Sweden, the increase in height per decade for Stockholm schoolchildren born in 1933, 1943, 1953, and 1963 was more marked between children born in 1933 and 1943 than those born later (Table A1.3). While mean height for 7-year-old boys increased by 0.8 cm between 1940 and 1950, it was almost unchanged between 1950 and 1970. For 13-year-old children the increase was 2.2 cm (boys) and 1.9 cm (girls) per decade between 1946 and 1966, but it was smaller between 1966 and 1976 (0.9 cm per decade for boys and 0.8 cm for girls). In Norway, height increased by 4 cm per decade in 8 to 14 year old boys and girls in Oslo between 1920-40. There was a drop of about 1.5 cm during the war, and since 1950 height has increased only moderately [89]. In Germany, the trend for 6-year-old Bremerhaven children born between 1968-87 was 0.7 cm per decade for boys and 0.5 cm for girls [116]. Table A1.3 shows that a rapid increase in growth (associated with an increase of leg length) of Japanese children

occurred after the Second World War, due mainly to better nutritional status associated with a rapid improvement of socio-economic conditions [117].

In Britain, the secular trend in height continued [117], with English children in most age groups (5-11 years) increasing in height by more than 1 cm and in Scotland by more than 2 cm during the period 1972 to1994 [99]. The increase is greater at older than younger ages among English boys and girls, indicating the secular trend towards early maturation. Rona and Chinn (1984) found that about 50% of the increased height from 1972 to 1979 for English and Scottish children was accounted for by decreases in family size, with some contribution from increases in parental height and birthweight, but little from the change in social class distribution [118]. However, the recent trend towards increasing maternal age [119] and the improvement of social and material conditions are likely to have contributed to the secular trend towards increasing height in Britain.

1.4 Timing of maturation

Puberty is a period of rapid skeletal and sexual maturation. Breast development, pubic hair, and the onset of menstruation are most prominent characteristics of sexual maturation in girls, whereas growth of testes, genitalia, and pubic hair are indications for sexual maturation in boys [120]. Menarche, or first menstruation, is considered as the technical start of puberty for girls and is an important indicator of physiological and psychological development. Like height, age of menarche is also a health indicator. For example, early maturation in girls is an established risk factor for breast cancer [121] and overweight [122;123].

Age of menarche has also been used as an indicator of socio-economic circumstances in early life [48;124;125] and it is considered to be the best measure for secular changes in the tempo of growth [112].

1.4.1 Secular trends in timing of maturation

The onset of puberty has shown a trend towards a lower age in many populations, although this trend seems to have halted in many parts of the world. In America, a study comparing height and pubertal development of 8-18 year old boys in a 1988-94 survey to the 1963-70 survey showed that differences in height between the two samples existed only among younger boys, with those from the recent survey being taller. Boys from the recent sample also matured earlier than those from older sample, suggesting a faster growth rate and earlier maturation in the younger generation [126]. A recent American study showed a racial difference in the rate of the secular change in menarcheal age between 1973 and 1994, with the median menarcheal age decreasing by 9.5 months among black girls and by 2 months among white girls [127]. Chinese schoolgirls in Hong Kong demonstrated a significant downward secular trend in sexual maturation with a median age of menarche of 12.4 years, which is earlier than many European countries [128]. A decrease in menarcheal age has also been observed in the Netherlands [120]. However, a stabilization of the age of menarche is found in some countries. In Norway, age of menarche was close to a stable level of about 13.3 years since 1950 [129]. In Belgium the secular trend has stopped since the early 1960s [103], while an increase was observed in Sweden [107].

1.4.2 Factors influencing timing of maturation

The age of onset of puberty is influenced by genetic and environmental factors, as well as race, geographical location, and early nutrition [41]. Mother's age at menarche is positively associated with daughter's age at menarche, though the relationship is weak (r=0.19) [130]. Tall maternal stature is associated with later menarche [130]. However, environmental factors seem to be important, with higher socio-economic status and smaller family size being both associated with earlier maturation [46;130]. The age of onset of puberty differs between races. In America, the mean age at menarche was reported at 12.1 years for black girls, 12.2 years for Mexican American girls, and 12.7 for white girls [131]. Seasonal variation in incidence of menarche has been found, although the effect is small [132].

Recent evidence has suggested that prenatal exposures may be linked to age of maturation [130;133;134], with some studies showing that those with higher birthweight have a later menarche [133;134]. In the 1946 cohort, Cooper et al (1996) found opposite trends of birthweight (intrauterine growth) and weight at seven (postnatal growth): girls who were heavier at 7 years had an earlier menarche, but those who were heavier at birth had menarche at a later age [133]. A study of Filipino infants born in 1983-84 showed that birthweight alone was not significantly related to age of menarche, but being relatively long and thin at birth (> 49 cm, < 3 kg) was associated with an earlier menarche, even after maternal nutritional status during pregnancy, girl's current diet, and socio-economic indicators were taken into account [130].

Influences during the period around or after birth may also affect the timing of menarche [129]. Faster growth rate (weight or height) in early infancy is associated with an early menarche [130]. In the 1946 cohort, the effects of birthweight and growth in infancy on the

timing of menarche seem to be mediated through growth in early childhood [135], indicating that the timing of menarche may be set in utero or infancy, though mediated through early childhood growth. However, studies on intrauterine, early postnatal, and childhood growth remain scarce and further research is needed to improve our understanding of their interrelationships.

More work is also needed to explore how the early environmental factors influence growth trajectories, timing of maturation, and final height. For this research, longitudinal data are needed with information from birth at least to attainment of adult height. A birth cohort is an ideal study design as it usually starts at birth or even before birth, with data collected prospectively throughout the life-course. Such studies therefore offer unique opportunities for testing life-course hypotheses.

1.5 Methodology in life-course studies

The main advantage of a birth cohort study is that psychosocial and biological exposures are usually measured repeatedly [136;137]. Information is available from many stages of life, from the start to later life, on the same sample of people and more complicated questions can be addressed. For example, outcomes can be investigated in terms of change with time (e.g. change in height or body weight); later health outcomes can be explored in relation to an early life risk factor or risk factors that have accumulated throughout the life-course, and the temporal sequence of exposure variables and their inter-relationships with the outcome measure can be identified directly or through intermediate variables. Longitudinal data also

minimize potential sources of bias due to selection. In some instances, all cohort members may be at the same age and have the same broad social context.

1.5.1 Longitudinal data

In Britain, there are three established national birth cohort studies which comprise up to 40,000 individuals across three post-war generations: the 1946 cohort (National Study of Health and Development), the 1958 cohort (National Child Development Study) and the 1970 cohort (Birth Cohort Study), respectively [138]. All three studies now have information from birth to adulthood. Although there are some differences in emphasis, each study has collected information on a range of circumstances, experiences and personal characteristics relevant to development at different ages. Health is covered at all ages. More recently, the Millennium cohort has started with some 20,000 babies surveyed at age 9 months, who will be followed-up at around 3 years of age.

The 1958 cohort, including all births in one week in 1958, is used in the current study. Details of the sample and data collection are described in Chapter 2. The most distinctive advantage of the 1958 cohort is that it has information on three generations, namely, cohort members, their parents and offspring. The availability of this information allows direct measurement of secular trend in some measures, such as growth. Furthermore, it provides a unique opportunity to investigate whether influences on height have changed over time, i.e. across generations. Even with detailed information from birth onwards, life-course study is both theoretically and methodically complex.

1.5.2 Statistical approaches

Multiple regression is commonly used in life-course analysis for studying a simple relationship between early exposures and a later outcome, such as height, morbidity or mortality. The association between early exposures and the later outcome is usually assessed first, and then exposures from later life stages are entered into the model, to examine (1) whether the effects of early exposures act independently of or are modified by later exposure measures, or (2) whether the effect of later exposures act in addition to the early life exposures. However, life-course hypotheses can be complicated. For example, the temporal ordering of exposure variables and their inter-relationships are difficult to disentangle with methods such as multiple regression models. In particular, life-course analyses sometimes require repeated outcome measures and repeated exposure data. Traditional statistical techniques may not be adequate and more complicated techniques may be required for dealing with life-course studies.

When response variables are measured repeatedly, the within-individual variation in these measures needs to be accounted for in the analyses. There is a large literature for analysing repeated outcome variables, such as random effect models [139] or marginal models fitted using generalized estimating equations [140]. Life-course studies may also include linking repeated or time dependent exposure variables to a single later life outcome, and in this instance G-estimation is sometimes useful [141]. In other instance, testing of life-course hypotheses can involve causal pathways over different life stages, and here structural equation modelling or latent variable models (or latent class analysis) are useful when dealing with complicated pathway relationships [142-145]. Life-course research also includes cross-generational studies. When two generations are from the same families, the fact that individuals are clustered within a family needs to be taken into account in the analysis.

The methodological approach for analysing changes in health and related influences over time also needs to take account of several potential problems of cohort data or longitudinal data. *First*, the measurements may change over time (e.g. cognitive function, which normally changes with age) and therefore a standardised measure, which is independent of time, is required. *Second*, in cohort studies there are often large time gaps between measurements and not many repeated measures. Consequently, growth or social trajectories can be modelled only very crudely. More importantly, the measure at a vital time point, for example, the start of the growth spurt or the maximum growth velocity, may be missing. *Third*, the sample size of a cohort study is often not large enough for less common diseases and as a result the power of any study will be affected when studying the relationship between the exposure and the health outcome. To illustrate, in a study of the relationship between childhood development and adult schizophrenia in the 1946 cohort, only 30 cases were identified between ages 16 and 43 years from over 5000 subjects [146] and this limits the statistical power or the strength of conclusions draw from the cohort. For example, having below average mothering skills was a predictor of schizophrenia, with an odds ratio of 5.8, but the 95% confidence interval for the odds ratio was between 0.8 and 31.8. Furthermore, loss of individuals to follow-up may introduce a source of bias. It has been argued that cohort studies in support of the fetal origins and life-course hypotheses could often trace only a small proportion of the original study sample [147].

Sample attrition and missing data are unavoidable in a long running cohort study, which can lead to problems regarding validity of results obtained from analysis. It is therefore important to make every effort to ensure high response rates in follow-ups. When the response is incomplete, it is important to determine whether a missing data item can be considered as a random event, or it is informative and the result of a non-random

mechanism (§3.3.1). Possible approaches to deal with missing data when missing is at random include: (1) imputing each missing item with a value predicted from the observed data (i.e. multiple imputation). Standard methods of analysis can then be carried out as if data were complete, or (2) adopting a statistical model that provides efficient estimation for incomplete data if missing is at random. When missing is informative, one possible approach is imputation for missing values based on the non-random missing patterns [148].

1.5.3 A life-course approach to growth in height

As demonstrated in §1.2.2, the possible contributions of genetic, prenatal and childhood environmental factors on growth and final height have been explored extensively, but almost all studies focus on height at one particular age. There are very few longitudinal analyses of these relationships [83;149;150]. In particular, the effects of early environmental influences on growth trajectories have been neglected. Studying the early influences on childhood height at one age does not tell us, however, whether similar influences on final height can be expected, because it is uncertain to what extent differences in growth during one part of childhood will be compensated for by catch-up growth during a later period, and/or by an extension of the growth period [151]. Furthermore, a longitudinal approach allows us to explore whether the effect of an early life factor stays constant or changes with time. Therefore, determining the ages when the impact of early influences start and are the strongest is particularly valuable for identifying the "critical period" of early exposures for adult diseases. A study of early influences on growth at different stages may contribute to our understanding of the biological and social mechanisms which underlie the stature-disease association.

There has been little evidence so far on whether early environmental factors that were important for past generations are still relevant today. This issue is important because inferences made from studies of the current generation provide evidence for the future health inequalities. Secular trends in height have been found to be greater among children from lower socio-economic backgrounds, among shorter populations, and in developing countries [151]. However, evidence of diminishing height differences between social groups is not entirely consistent [88]. Little is known about how social differences in height have changed over time in Britain.

The 1958 British birth cohort, a large national representative sample, with information on height, social position, and other potential influences on growth across three generations, provides a unique opportunity to explore early influences on growth at several stages of childhood, age of maturation, and final achieved height in detail in one generation, i.e. the cohort born in 1958. As cohort members were born over four decades ago, the relationships between social environmental factors and height found in the 1958 cohort may not reflect the circumstances in the current society [152], but they can still be valuable for understanding relationships between fetal and early exposures, early growth, and adult health outcomes in contemporary society. Furthermore, data on the offspring of the cohort enable us to assess recent growth trends and current inequalities in children's height in Britain, which in turn are likely to affect future inequalities in adult health.

Previous analyses of the 1958 cohort have identified a range of early life factors associated with height, including parental height, maternal smoking during pregnancy [57;68;70;153], birthweight [154], family size (parity and younger siblings) [57;155], maternal age [57], social class [57;156], region [157], family income [84], housing tenure [158], household crowding [158], family

conflict [94] and enuresis [92]. Importantly, these studies were all based on analyses in which the relationships were assessed for height at a specific age. Although it is recognized that many of these factors influence not only height as already discussed (§1.2.2), but also the tempo of growth, there has been no study relating early life factors to growth trajectories of the 1958 cohort.

1.6 Objectives

The main objectives of this thesis are:

1) to establish the impact of early environmental factors and childhood health on growth trajectory and pubertal development, and to a lesser extent to assess the impact of genetic influences as indexed by parental height. A main focus here is to identify the life stages when these influences started and are at their strongest;

2) to compare early life influences on height in two generations, that is, in the cohort generation and in their offspring, in order to determine whether the impact of early environment has changed over time; and

3) to assess whether social inequalities in height have varied with age or over time, by exploring (a) the impact of social class on height from childhood through to adulthood and (b) the effect of social class on childhood height in the cohort members and their offspring.

Methodologically, the questions to be addressed are complicated. Objectives (1) and (3) require longitudinal analyses of early life influences on growth, while the cross-generational comparisons for objectives (2) and (3) pose an additional challenge, since not only are offspring from same families, but also the characteristics of cohort members and their offspring will be correlated. For these reasons, traditional statistical methods are likely to be inadequate and more complex methods are required to take into account the within- and between-generation correlations. There is a wide range of models that deal with hierarchical data. However, not all of them are appropriate for our study purposes and the unique data structure. Therefore, an additional methodological objective of the thesis is:

4) to explore statistical methods that are suitable for assessing the longitudinal effects of early life influences on growth and comparing these influences across two generations taking into consideration of the complex data structure.

In Chapter 2, the 1958 cohort and their offspring are described and the responses and representativeness of the two generations are examined. Details of height measurements, early life factors and derived measures, such as height standard deviation scores are also identified and data handling is discussed. Chapter 3 describes statistical methods that are relevant to life-course analyses, with a focus on multivariate response models for studying the growth trajectory and multilevel models for cross-generational comparisons. The applications of these models to the subsequent analyses are discussed.

Chapter 4 presents the analyses on influences of early environmental factors, childhood health and parental height on age of maturation and height at different ages, to determine their influence on growth trajectory, whilst Chapter 5 compares the influence of early life

factors on height in two generations to establish whether relationships have changed over time. In Chapter 6, social inequalities in height are investigated among cohort members, from their childhood through to full height in adulthood. In addition, social class differences in childhood height are compared across generations, the cohort members and their offspring, to establish whether inequalities in height have narrowed in the younger generation. Finally, in Chapter 7, the findings and methodology applied are reviewed, and the contribution of this study and potential area for future development in relation to life-course influences on adult health are highlighted.

Appendix 1

Table A1.1 Adult height and mortality/morbidity risk for various diseases (selected studies)

Study	Disease	Height categories (cm)	Men	Women
	related to short stature			
Nystrom Peck & Vagero [12]			SMR[1]	
	All-cause mortality	Short 145-174(m) 129-162(f)	102	107
		Medium 175-180(m) 163-167(f)	103	95
		Tall 181-206(m) 168-186(f)	90	92
	Coronary heart disease		107	120
			98	80
			86	74
	Cardiovascular disease		101	111
			106	86
			88	94
Gunnell et al [23]			HR[2]	
	Coronary heart disease	Lowest vs highest quintile of childhood leg length	2.50	3.90
Goldbourt & Tanne [18]				
	Stroke	≤ 162 cm vs ≥ 172 cm	1.54	
Wannamethee et al [19]			RR[3]	
	Fatal stroke	<167.7 cm vs ≥ 178.9 cm	2.08	
	Coronary heart disease		1.61	
Davey-Smith et al [15]				
	All cause mortality	Per 10 cm decrease in height	1.13	1.19
	Coronary heart disease mortality		1.14	1.29
	Stroke		1.32	1.23
	Respiratory diseases		1.45	1.75
	Stomach cancer		1.43	1.54
	Breast cancer		-	1.13
McCarron et al [21]				
	Fatal ischaemic stroke	Per 10 cm decrease in height	1.85	
Hart et al [20]				
	Stroke mortality	Per SD decrease in height	1.21	1.13
Davey-Smith et al [35]			OR[4]	
	Coronary heart disease	Per SD decrease in height	1.11	
McCarron et al [16]			HR[5]	
	Cardiovascular disease mortality	Per 10 cm decrease in height	1.30	
	Coronary heart disease mortality		1.33	
	Stroke		1.32	
	Respiratory disease mortality		1.47	

Table A1.1 Adult height and mortality/morbidity risk for various diseases (selected studies) (cont.)

Study	Disease	Height categories (cm)	Men	Women
	related to tall stature			
Albanes et al [22]			RR[3]	
	All-site cancer	2nd vs 1st quartile	1.60	
		3rd vs 1st	1.50	
		4th vs 1st	1.60	
Meyer et al [25]				
	Hip fracture	<155 cm vs ≥ 170 cm (f)	2.92	3.62
		<170 cm vs ≥ 185 cm (m)		
Davey-smith et al [15]				
	Colorectal cancer	Per 10 cm increase in height	1.41	1.25
Davey-smith et al [24]			RR[6]	
	Smoking unrelated cancers	>72 in vs <66 in	1.33	
Gunnell et al [23]			HR[2]	
	Cancer	Lowest vs highest quintile of	0.50	0.9
	Prostate cancer	childhood leg length	1.30	
	Haematopoietic cancer		1.59	2.22

[1] standardised mortality ratio adjusted for age and childhood socio-economic group
[2] hazard ratio
[3] risk ratio adjusted for age
[4] odds ratio adjusted for age
[5] hazard ratio adjusted for age
[6] risk ratio adjusted for age, employment grade, and smoking

Table A1.2 Influences on height (selected studies)

Factors		Country	Birth year	Categories	Age	Difference		
Genetic factors						**Men**	**Women**	**Both**
Mid-parental height	†2	Britain [85]	1946	Increase per cm	36			0.54[1]
Maternal height	†2	Britain [57]	1958		7			0.30[1]
	†4	England/Scotland [58]	1976-82		5-11			0.05[2]
	†4	Netherlands [59]	1988-89		2			0.04[2]
	†4	Czech Republic [60]	1986-89		3-6			0.05[2]
Paternal height	†4	England/Scotland [58]	1976-82		5-11			0.04[2]
	†4	Czech Republic [60]	1986-89		3-6			0.04[2]
	†4	Netherlands [59]	1988-89		2			0.03[2]
Fetal/infancy factors								
Maternal smoking	†4	Britain [68]	1958	Nonsmoker vs 10+/day	11			1.00[1]
	†4	Britain [57]	1958	Nonsmoker vs heavy smoker	7			0.70[1]
	†1	Canada [159]	1980-83		1			-0.40[2]
					2			-0.04[2*]
	†4	Czech Republic [60]	1986-89	Nonsmoker vs smoker	3-6			0.02[2*]
	†1	Norway&Sweden [160]	1986-88		Birth			0.80[1]
	†1				5			0.50[1*]
Birthweight	†4	Britain [85]	1946	Increase per kg	36			2.26[1]
	†4	Britain [57]	1958		7			2.10[1]
	†4	England/Scotland [58]	1976-82		5-11			0.33[2]
	†1	USA [161]	1975-84		2-5			0.50[2]
	†4	Netherlands [59]	1988-89		2			0.47[2]
	†4	Czech Republic [60]	1986-89		3-6			0.34[2]
Gestation	†4	Britain [57]	1958	38-42 vs <38wks	7			2.90[1]
	†5	England/Scotland [58]	1976-82		5-11			-0.15[2]
Breastfeeding	†2	Britain [81]	1922-37	Breasrfed vs bottle fed	2-14	0.20[2]	0.14[2]	
	†2	Britain [81]	1922-37		Adult	2.50[1]	1.00[1]	
	†4	Britain [34]	1946	Ever vs never	Adult			0.09[2d]
	†4	Britain	1970	>2mths vs never	7			0.20[1*]
	†4	Czech Republic [60]	1986-89	Ever vs never	3-6			0.01[2*]
		Zambia [80]	1979-86		0-5			
Early environment factors								
Maternal age	†1	Sweden [162]	1933	Increase per year	10	0.02[1]	0.03[1]	
	†1	Sweden [162]	1943		10	0.06[1]	0.05[1]	
	†1	Sweden [162]	1953		10	0.07[1]	0.05[1]	
	†1	Sweden [162]	1963		10	0.34[1]	0.32[1]	
	†4	Britain [57]	1958	<25 vs 25-34y	7			0.60[1]
	†4	England/Scotland [58]	1976-82	≥ 32 vs ≤ 19y	5-11			0.12[2]

Table A1.2 Influences on height (selected studies) (cont.)

Factors		Country	Birth year	Categories	Age	Difference		
						Men	Women	Both
Crowding	†2	Britain [163]	1923-37	Increase per person	2-14	-0.07[2]		
	†1	Sweden [162]	1933		10	-.0.50[1]	-0.50[1]	
	†1	Sweden [162]	1943		10	-.0.20[1]	-0.20[1]	
	†1	Sweden [162]	1953		10	-.0.20[1]	-0.30[1]	
	†1	Sweden [162]	1963		10	-.0.20[1]	-0.20[1]	
	†4	Britain [85]	1946	≤1.5 vs >1.5 persons/room	36			0.84[1]
	†3	Britain [94]	1958	≤1 vs >2 persons/room	7			3.07[3]
	†2	Britain [158]	1958	≤1.5 vs >1.5 persons/room	16	1.60[1]	0.50[1*]	
	†4	Czech Republic [60]	1986-89	≤1 vs >1 persons/room	3-6			0.01[2*]
Housing tenure	†2	Britain [158]	1958	Owner vs council rental	16	1.00[1]	0.70[1]	
Household amenities	†2	Britain [158]	1958	Sole vs others	16	0.40[1*]	0.60[1*]	
Family size	†1	Sweden [162]	1933	Increase per child	10	-0.60[1]	-0.60[1]	
	†1	Sweden [162]	1943		10	-0.60[1]	-0.60[1]	
	†1	Sweden [162]	1953		10	-0.40[1]	-0.40[1]	
	†1	Sweden [162]	1963		10	-0.50[1]	-0.50[1]	
	†2	Britain [163]	1923-37		2-14	-0.06[2]	-0.06[2]	
	†2	Britain [158]	1958	1 vs >3 children	7	3.90[1]	3.10[1]	
	†2	Britain [158]	1958		11	3.80[1]	4.10[1]	
	†2	Britain [158]	1958		16	3.50[1]	1.80[1]	
	†4	England/Scotland [58]	1976-83	1 vs >4 children	5-11			0.35[2]
Birth order	†4	Britain [85]	1946	Increase per child	36			-0.82[1]
Parity	†2	Britain [84]	1958	0 vs >2	7	2.40[1]	2.10[1]	
	†2	Britain [84]	1958		11	2.50[1]	2.60[1]	
	†2	Britain [84]	1958		16	2.90[1]	2.60[1]	
	†4	Britain [57]	1958		7			2.80[1]
	†4	Netherlands [59]	1988-89	<2 vs ≥3	2			0.28[2]
N of younger siblings	†4	Britain [85]	1946	Increase per child	36			-0.63[1]
	†2	Britain [84]	1958	0 vs >2 siblings	7	2.60[1]	2.40[1]	
	†2	Britain [84]	1958		11	3.30[1]	3.00[1]	
	†2	Britain [84]	1958		16	3.30[1]	1.10[1]	
	†4	Britain [57]	1958	0 vs >1 siblings	7			1.10[1]
	†1	Sweden [90]	1981	<2 vs ≥2 siblings	10	0[1*]	0.20[1*]	

Table A1.2 Influences on height (selected studies) (cont.)

Factors		Country	Birth year	Categories	Age	Difference		
						Men	Women	Both
Social groups	†1	Sweden [88]	1933	I vs III [a]	7	1.20[1]	1.80[1]	
	†1	Sweden [88]	1943		7	1.40[1]	1.20[1]	
	†1	Sweden [88]	1953		7	0.10[1*]	0.50[1*]	
	†1	Sweden [88]	1963		7	1.60[1]	0.80[1*]	
	†1	Sweden [164]	1933	More vs less privileged [b]	10	3.20[1]	3.20[1]	
	†1	Sweden [164]	1943		10	2.10[1]	2.40[1]	
	†1	Sweden [164]	1953		10	0.40[1*]	0.90[1*]	
	†1	Sweden [164]	1963		10	1.80[1]	1.90[1]	
	†1	Sweden [90]	1981		10	1.10[1]	0.20[1*]	
	†1	Norway [89]	1906	Higher schools vs compulsory schools	14		3.80[1]	
	†1	Norway [89]	1941		14		1.00[1]	
	†1	Finland [165]	1953		10	4.50[1]	4.40[1]	
	†1	Finland [165]	1981		10	1.40[1]	0.60[1]	
Social class	†2	Britain [163]	1923-37	I&II vs V	2-14		0.38[2]	
	†4	Britain [85]	1946	Increase per category (I-V)	36			0.42[1]
	†1	Britain [87]	1946	I&II vs IV&V	7	2.30[1]	2.40[1]	
	†1	Britain [87]	1946		11	2.20[1]	2.40[1]	
	†1	Britain [87]	1958		7	1.60[1]	1.70[1]	
	†1	Britain [87]	1958		11	2.00[1]	2.00[1]	
	†4	Britain [57]	1958	I&II vs V	7			1.30[1]
	†3	Britain [94]	1958	I vs V	7			1.45[3]
	†2	Britain [84]	1958	I&II vs IV&V	7	2.20[1]	1.80[1]	
	†2	Britain [84]	1958		11	2.30[1]	1.90[1]	
	†2	Britain [84]	1958		16	2.10[1]	2.40[1]	
	†1	Britain [87]	1970		11	1.90[1]	1.30[1]	
	†1	Britain [87]	1980/81		7	1.20[1]	2.60[1]	
	†1	Sweden [166]	1980	Upper vs manual class	0-5	0.40*	0.60*	
Mother's employment	†4	England/Scotland [58]	1976-82	Employed vs unemployed	5-11			0.19[2]
Father's education	†4	Britain [85]	1946	Increase per category	36			0.34[1]
Mother's education	†4	Britain [85]	1946		36			0.62[1]
	†4	Czech Republic [60]	1986-89	University vs primary	3-6			0.31[2]
	†1	Sweden [90]	1981	More vs less educated[c]	10	0.80[1]	0.10[1*]	
Region	†4	England/Scotland [58]	1976-82	England vs Scotland	5-11			0.07[2]
Latitude	†4	England/Scotland [58]	1976-82	Per degree north	5-11			0.03[2]

Table A1.2 Influences on height (selected studies) (cont.)

Factors		Country	Birth year	Categories	Age	Difference		
Psychosocial factors						**Men**	**Women**	**Both**
Distress	†1	Poland [93]	1953	No vs yes	13		2.00[1]	
Family conflict	†3	Britain [94]	1958		7			1.62[3]
Enuresis	†4	Britain [92]	1958	No vs yes at 7&11y or 11y	11			1.50[1]
	†4	Britain [92]	1958	No vs yes at 7&11y or 11y	16			0.90[1]
	†4	Britain [92]	1958	No vs yes at 7&11y or 11y	23			1.10[1]
Childhood health								
Respiratory symptoms	†4	Czech Republic[60]	1986-89	No vs yes	3-6			0.06[2]

[1] difference in cm
[2] difference in SDS
[3] odds of being in the lowest fifth at age 7
†1 unadjusted
†2 adjusted for environmental factors
†3 adjusted for environmental factors and adult height
†4 adjusted for environmental factors and parental height
†5 adjusted for environmental factors, birthweight, and parental height
* p>0.05
[a] "groups I"-self employed, professionals, higher civil servants and executives and "group III"-manual workers
[b] "less privileged"-manual class with more than one sibling and "more privileged"- non-manual with no more than one sibling
[c] "less educated"-manual or non-manual occupations require less than 2 years of post-comprehensive school education, "more educated"-non-manual occupations require more than 2 years of post-comprehensive school education
[d] leg length

Table A1.3 Secular trends in height (increase per decade)

Country	Study	Period	Age	Increase	
	Adult height			**Males**	**Females**
Norway	Meyer & Selmer [167]	1926-41		1.8	1.9
	Liestol & Rosenberg [106]	1975-85			0.3
Sweden	Lindgren & Hauspie [107]	1952-82		0.3	
Austria	Weber [168]	1980-93		0.5	
Italy	De Stefano & Froment [169]	1874-1960		0.7	
Britain	Kuh et al [87]	1946-58		0.6	0.4
Croatia	Prebeg et al [170]	1982-91		1.6	2.2
Portugal	Padez & Johnston [171]	1930-40		1.2	
		1940-50		0.7	
		1950-60		0.7	
		1960-70		1.1	
		1970-80		2.7	
		1980-96		1.8	
Japan	Takaishi [104]	1950-60		3.0	
		1980-90		1.0	
Netherlands	Fredriks et al [105]	1955-65		2.7*	
		1965-80		2.0*	
		1980-97		1.3*	
Poland	Bielicki et al [172]	1965-76		2.4	
		1976-86		2.1	
		1986-95		1.8	
Czech Republic	Prebeg [170]	1973-82			3.0
Spain	Prado [173]	1955-85		2.0	2.0
Hungary	Gyenis [174]	1976-85		2.2	3.1
	Childhood height			**Boys**	**Girls**
England	Cameron [113]	1905-66	7.5	1.2	1.2
England	Hughes et al [99]	1972-94	5-11	0.7	0.6
Scotland		1972-94	5-11	1.3	1.2
Norway	Brundtland [89]	1920-40	8-14	4.0	4.0
		1950-70		1.0	1.0
Sweden	Cernerud&Lindgren [175]	1940-50	7	0.8	0.2
		1950-70		0.1	0.2
		1943-73	10	0.9	1.2
		1946-66	13	2.2	1.9
		1966-76		0.9	0.8
Netherlands	Gerver et al [115]	1980-89	17	2.6	1.4
Germany	Danker-Hopfe & Roczen [116]	1974-93	6	0.7	0.5
Japan	Takaishi et al [176]	1950-60	6	3.5	2.8
		1980-86	6	1.0	1.5
		1950-60	12	7.5	6.7
		1980-86	12	2.0	0.7

* men and women are combined

Chapter 2

Measures and sample representativeness

Two datasets used to investigate the associations between early environmental and genetic factors and growth are those concerning the 1958 birth cohort and the offspring. Height and social positions were obtained on three generations: cohort members (G2), their parents (G1) and their children (G3). This chapter provides descriptions for the study samples (§2.1), the rate of response to the survey at each follow-up (§2.2), key variables and derived measures used in the study (§2.3), and data handling (§2.4). Potential problems of non-response and sample reprsentativeness are discussed in §2.5.

2.1 Study samples

The 1958 birth cohort is a continuing, multi-disciplinary longitudinal study, which includes all children born in Britain between 3rd and 9th March, 1958 [177]. Information was obtained on about 98% of subjects from a target population of 17,733 births. The study had its origins in the "Perinatal Mortality Survey" and was designed to examine factors that were associated with stillbirth and death in early infancy. Cohort members were followed up at 7 (in 1965), 11 (1969), 16 (1974), 23 (1981), and 33 (1991) years of age [178], and most recently at age 41 years (1999-2001). Height and weight were measured at regular

intervals. In 1991, information was collected on offspring (G3) of a random sample of one-third of the cohort (G2).

The 1958 cohort was designed to monitor the physical, educational, behavioural, social and economic development of the cohort and to study the change in health, social-economic and demographic circumstances and their interrelationships within and between generations [177].

Immigrants born in the study week were added to the target sample in the first three sweeps in 1965, 1969, and 1974 [178]. As shown in Table 2.1, information on the cohort was collected from a variety of sources. During the earlier follow-ups, data were collected from parents, schools (teachers and doctors), as well as from cohort members themselves. Additional collection of exam results was obtained from schools in 1978. At ages 23 and 33 years, each study subject was interviewed. Partners of the subjects and their selected offspring were also interviewed in 1991. Unlike the earlier sweeps, no attempts were made to include new immigrants in the adult surveys in 1981 and 1991. The target samples for the adult surveys included anyone who had participated in at least one of the earlier sweeps.

Table 2.1 Sources of data in the 1958 birth cohort study

	1958 Birth†	1965 Age 7	1969 Age 11	1974 Age 16	1978 Age 20	1981 Age 23	1991 Age 33	1999 Age 41
Target sample	17,733	16,724	16,134	15,798	16,906	16,066	15,761	14,857
Source of data	Mother Medical	Parents School Test Medical Subject	Parents School Test Medical Subject	Parents School Test Medical Subject Census	School	Subject Census	Subject Partner Offspring [1] Mother [2]	Subject
Achieved sample	17,415	15,425	15,337	14,647	14,370	12,537	11,407	11,419

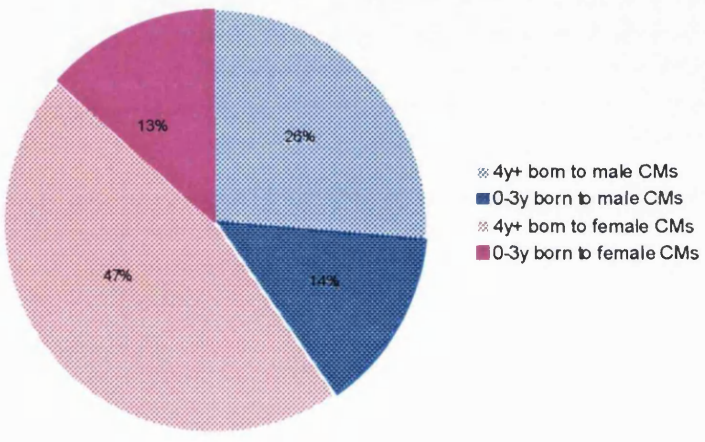
† Prenatal Mortality Survey

[1] children of a random sample of one in three cohort members

[2] female cohort member or female partner of the male cohort member

At the 33-year follow-up, the majority of men (78%) and women (80%) were living with a spouse or partner whose information was also collected. A sample of one in three cohort families with children was selected entirely at random for the "Mother and Child Study" in 1991. Mother figures for the offspring were interviewed. Information on family life, details of pregnancy and birth, health history, separations from the mother, experience of being "in care", pre-school experience, schooling history, and experience of daycare for each child was recorded [178]. Information was obtained for 4271 children (G3). Among them 2547 children (60%) were born to female cohort members (n=1515) and 1724 (40%) were to male cohort members (n=1069).

Figure 2.1 Offspring (G3) under or above 4 years by cohort members (G2)



Children aged 4 years or older (n=3095, 73%) were assessed with a series of age-specific tests of cognitive and behavioural development. A graphic display of children (G3) born to cohort members by age (0-3y or 4y+) is shown in Figure 2.1. More children were born to female cohort members than male cohort members, especially those aged 4 years or older (47% compared to 26%). The mother and child questionnaire was based on instruments used for the US "National Longitudinal Survey of Youth" (NLSY) of children born to women in a nationally representative sample between 1958 and 1965. Appropriate modifications were made for the British sample [179] to enable comparisons of the determinants of healthy development of children in Britain and USA [180]. As described below (§2.3), children aged 4 years or older in the G3 sample were also weighed and measured during the 1991 interview.

2.2 Response

2.2.1 Cohort members (G2)

Numbers of response at each sweep and reasons for non-response are provided in Table 2.2. The response rate has remained relatively high, although it declined from 98% in 1958 to 72% in 1991, when information included in this study was collected. The greatest reduction of response occurred after age 16. The sample reduction is largely due to the increasing number of refusals and untraced subjects (both at nearly 12% at age 33). There are also losses through emigration and deaths; a total of 2768 subjects (15.9%) emigrated, although some of the emigrants at early ages returned later and were included in the later sweeps (n=32). A further 598 (3.4%) cohort members had died by age 33 [181].

Table 2.2 Reasons for non-response in the 1958

	NCDS1 Age 7		NCDS2 Age 11		NCDS3 Age 16		NCDS4 Age 23		NCDS5 Age 33	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Data	15,425	87.9	15,337	91.1	14,647	88.2	12,537	76.1	11,407	69.8
Emigrated	421	2.4	688	4.1	785	4.7	392	2.4	482	2.9
Refused	80	0.5	797	4.7	1151	6.9	1194	7.2	1898	11.6
Dead	424	2.4	17	0.1	32	0.2	21	0.1	104	0.6
Untraced	1193	6.8	-		-		1902	11.5	1927	11.8
Traced no interview	-		-		-		433	2.6	529	3.2
Total	17,543		16,839		16,615		16,479		16,347	
Target sample*	16,724		16,134		15,798		16,066		15,761	
Achieved sample	15,425		15,337		14,647		12,537		11,407	
With some data (%)	92%		95%		93%		78%		72%	

* target sample=total-(emigrations+ deaths + permanent refusals)+immigrants

2.2.2 Offspring (G3)

The response rate of the Mother and Child Study was high: 98% of selected mothers were interviewed (Table 2.3). The high response rate in G3 is due to the fact that the sample was selected from cohort members who were interviewed in 1991.

Table 2.3 Reasons for non-response in the Mother and Child Study

Mother Interview†	*n*	%
With data	2584	98.0
Mother refused	32	1.2
Proxy Refusal	4	0.2
Broken appointment	3	0.1
Hospital/holiday	1	-
Other not completed	13	0.5
Total	2637	

† each mother as a subject

A total of 4271 offspring of 2584 cohort members were identified from the Mother and Child Study. Most offspring (>95%) were under 14 years in 1991 (Table 2.4). Natural and adopted children would have shared similar home environment, however, adopted children (n=23) were excluded from the offspring sample because information on their biological parent (e.g. height) was not available.

Table 2.4 Age composition for offspring (G3)

Age (years)	*n*	%
<4	1171	27.6
4-13	2877	67.7
>13	200	4.7
Total	4271†	100

† including 23 adopted children

In Chapters 5 and 6, where the offspring are concerned, the analyses mainly focus on 2931 natural children aged 4 years or more with a height measure (1448 boys and 1483 girls, 95.3% of all eligible children).

2.3 Measures

As mentioned earlier, a broad range of information, including details of the cohort member's family background, social and physical development, educational attainment, and family composition was recorded. Data on their parents, their children, and their partners were also collected. Characteristics are identified for three generations:

2.3.1 Parents of cohort members (G1)

Anthropometric measurements

Mother's (G1) height was measured to the nearest inch in 1958 and also reported in 1969 when the cohort member was aged 11 years. Measured maternal height in 1958 was used here, and reported height was added if the mother was not measured. Father's height (in inches) was reported in 1969, and in most cases was reported by the mother. Heights of G1 were converted into centimetres (mean height for G1 females 161.0 cm and for G1 males 174.5 cm).

Other factors

The *age of the mother* at childbirth was also recorded (mean 27.5, range 14-48 years).

Parity was collected by questionnaire soon after birth and categorized as (1) no, (2) one, (3) two, and (4) three or more previous pregnancies. *Mother's education* (G1) was collected in 1958 based on whether she stayed at school after the minimum school-leaving age (15 years for mothers under 25 years and 14 years for mothers 25 years or older).

2.3.2 Cohort members (G2)

Prenatal and infancy measures

Birthweight of each cohort member was measured at birth in ounces and then converted into grams (mean 3332g). Exposure to tobacco is available from information on maternal smoking habit during pregnancy (G1) recorded at birth.

It was shown by others that the effect of smoking on increasing risk of perinatal mortality and decreasing birthweight was determined by smoking habits after the fourth month of pregnancy [66]. Therefore information on maternal smoking was pre-coded as "non-smoker (<1 per day)", "medium smoker", "heavy smoker (10 or more per day)", and "variable smoker" after the fourth month of pregnancy. Smoking mothers are defined as "medium", "heavy" and "variable" smokers.

Duration of breastfeeding was reported in 1965 when the cohort member was age 7. It was coded as (1) no breastfeeding at all, (2) breastfed for under one month, and (3) breastfed for over one month. In Chapter 5, two broad categories "never breastfed" and "ever breastfed" were used.

Anthropometric measurements

Height of each cohort member was measured without shoes to the nearest inch by trained medical personnel at the ages of 7, 11, and 16, and later converted to centimetres. Self-reported height was obtained at age 23.

At age 33, height was measured to the nearest centimetre. The 33-year height of 3557 subjects has been edited for coding errors and missing values by others, and details are described elsewhere [182]. In summary, additional data on height measures from a sub-sample of some 2000 cohort members obtained from a separate study of respiration function in 1993 [183] were used for those without a height measure in the main 33-year survey. When differences in height from the two sources were more than 5 cm, the height measures at all previous available ages were compared to centile charts and the 33-year measure that was closer to the height centiles was used. If height at 33 was missing, height at 23 was used instead. For cohort members with improbable height at age 33 (i.e. >1.98 m for men or <1.46 m for women), their previous height measures (ages 7, 11, 16, and 23 years) were compared to centile charts. The reported height at 23 was used as the 33-year height if it seems to be more reasonable. Cohort members with large changes in height between ages 16 and 33 (i.e. >18 cm for men and >12 cm for women) and between ages 23 and 33 (>15 cm) were investigated by comparing their heights to centile charts. For women with height at 33 missing, a prediction using height at 16 years plus the mean increment between ages 16 and 33 years was imputed for the height at 33 years (n=3). Measures recorded as less than 1 m were considered as typing errors and height at 33 was obtained by adding 1 metre to the recorded height and then compared to centile charts to ensure the consistency with previous height measures [182]. The mean height of cohort members at each age using edited data is provided in Table 2.5.

Table 2.5 Mean (s.d.) height (cm) of cohort members (G2) at each age (*n*)

Age (years)	Boys		Girls		Difference
	Mean (s.d.)	*n*	Mean (s.d.)	*n*	(boys-girls)
7	122.8 (5.8)	7036	121.9 (6.1)	6598	0.9
11	143.9 (6.9)	6494	144.7 (7.5)	6195	-0.8
16	170.2 (7.9)	5746	160.9 (6.2)	5382	9.3
33	176.8 (6.9)	7105	162.4 (6.5)	7515	14.4

Table 2.5 shows that the height difference between boys and girls was much greater in adulthood than in childhood. There was only a small difference in prepubertal height; at age 7, boys were on average taller than girls by 0.9 cm. Girls became taller (by 0.8 cm), with a greater variance at age 11 due to their earlier growth spurt and maturation compared to boys. By age 16, boys overtook girls in height and were much taller (by 9.3 cm) with a greater variance compared to girls, reflecting the fact that most 16-year-old girls had reached their final height, whereas boys were still at different stages of puberty. Therefore the variance of height at 16y for boys included differences in stage of puberty as well as variation in adult height.

Pubertal development

During the medical examination at ages 11 and 16 years, the stage of pubertal development of each cohort member was assessed by medical officers using ratings based on Tanner's stages [184].

At age 11, boys were assessed using ratings in the range 1-5 (1 for preadolescent stage, 5 for mature stage) for (a) genitalia and (b) pubic hair (absent, sparse, intermediate or adult). At 16 years, ratings were obtained for facial hair, axillary hair, pubertal hair (absent, sparse, intermediate or adult), and voice broken (yes or no). Girls at 11 years were assessed using ratings for (a) breast and (b) pubic hair (absent, sparse, intermediate or adult). At 16 years, ratings were obtained for (a) breast development, (b) pubic hair, and (c) axillary hair (absent, sparse, intermediate or adult). Girls were also asked to recall at what age menstruation had started; those who had not yet started (2.1%) were included in a 16y+ category.

A variable indicating the stage of puberty of boys at 16 was derived using the total score of ratings for facial hair, axillary hair, pubertal hair, and voice broken and was then categorised as "early developer" (23.9%), "average developer" (65.3%) and "late developer" (10.8%). For girls, age of menarche was categorised as "early developer" (15.4%), defined as between 9 and 11 years, "average developer" (77.5%), defined as between 12 and 14 years, and "late developer" (7.2%), defined as after 14 years.

Early environmental factors

Family size at age 7 was derived based on the extended household under the age of 21 years. In Chapter 4, family size was divided into two broader categories as "small families" if there were ≤ 2 children and "large families" if there were ≥ 3 children in the household.

Social class at birth was based on the occupation of the male head (G1) of household as reported by the mother in 1958. Social class at age 7 was based on the male head's occupation obtained during the parents interview, and at ages 23 and 33, on the cohort

member's own current or most recent occupation. At age 33, the occupation of the partner was also recorded. *Social class of origin* used in subsequent analyses was defined as social class at age 7 or at birth if missing. Social class was classified into 4 categories: (1) I&II-professional or managerial, (2) IIINM-skilled non-manual, (3) IIIM-skilled manual, and (4) IV&V-semi-skilled or non-skilled occupations.

In 1991, information on any academic, vocational, and other training courses the cohort member received was recorded. The highest *education level* the cohort member achieved at age 33 was derived and classified into five categories: (1) no education, (2) <O-level, (3) O-level, (4) A-level, and (5) higher education.

Housing circumstances of G2 were collected at ages 7 and 33 years. Type of tenure was classified into three categories: (1) owner occupied, (2) private rental, and (3) council or housing association rental accommodation (social housing). Measures of household crowding at both ages were based on the number of people per room, excluding kitchens and bathrooms. Level of crowding was divided into three categories: (1) <1, (2) 1-1.5, and (3) >1.5 persons per room. In some analyses (Chapter 4), two broader categories, <1.5 persons per room (uncrowded) and ≥ 1.5 persons per room (over-crowded) were used.

Parental separation

During the interview in 1991, cohort members (G2) reported whether their parents (G1) ever separated or divorced and their age when their parents last lived together. The age of parental separation or divorce could range from birth to 33 years. For the purpose of this study, the timing of separation or divorce was divided into three categories (1) before 4 years (1.6%), (2) 4-7 years (1.9%), and (3) no divorce by age 7 years (96.5%). Age 7 years

was chosen to be consistent with other childhood variables. Details of household composition were also obtained at the 33-year survey, including whether the cohort member was living with a spouse or a partner. Family structure was derived for those with children and categorised as (1) lone-mother, (2) lone-father, and (3) couple families. The employment status of the cohort member and their partner were also recorded in 1991.

Health in childhood

Disability in childhood (approximately 5%) was identified for cohort members from (i) school doctor's reports of moderate or severe handicap in respect of ordinary schooling for one or more specified "abnormal conditions" (such as epilepsy or diabetes), and (ii) mother's reports of a physical handicap or disabling condition at age 7.

2.3.3 Offspring (G3)

The average age of selected offspring (G3) was 6.4 years (range from under one year to 18 years) and 8.2 years (range from 4 to18 years) for those with a height measurement. Their parents (i.e. G2) were on average at 26.6 years (range from 15 to 33 years) at childbirth. Maternal age (G2) at childbirth was derived as the difference between the age of the natural mother (G2) and the age of the child (G3).

Prenatal and infancy measures

Cohort members reported details for each pregnancy in the 33-year interview, including date of birth and birthweight. Average birthweight for all G3 was 3325g. Other information reported on each pregnancy included maternal smoking habit and breastfeeding duration. Maternal smoking (G2) was categorized as "non-smoker (<1 per day)", "medium smoker",

and "heavy smoker (10 or more per day)". Mothers were also asked whether they had breastfed each child and the age in months when she had stopped breastfeeding. In Chapter 5, two categories "never breastfed" and "ever breastfed" were used. *Parity* was derived based on the number of births reported and categorized as (1) no, (2) one, (3) two, and (4) three or more previous pregnancies.

Anthropometric measurements

Height and weight of G3 were measured to the nearest centimetre and 0.1 kilogram using portable measuring equipment. Body mass index (BMI) was calculated at each sweep using weight(kg)/height(m)^2.

Early environmental factors

Family size, defined as the number of natural or adopted children was based on reported household composition in 1991. Social class of G3 was based on the current or the most recent occupation of the G2 male head of household (the male cohort member or the male partner of a female cohort member) in 1991. The employment status of the household was based on whether one or both parents were working at the time of the 1991 survey. Both measures were classified as described above for G2.

The type of family was based on household composition in 1991. One-parent families were defined according to the General Household Survey (GHS), as parents with dependent children who were living without a spouse or partner [185]. Type of family structure was classified into three categories: (1) lone-mother, (2) lone-father, and (3) both parents (as for G2).

Disability of the offspring (3.9%) was identified from the mother's or mother figure's reports of any physical, emotional or mental difficulties that limited the offspring's ability to do normal school work or usual childhood activities.

2.3.4 Reliability and validity of reported or recalled measures

Some measures used here were recorded after a period of time and therefore might be subject to bias.

Reported height of G1 and G2

Unlike G1 maternal height, which was measured in 1958, G1 paternal height was reported in 1965, in most cases by the mother. Self reported height was also obtained at age 23 for G2. Although reported height is prone to errors, it is generally valid and reliable [186].

Recalled birthweight of G3

While the birthweight of each cohort member (G2) was measured, birthweights of G3 were reported by the cohort member during the interview in 1991, when G3 were on average 6.4 years of age (range from under one year to 18 years). A number of studies have shown that recalled birthweight, especially by the mother, correlates well with recorded birthweight, and is sufficiently accurate for epidemiological use. It has been reported that as many as 75% of birthweights recalled after 6 to 15 years by the mother were within 50 g of the hospital record [187]. However, there is also evidence of an average 63 g over report in birthweight [61].

There have been reports of a tendency to underestimate low birthweights [188;189] and over estimate high birthweights [189], but there is also a suggestion that mothers are likely to recall a lower birthweight more accurately [190]. Some evidence shows that parents of younger children [191], or younger mothers, or those with fewer children recall more accurately [192]. However, it has been found that reported birthweight is not associated with sex of the baby [187], maternal age [188], time interval since birth [188], maternal education [188;191], or social class [187;191]. Birthweight recalled by mothers tends to be more accurate than by fathers [191]. Recall is best when children are less than 4 years old, but is also remarkably accurate for children over 15 years old [188;189;193].

Recalled breastfeeding for G2 and G3

Information on breastfeeding of G2 was reported by the mother when the cohort member was age 7. Breastfeeding duration of G3 was reported by the mother in 1991 when the offspring were on average 6.4 years of age (range from under one year to 18 years). Mother's reporting of breastfeeding history shows close agreement between long-term recall and clinic records, and therefore is regarded as a valid estimate of breastfeeding behaviour [194]. However, a study of reported breastfeeding duration at ages 11, 23, and 47 months showed that recall could be affected by the length of the recall period with its accuracy reducing with increasing age of the child. Mothers who were better educated were also found to be more likely to report a longer breastfeeding duration [195]. Therefore potential confounding variables should be controlled to minimise the effect of recall bias [196].

Recalled maternal smoking of G2 and G3

Whereas maternal smoking habit during pregnancy was recorded around the time of birth for G2, the mothers of G3 reported their smoking behaviour in 1991 when their children were aged from birth to 18 years. Recall bias in maternal smoking is normally small [197]. A study showed that the recalled smoking during pregnancy after thirty years was still highly accurate compared to data recorded during pregnancy [198].

Recalled parental divorce of G2

The timing of parental separation or divorce was collected when the cohort member was age 33. The accuracy of the recall might depend on the duration itself, as recall is normally better for more recent events. However, an event such as parental divorce, even if it happened in early childhood is likely to be known and well-recorded.

2.4 Data handling

The data of the 1958 cohort have been examined extensively. The heights of cohort members at age 33 have been edited by others [182] and described in §2.3.2. The offspring sample has only been used in a few studies [180;199;200] and anthropometric measures of the offspring have not yet been investigated before. Therefore, some key measures for G3 were checked for coding errors and missing data in order to minimise the loss of information.

2.4.1 Data editing for the offspring (G3)

Baseline characteristics such as date of birth, sex, the order in the family, height and weight of G3 were examined. Data from the offspring (G3) have been edited for missing values and coding errors using records in the original questionnaires and information on household composition obtained from the cohort member interview. Details of all changes made are listed in Appendix 2.

Missing data

Information on age and sex of the child obtained from the cohort member's household composition recorded in the 1991 interview was added for children with missing data. Heights and weights that were missing, but recorded in the questionnaire were added to the data (n=47).

Inconsistency

Age and sex recorded in the Mother and Child Study was compared to the information on household composition. For those with inconsistent sex (n=8), corrections were made based on the name of the child. For those with inconsistent age (n=9), their height and weight were compared to the growth centiles to determine the probable age and corrections were made according to their height and weight.

Four children from two cohort families were recorded in the wrong order. The correct orders were assigned to them according to their age.

Measures recorded as less than 70 cm or below 10 kg were considered as typing errors as children were at least 4 years old. For 9 children with miscoded height (i.e. between 20 cm

and 60 cm), height was obtained by adding 100 cm to the recorded height and then compared the height to centile charts to ensure that they were reasonable. For 7 children with a coding error for weight, e.g. 2.5 kg, weight were corrected by multiplying the miscoded weight by 10 (to 25 kg). Self-reported height and weight of 13 children were added due to broken equipment at the interview.

Improbable measures for height or weight

Improbable heights and weights, i.e. those with height (SDS) and BMI (SDS) below –6 or above +6 were set to missing because the probability of a measure outside 6 SD is nearly zero (SDS: standard deviation scores are described below).

2.4.2 Derived measures

Height is usually Normally distributed for a given age and sex, which was true in both the 1958 cohort and the offspring data. The mean and standard deviation (SD) of height depend on age and sex. As shown in Table 2.5 (§2.3.2), height of boys had a greater SD at age 16 (7.9 cm) than girls at the same age (6.2 cm) and boys at age 7 (5.8 cm). A 7.9 cm increase in mean height is equivalent to the 68th centile at 16 years for boys, but it is the 80th and the 83rd centile for 16-year-old girls and 7-year-old boys, respectively. Moreover, variance of height may also differ between samples (two generations G2 and G3). Therefore height should be standardised so that it is directly comparable across age, sex, and generations. Height is standardised in two different ways in this study according to the purpose of the analysis.

Height standard deviation score derived within a sample - internal standardisation

When comparing height measured at different ages, height needs to be standardised at each age and sex within the sample. A standard deviation score (SDS or *Z* score) for height is defined as the difference between the child's height and mean height (*M*), divided by the standard deviation of height for the sample at the child's age and sex (*SD*) [201]. This is equivalent to:

$$Z = \frac{(\frac{height}{M}) - 1}{S} \qquad (2.1)$$

where *S* is the coefficient of variation, which is defined as *SD/M*. The height SDS (for all ages and both sexes) follows a Normal distribution with mean zero and variance one, and can be converted to a centile and vice versa using the Normal distribution table. The SDS removes the effects of age and sex on height and also standardises the increasing variance between height and age. Every unit increase of an internally derived SDS corresponds to *S* (cm) increase in height at a given age and sex.

In the 1958 cohort, although the height of each cohort member was not measured at exactly the same time, in fact was over a period of several months, the analysis of the relationships between some key factors (i.e. parental height and social background) and growth trajectories using growth models did not show differences when we used the exact age of measurement or the fixed ages of 7, 11, 16 years. Therefore, heights of G2 at all ages were standardised by converting to internally derived standard deviation scores (SDS) which were used to study the influence of early life factors on heights of G2 across ages in

Chapters 4 and 6. Maternal height SDS and paternal height SDS were derived internally using (2.1). Mid-parent height SDS was calculated for each cohort member (G2) as the average of height SDS of the parents (G1) (note: it is not an SDS).

Height standard deviation score derived with respect to a reference sample - external standardisation

When comparing heights of different samples, for example, two generations, the variances of the two samples may differ. Therefore, height needs to be standardised against a common reference sample.

Given the exact age and sex of a child, height can be converted to a standard deviation score (SDS or *Z* score) using (2.1), where *M* is the mean and *S* is the coefficient of variation for height at the specific age and sex in the reference sample. When comparing childhood height between G2 and G3, height SDS based on the same reference data, the 1990 British growth reference data, was derived for G2 at age 7 and for G3 at ages 4-18y using (2.1).

In Chapter 5, mid-parental height SDS was also calculated for each cohort member as the average of maternal and paternal height SDS, derived externally using the 1990 British growth reference sample. For G3, parental height was only available for the cohort member, not the other parent. So it was not possible to look at joint maternal and paternal effects on height, or to look separately at maternal or paternal effect on the whole sample. The externally derived height SDS of each cohort member at age 33 was used as the parental height SDS measure for G3 regardless of whether the cohort member was the father or the mother. This is possible because height SDS is independent of sex. However, such a measure has its weaknesses, as it does not differentiate between maternal and

paternal height effects. External standardisation with respect to the 1990 British growth reference sample was used in Chapters 5 and 6, to compare influences on childhood height in two generations (G2 and G3).

Every unit increase of an externally standardised SDS is approximately equivalent to a 5 cm increase in height for a 7-year-old and 7 cm for an adult man. Some given differences in height SDS and their corresponding differences in actual height (cm) for children seven years of age and adults are shown in Table 2.6.

Table 2.6 Conversion between externally derived SDS and height (cm)

	Difference in height (cm)		
Difference in height SDS	**7-year-old**	**Male adult**	**Female adult**
0.06	0.31	0.41	0.36
0.08	0.41	0.55	0.48
0.10	0.52	0.68	0.60
0.12	0.62	0.82	0.72
0.14	0.72	0.96	0.84
0.16	0.83	1.09	0.96
0.18	0.93	1.23	1.09
0.20	1.03	1.37	1.21
0.22	1.13	1.50	1.33
0.24	1.24	1.64	1.45
0.26	1.34	1.77	1.57
0.28	1.44	1.91	1.69
0.30	1.55	2.05	1.81
0.32	1.65	2.18	1.93
0.34	1.75	2.32	2.05
0.36	1.86	2.46	2.17
0.38	1.96	2.59	2.29
0.40	2.06	2.73	2.41
0.42	2.17	2.87	2.53
0.44	2.27	3.00	2.65
0.46	2.37	3.14	2.77
0.48	2.48	3.28	2.89
0.50	2.58	3.41	3.01
0.52	2.68	3.55	3.13
0.54	2.78	3.69	3.26
0.56	2.89	3.82	3.38
0.58	2.99	3.96	3.50
0.60	3.09	4.10	3.62
0.62	3.20	4.23	3.74
0.64	3.30	4.37	3.86
0.66	3.40	4.50	3.98
0.68	3.51	4.64	4.10
0.70	3.61	4.78	4.22

2.5 Sample representativeness and potential problems of non-response

In Section 2.1, it was mentioned that there have been six follow-ups from birth up to age 44 years (33 years in this current study). The original survey of cohort members formed a large nationally representative sample, but a longitudinal study like this often suffers losses to follow-up over time. In the 1958 cohort, the response rate of each follow-up has declined from 98% in 1958 to 72% in 1991. Non-response can lead to selection bias. As a result the remaining sample may not be representative of the original sample. For example, particular groups may be under-represented among the respondents. Although the offspring sample was studied only once in 1991 and was not followed up thereafter, the selection of the sample was restricted by the age of the cohort member in 1991. It is therefore necessary to assess its representativeness of children in Britain.

Section §2.5.1 examines whether the samples of cohort members (G2) used in subsequent analyses are representative of the original cohort, or, of the general population of their age. Section §2.5.2 describes the sampling frame for the offspring and examines its representativeness compared with children of their age in Britain.

2.5.1 Representativeness of the cohort (G2)

Generally satisfactory response rates have been achieved, with the response rate at each stage of the study remaining relatively high and at 72% of the target population in 1991 (Table 2.2). The remaining samples at ages 16, 23, and 33 years have been examined in

detail elsewhere [136;178]. Response at 16 years was generally reassuring, although slightly lower test scores in reading, mathematics and general ability at age 11 were found among children with no data at age 16 [202]. The sample at 23 years slightly under-represented of those who were disadvantaged with regard to family, housing, and financial circumstances [203]. Patterns of non-response at 33 years were similar to those reported for the previous survey (23 years) in terms of distributions of social and economic status, education, health, housing and demography. The 33-year sample was also compared with national samples such as the General Household Survey (GHS) and New Earnings Survey (NES), and the differences found were small [178].

This study focuses on different sub-groups of G2, including:

- Sub-sample 1: G2 with a height measure at age 33 (n=14620).
- Sub-sample 2: a third of G2 with children in the "Mother and Child Study" (n=2584).
- Sub-sample 3: G2 in sub-sample 2 with children aged 4 years or older and with a height measure (n=1931).

Although the 33-year sample is generally representative, the question arises as to whether each sub-group is biased in any way. Thus sub-samples were compared to all G2 with available data, in terms of demographic characteristics (i.e. social class of origin, adult social class, highest education level and housing tenure at age 33). Table 2.7 shows that the distributions of these characteristics were broadly similar for each sub-sample, except for female cohort members who had children by 33 years (sub-samples 2 and 3), who had a tendency to have a lower social class (e.g., 31% in sub-sample 3 were in classes IV&V compared with 24% of all G2 females) and to have lower education levels (e.g., 72% in sub-sample 3 had less than A-level compared with 64% of all G2 females).

Table 2.7 Composition of social demographic characteristics for sub-samples of G2

Character		All cohort members	Sub-sample 1	Sub-sample 2	Sub-sample 3
			n=14620	*n*=2584	*n*=1931
		n (%)	*n* (%)	*n* (%)	*n* (%)
Social class of origin					
Males	I&II	1780(19.6)	1379(20.3)	208(20.2)	125(17.9)
	IIINM	877(9.7)	687(10.1)	97(9.4)	59(8.5)
	IIIM	4204(46.4)	3069(45.1)	483(46.9)	332(47.6)
	IV&V	2205(24.3)	1671(24.6)	241(23.4)	182(26.1)
	Missing	578	299	40	26
	Total	9644	7105	1069	724
Females	I&II	1605(19.3)	1406(19.8)	258(17.6)	175(15.0)
	IIINM	840(9.9)	716(10.0)	137(9.4)	105(9.0)
	IIIM	3947(46.5)	3303(46.1)	697(47.6)	573(49.1)
	IV&V	2065(24.3)	1747(24.4)	373(25.5)	315(27.0)
	Missing	473	343	50	39
	Total	8960	7515	1515	1207
Social class at 33y					
Males	I&II	2100(39.8)	2095(39.9)	393(38.9)	246(35.6)
	IIINM	563(10.8)	561(10.7)	100(9.9)	75(10.9)
	IIIM	1754(33.3)	1743(33.2)	353(35.0)	256(37.0)
	IV&V	858(16.3)	852(16.2)	163(16.2)	114(16.5)
	Missing	349	1854	60	33
	Total	5606	7105	1069	724
Females	I&II	1727(32.6)	1722(32.5)	365(26.4)	249(22.8)
	IIINM	1936(36.5)	1935(36.5)	523(37.8)	431(39.4)
	IIIM	390(7.4)	390(7.4)	94(6.8)	75(6.9)
	IV&V	1252(23.6)	1250(23.6)	400(28.9)	338(30.9)
	Missing	494	2218	133	114
	Total	5799	7515	1515	1207
Housing tenure at 33y					
Males	Owner	4004(80.6)	3992(80.7)	824(79.8)	539(76.8)
	Renter	294(5.9)	294(5.9)	53(5.1)	37(5.3)
	Social housing	670(13.5)	663(13.4)	155(15.0)	126(17.9)
	Missing	638	2156	37	22
	Total	5606	7105	1069	724
Females	Owner	4208(77.7)	4205(77.7)	1117(76.1)	878(75.0)
	Renter	290(5.4)	290(5.4)	61(4.2)	44(3.8)
	Social housing	918(16.9)	915(16.9)	290(19.8)	249(21.3)
	Missing	383	2105	47	36
	Total	5799	7515	1515	1207
Education by 33y					
Males	None	502(9.2)	498(9.2)	92(8.8)	70 (9.9)
	<O-level	742(13.6)	738(13.6)	146(14.0)	108(15.3)
	O-level	1302(23.9)	1293(23.8)	246(23.6)	174(24.6)
	A-level	1317(24.1)	1316(24.2)	268(25.7)	188(26.6)
	High education	1592(29.2)	1588(29.2)	290(27.8)	167(23.6)
	Missing	151	1672	27	17
	Total	5606	7105	1069	724
Females	None	611(10.7)	608(10.7)	192(13.0)	158(13.4)
	<O-level	957(16.8)	956(16.8)	271(18.3)	226(19.2)
	O-level	2059(36.2)	2058(36.2)	557(37.6)	461(39.1)
	A-level	588(10.3)	588(10.4)	137(9.2)	115(9.8)
	High education	1470(25.9)	1468(25.9)	325(21.9)	218(18.5)
	Missing	114	1837	33	29
	Total	5799	7515	1515	1207

Mean birthweight, height at ages 7 and 33 years, and maternal age at childbirth of sub-samples were compared to those of all cohort members (Table 2.8). Differences in these measures were small, although female cohort members in sub-sample 3 were on average lighter at birth (by 34g) and shorter at 7 years (by 0.4 cm) than all female cohort members. But they were not shorter in adulthood.

Table 2.8 Mean (s.d.) birthweight, maternal age, and height at ages 7 and 33 for sub-samples of G2

Characteristic	All cohort members		Sub-sample 1		Sub-sample 2		Sub-sample 3	
	Mean (s.d.)	*n*	Mean (s.d.)	*n*	Mean (s.d.)	*n*	Mean (s.d.)	*n*
Birthweight (g)								
Males	3400(528)	8239	3405(526)	6467	3427(516)	969	3424(514)	661
Females	3262(511)	7813	3260(510)	6853	3244(521)	1408	3228(530)	1123
Total	3332(524)	16052	3331(523)	13320	3319(526)	2377	3301(524)	1782
Maternal age (y)	27.5(5.7)	17397	27.5(5.7)	13767	27.3(5.7)	2456	27.2(5.7)	1850
Range (y)	14-48		14-47		14-46		14-46	
Height at 7 (cm)								
Males	122.8(5.8)	7035	122.9(5.8)	5789	122.9(5.7)	882	122.7(5.9)	594
Females	121.9(6.1)	6598	121.9(6.0)	6056	121.7(5.9)	1236	121.5(5.8)	998
Height at 33 (cm)								
Males	176.8(6.9)	7105	176.8(6.9)	7105	176.8(6.5)	1063	176.6(6.8)	721
Females	162.4(6.5)	7515	162.4(6.5)	7515	162.7(6.2)	1513	162.5(6.2)	1206

In summary, the sub-samples resemble all cohort members on most of the measures examined, except that female G2 who had children early (by age 33 or age 29) tend to have lower education levels and lower social class of origin, compared to other women. It is known that women from lower social classes or lower education level are more likely to

have children earlier [204;205]. For a large sample like the 1958 cohort, some small differences are likely to be statistically significant. Thus comparisons were made based on the magnitude of the differences.

2.5.2 Representativeness of the offspring sample (G3)

There was a high response rate (98%) for G3, though no follow-up of these children has been attempted. The main concern with the G3 sample relates to the sampling strategy. The sample was selected based on the parent population and was constrained by the age of their parents. G3 was chosen at a particular age of cohort members (G2): the selected offspring (G3) all had one parent born in one week of 1958. Hence the older the child was, the younger the parent would be at the time of birth.

The age of female G2 at childbirth ranged from 15 to 33 years, and for children (G3) aged four years or older with a height measure it ranged from 15 to 29 years. For G3 of male cohort members, there was a wider range of maternal age, but predominantly younger than 33 years (97%). Thus the selection of the sample imposed an artificial inverse association between age of offspring (G3) and the age of the mother at childbirth, with a correlation coefficient of –1 for G3 born to female cohort members and –0.72 for those born to male cohort members. Therefore the G3 sample over represents children of younger mothers. No children born to old parents (i.e. both parents over 33 years) were included, nor were any children born to recent immigrants.

G3 selected for the "Mother and Child Study" were aged from less than 1 year to 18 years in 1991 and were on average younger for those born to male G2 (5.4y) than those born to

female G2 (7.1y), with nearly 60% of offspring born to female cohort members (Table 2.9). The difference in the age composition reflects the fact of earlier family formation of women compared with men.

Table 2.9 Mean (s.d.) age (years) of the offspring (G3) born to cohort members (G2)

Cohort member	G3 all ages			G3 aged 4+ †		
(G2)	Mean (s.d.)	*n*	%	Mean (s.d.)	*n*	%
Male	5.4(3.6)	1724	40.4	7.4(2.7)	1072	36.6
Female	7.1(4.1)	2547	59.6	8.6(3.2)	1859	63.4
Total		4271			2931	

† offspring with a height measure

Because of the age constraint imposed on the offspring sample, it is necessary to examine whether G3 is representative of children of their age in general with respect to some key characteristics such as anthropometric measures, type of family, social class, and employment status of parents.

Birthweight

Unlike height and weight, which were measured only for a sub-sample of G3, birthweight was reported for all live births to G2. The birthweight distributions for all offspring (G3) (second column) and those in the one-third sub-samples (third and fourth columns) resemble that for all live births in England and Wales in 1991 (Table 2.10).

Table 2.10 Birthweight distributions for offspring (G3) and all live births in England/Wales in 1991$

Birthweight (g)	All live births in England&Wales (1991)$		All G3 †		G3 in 1-in-3 sample		G3 aged 4+ with a height measure	
	n	%	*n*	%	*n*	%	*n*	%
<1500	6474	1.0	142	1.0	32	0.8	21	0.7
1500-1999	9131	1.4	174	1.2	48	1.2	31	1.1
2000-2499	30764	4.6	701	4.7	208	5.1	147	5.2
2500-2999	113813	16.9	2493	16.8	705	17.1	510	18.0
3000-3499	249729	37.1	5679	38.2	1604	39.0	1137	40.1
3500+	263388	39.0	5663	38.1	1519	36.9	990	34.9
Missing					155 ‡		95	
Total	673299		14852		4271		2931	

$ Source: OPCS mortality statistics [206]
† all livebirths born to cohort members by 1991
‡ missing includes adopted children whose birthweight were not reported

Anthropometric measurements

The composition of G3 was also examined by comparing their height, weight, and BMI with the 1990 British growth reference data [201]. Height standard deviation score (SDS) calculated using the reference sample (§2.4.2) had a mean close to zero (–0.007 in boys and –0.018 in girls) and the variance close to one (1.06 in boys and 1.08 in girls), indicating that its height distribution resembles the growth reference standard. Therefore, G3 was representative of British children with respect to height.

Among G3, older children were born to younger mothers while younger children were born to relatively older mothers. Although height SDS was age and sex standardised, a simple linear regression analysis showed a weak but significant inverse relationship between height SDS and the age of the offspring, suggesting that older children were shorter on average than those in the reference sample. In particular, as shown in Table 2.11, offspring

aged 14 years or older were significantly shorter than those of the same age in the reference sample by a height SDS of 0.22 in boys and 0.34 in girls. Therefore, the age of the child has been adjusted for throughout the G3 analyses to reduce the confounding effect of maternal age. Since G3 were born between 1973 and 1987, the age adjustment is also necessary to adjust for the possible effect of secular trend.

Weight and BMI SDS based on the 1990 British growth reference data [207] given in Table 2.11 show that offspring were heavier and fatter than children of their age.

Height, weight, and BMI of cohort offspring were further compared to the Health Survey for England 1995 (HSE) [208]. 1995 was the first year that height and weight were measured for children in the Health Survey for England, replacing the National Study of Health and Growth (NSHG). The differences (G3-HSE) in mean height, weight, and BMI at each age up to 15 years for boys and girls in the two samples are displayed in Figures 2.2-2.4.

Mean height of younger offspring (G3) was similar to the HSE sample, whereas older offspring tended to be shorter than the HSE sample. This result agrees with the comparison with the 1990 British growth reference sample. While G3 were on average heavier and fatter than the 1990 British growth reference sample, they were found to be lighter and thinner than children in HSE 1995. This is probably due to (1) the secular increase in weight and BMI in English children [99] and (2) the sample difference as the HSE did not include children in Scotland and Wales. The tendency of shorter and lighter (thinner) offspring of older ages did not affect the general representativeness of G3 sample with respect to anthropometric measures as the number of older children was small.

Table 2.11 Mean height/weight/BMI (SDS) and number of offspring (G3) at each age *

Age	Height SDS		Weight SDS		BMI SDS	
(years)	Mean	*n*	Mean	*n*	Mean	*n*
Boys						
4	0.16	176	0.39	178	0.41	176
5	-0.11	176	0.15	176	0.30	175
6	-0.08	177	0.09	178	0.17	176
7	0.06	146	0.13	145	0.12	145
8	0.17	150	0.24	148	0.19	148
9	-0.02	148	0.05	147	0.10	147
10	0.06	127	0.11	127	0.13	126
11	-0.22	117	-0.01	118	0.12	117
12	-0.03	78	0.16	77	0.17	77
13	0.01	70	-0.03	70	-0.13	70
14	-0.19	42	-0.04	42	0.07	42
15	-0.01	28	-0.02	28	0.03	28
16	-0.75	11	-0.06	11	0.48	11
17	-0.82	1	0.07	1	0.73	1
18	-1.04	1	1.01	1	1.73	1
Total	-0.007	1448	0.14	1447	0.18	1440
s.d.	1.06		1.04		1.15	
>13y	-0.22	83	-0.02	83	0.14	83
s.d.	1.29		1.16		1.05	
Girls						
4	0.20	152	0.22	150	0.19	150
5	-0.01	193	0.24	193	0.29	191
6	0.02	192	0.16	190	0.16	190
7	-0.11	158	-0.03	156	0.01	156
8	-0.01	157	0.12	157	0.19	157
9	-0.21	149	-0.12	148	0.01	148
10	-0.01	119	0.21	119	0.27	119
11	0.05	117	0.28	117	0.29	117
12	0.09	90	0.27	88	0.26	88
13	0.15	65	0.20	64	0.19	64
14	-0.22	44	0.15	44	0.33	44
15	-0.57	36	0.18	36	0.59	36
16	-0.23	8	0.50	7	0.66	7
17	0.52	3	0.10	3	-0.07	3
Total	-0.018	1483	0.15	1472	0.20	1470
s.d.	1.08		1.05		1.09	
>13y	-0.34	91	0.19	90	0.45	90
s.d.	1.08		1.31		1.21	

* natural children of cohort members with a height measure

Figure 2.2 Difference in mean height (cm) between offspring (G3) and the HSE 1995 (G3-HSE)

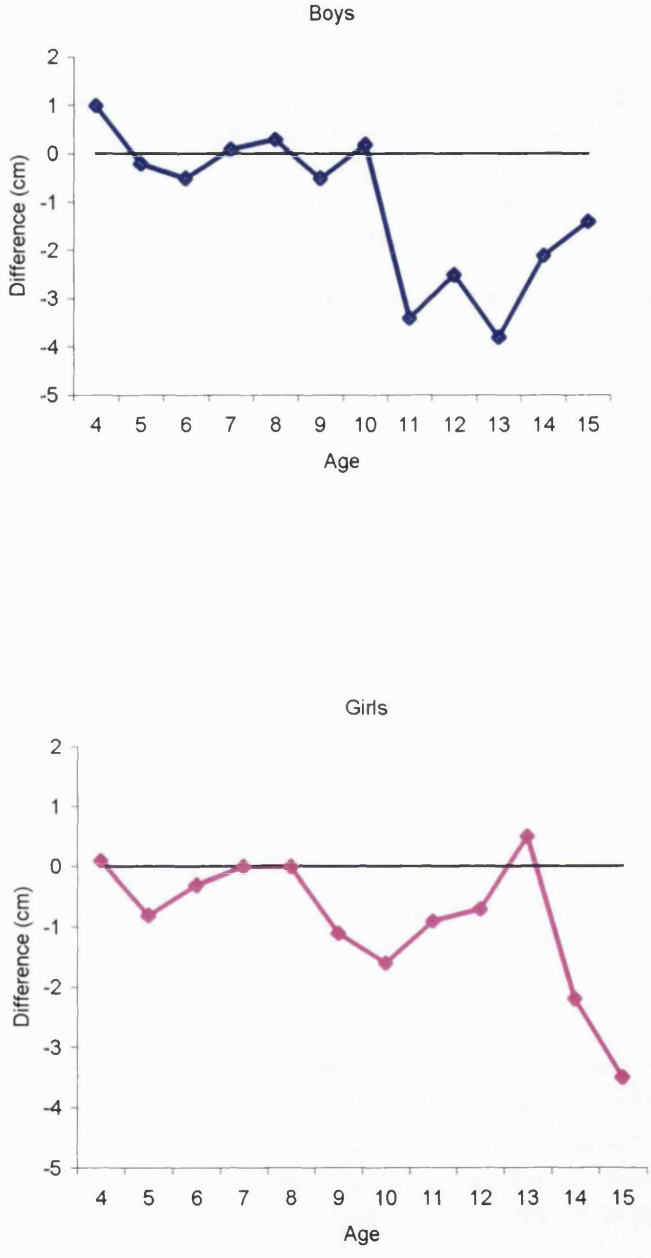
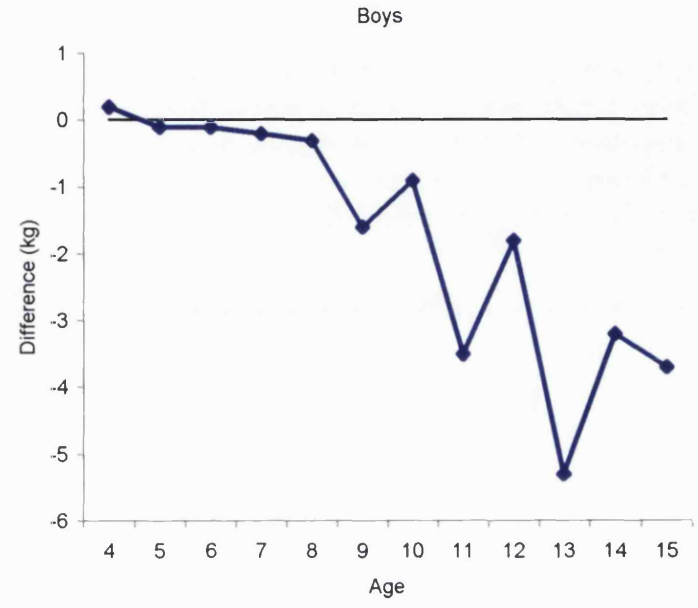


Figure 2.3 Difference in mean weight (kg) between offspring (G3) and the HSE 1995 (G3-HSE)



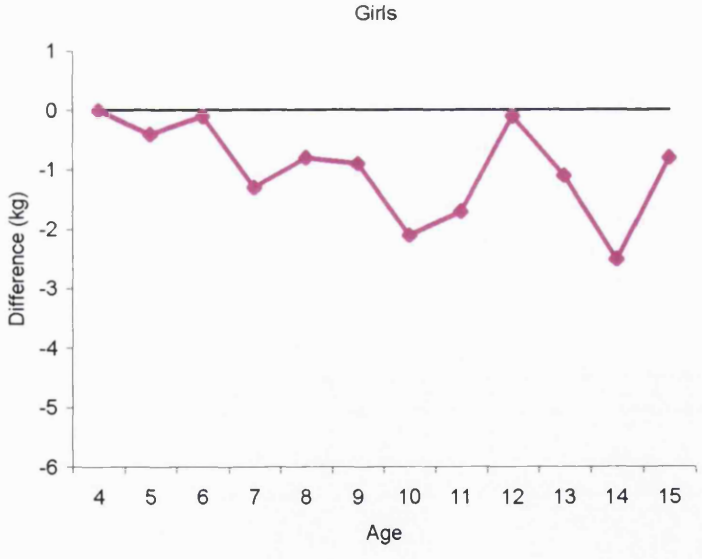
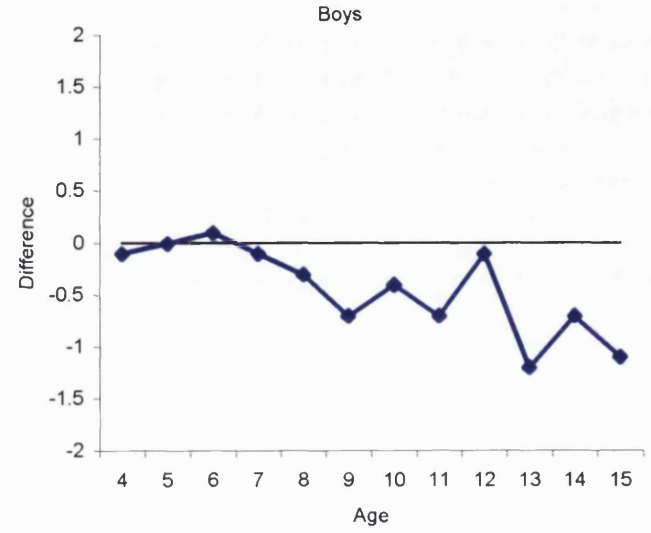
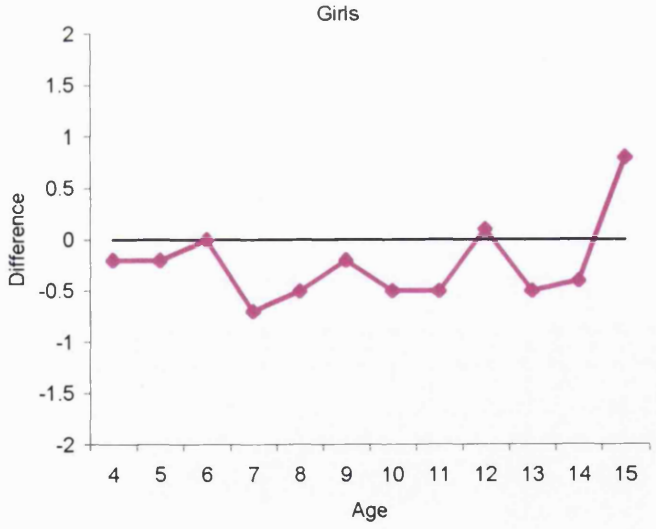


Figure 2.4 Difference in mean BMI (kg/m^2) between offspring (G3) and the HSE 1995 (G3-HSE)





Maternal age

G3 (those with a height measure) were born to mothers of an average age 24.4 years, whereas the average maternal age of all live births in Britain was 27 years in 1986 [209]. G3 sample is therefore more representative of British children born to younger mothers, rather than children of their age in general.

Social class

The distribution of the father's social class was compared to that of all live births within marriage by a mother 34 years or under registered in 1991 in England and Wales (Table 2.12) [206]. The social class compositions of G3 and that of all live births in England and Wales were broadly similar.

Table 2.12 Social class distributions for the offspring (G3) and all live births in England and Wales in 1991

Social class	G3 aged 4+ †		All live births to mothers <30y ‡	G3 all ages †		All live births to mothers ≤34y*
	n	%	%	*n*	%	%
I&II	893	32.0	29.6	1440	35.4	35.4
IIINM	349	12.5	10.8	495	12.2	11.0
IIIM	933	33.4	39.2	1309	32.1	35.9
IV&V	618	22.1	20.4	829	20.3	17.7
Missing	138			198		
Total	2931			4271		

† at least one parent aged 33y in 1991
‡ all live births within marriage registered in 1991 born to mothers age <30y in England and Wales [206]
* all live births within marriage registered in 1991 born to mothers age ≤ 34y in England and Wales [206]

Family employment status

Family employment status of the offspring (G3) was compared to the Family Expenditure Survey 1991 (FES) [210]. Table 2.13 shows that the proportion of G3 living in a household without a working parent was lower (11%) compared to the corresponding proportion in the FES representative sample (16.7%).

Table 2.13 Employment status of households with dependent children for the offspring (G3) and the FES 1991

Employment status	G3 all ages‡ *n* (%)	G3 aged 4+† *n* (%)	FES 1991 %
No-earner	429 (10.1)	320 (11.0)	16.7
Earner	3830 (89.9)	2601 (89.0)	83.3
Missing	12	10	
Total	4271	2931	

‡ selected a third of G3
† natural children with a height measure
Source: Family Expenditure Survey 1991 [210]

Type of family

The type of family (lone-parent/couple family) was compared to the General Household Survey 1991 (GHS), where each child was considered as a subject. As shown in Table 2.14, there was a lower proportion of offspring living in a lone-parent family (7.6%) compared to GHS (17.8%), where lone-parent is defined as a mother or a father living without a spouse and not cohabiting, with his/her never married dependent children, aged either under 16 or from 16 to (under) 19 and undertaking full-time education. Since lone-parenthood depends on the age of the parents, the type of family of cohort members (all 33 years) with children

was also compared to families in the GHS, whose head of household was aged 30-34 [185]. Treating family as a subject, Table 2.15 confirms that offspring to lone-parent families are under represented in G3.

Table 2.14 Family structures for the offspring (G3) and the GHS 1991 *

Type of family	G3 all ages‡	G3 aged 4+†	GHS 1991
	n (%)	*n* (%)	%
Lone-mother	297 (7.0)	238 (8.1)	16.6
Lone-father	25 (0.6)	20 (0.7)	1.2
Both parents	3937 (92.4)	2663 (91.2)	82.1
Missing	12	10	
Total	4271	2931	

* each child as a subject
‡ selected a third of G3
† natural children (G3) with a height measure
Source: General Household Survey 1991 [185]

Table 2.15 Family structures for the offspring (G3) and the GHS 1989-91 *

Type of family	G3 all ages‡	G3 aged 4+†	GHS 1989-91$
	n (%)	*n* (%)	*n* (%)
Lone mother	179(6.9)	149(7.7)	285(16.3)
Lone father	14(0.6)	13(0.7)	14(0.8)
Both parents	2383(92.5)	1762(91.6)	1451(82.9)
Missing	8	7	
Total	2584	1931	1750

* each household as a subject
‡ selected a third of G3
† natural children (G3) with a height measure
$ head of household aged 30-34, estimated for 1989-91 in Great Britain
Source: General Household Survey 1991 [185]

Further investigation showed that there were over 50% of offspring from lone-parent families, where the parent was not working, compared to 7.3% of offspring from families with both parents (Table 2.16). Thus the low proportion of no-earner households among G3 was due to the under representation of lone-parent families.

Table 2.16 Employment status by family structure for the offspring (G3)†

Employment status	Type of family			
	Lone-parent		Both parents	
	n	%	*n*	%
No-earner	132	51.2	194	7.3
Earner	126	48.8	2469	92.7
Total	258	100.0	2663	100.0

† natural children with height measurement

The under representation of lone-parent families in G3 was partly due to the sampling frame. Unlike the GHS, where each household with dependent children was a unit, G3 was selected from a cohort, which represents the population of adults living with dependent children. Consider cohort members were subjects in a random sample taken from such a population, households with two parents were more likely to be in the sample as they had a greater chance being selected than lone-parent households. As a result, children living in two-parent families were more likely to be in the sample and the chance of a child from a lone-parent family being selected was reduced.

To justify the difference in sampling frame, we examined family structure for female cohort members only and found that about 11% of G2 families were headed by a lone-mother. Haskey (1998) estimated that about 15% of mothers born in 1958 with dependent children were lone mothers at age 33 in Britain [211]. Therefore, the discrepancy reduced when only children of women were considered, although there was still some under representation of G3 in lone-mother families compared to the GHS. Other possible explanations include (1) the under-representation of ethnic minority children, as it is known that African-British families had a much higher proportion lone-parenthood than other groups and (2) the loss in the follow-ups may be higher among lone-parents.

A comparison of some key characteristics between children of lone-parent and two-parent families showed no significant difference in birthweight and height (SDS), although children of lone-mother families were on average 78 g lighter at birth than those of couple families. Children of lone mothers in G3 were on average 1.3 years older than those of couple families (Table 2.17), indicating that lone mothers tended to have children earlier than women who had a partner. Higher proportions of no-earner families, lower social class, lower parental education, and social housing tenancy were found among children of lone-parent families (Table 2.17).

Table 2.17 Distribution and mean (s.d.) for selected characteristics by family structure for offspring (G3)†

Characteristic	Lone-mother Mean(s.d.)	*n*	Lone-father Mean(s.d.)	*n*	Couple Mean(s.d.)	*n*	Mean(s.d.)	*n*	*p*
G3									
Birthweight	3230(559)	231	3322(589)	15	3308(541)	2588	3302(543)	2836	*
Height SDS	-0.056(1.13)	238	-0.306(0.84)	20	-0.004(1.06)	2661	-0.012(1.07)	2931	*
Age	9.4(3.3)	238	8.9(3.0)	20	8.1(3.0)	2661	8.2(3.1)	2931	<0.01
G2									
Maternal age	23.6(3.3)	238	-	-	24.5(3.3)	2604	24.4(3.3)	2849	<0.01
	n	%	*n*	%	*n*	%	*n*	%	
Social class									<0.01
I&II	31	15.2	1	5.3	856	33.4	888	31.9	
IIINM	58	28.4	3	15.8	288	11.3	349	12.5	
IIIM	21	10.3	8	42.1	900	35.1	929	33.4	
IV&V	94	46.1	7	36.8	517	20.2	618	22.2	
Education									<0.01
No education	60	25.3	8	40.0	324	12.4	392	13.7	
< O-level	54	22.8	0	0.0	483	18.5	537	18.7	
O-level	79	33.3	4	20.0	887	34.0	970	33.8	
A-level	18	7.6	4	20.0	408	15.6	430	15.0	
Higher	26	11.0	4	20.0	508	19.5	538	18.8	
Housing tenure									<0.01
Owner	73	34.3	7	35.0	1973	75.7	2053	72.3	
Private rent	15	7.0	1	5.0	100	3.8	116	4.1	
Social housing	125	58.7	12	60.0	534	20.5	671	23.6	

* $p>1$ 0.05
† natural children with height measurement

2.5.3 Potential effects of non-response

In a longitudinal study like NCDS, where data were drawn from different ages, numbers with complete data at each age can be reduced dramatically. The achieved sample of the 1958 cohort reduced from 17,415 subjects at birth (1958) to 11,407 subjects at the 5th sweep (1991) when information included in this study was collected. The loss of response at each sweep may introduce selection bias. Therefore it is necessary to monitor any potential bias caused by non-response.

As shown in §2.5.1, the remaining cohort members at age 33 did not differ from the original sample with respect to their birthweight, maternal age, height, social class, housing tenure, and education level. They also resembled other national samples such as the General Household Survey (GHS) and New Earnings Survey (NES) with respect to socio-economic factors at a particular age of 33 years as shown by others [178]. However, there have been suggestions that baseline characteristics are not always sufficient to ensure no non-response bias in the follow-up surveys [212].

Many traditional statistical methods require complete data. In multivariate analyses (multiple responses or multiple covariates), the possible approaches for missing data include case deletion and imputation. Case deletion often results in a large proportion of data being discarded and results may be less efficient. The inferences drawn from the data may be biased when the assumption that the missing is completely at random (MCAR, the probability of a missing response depends on neither the observed nor the unobserved response) or in some cases missing is at random (MAR, the probability of missing response does not depend on observed response) does not hold.

Alternative methods for dealing with missing data include substituting imputed values for missing data or adjusting for the non-response bias [213-215]. However, most methods of imputation can be applied either for missing at random or when we have knowledge of how responders and non-responders differ. Where data cannot be assumed to be missing at random, one approach is to attempt to model the missingness mechanism, and then to impute the missing values from this model. In the current analysis, missing height at age 33 has been imputed by others [182].

Although individuals of certain groups may be under-represented in the study sample, many of the findings in subsequent chapters are concerned with relationships, which are not necessarily affected. In Chapters 4 and 6, where repeated height measures of cohort members are considered as response variables, multivariate response models are applied to the unbalanced structure where all available data are used in analyses [139]. The assumption of missing at random (MAR) required by the models is examined in Chapter 3. The missing patterns of response variables (height) and their impact on the subsequent analyses are described in detail in §3.3.1.

In summary, the achieved sample of the 1958 cohort did not differ from the original sample or national representative samples with respect to some key factors. Although the sample has reduced over time, there is no evidence that there is a substantial effect on our analyses due to the no-responses. All analyses in subsequent chapters have been carried out using samples with complete data and samples with all available information. Similar results from these analyses suggest that the deletion of incomplete cases does not introduce bias to the results.

The offspring sample (G3) did not differ markedly from other British children of their age with respect to birthweight and height, although they were heavier and fatter. G3 represents children of young parents who were more likely to be disadvantaged. On the other hand, some socio-economic characteristics associated with lone-parenthood were likely to be under-represented in the sample, which appeared to some how counter balance the disadvantages associated with young parenthood. These counter-balancing effects probably explain the resemblance of birthweight, height, and social class composition of G3 and national samples.

Appendix 2

A2.1 Data editing for the offspring sample (G3)

Date of birth, sex, the order in the family, height and weight of G3 were examined. Information that was missing from the database but was recorded in the original questionnaires from the mother interview was added to the analyses. Information inconsistent with other sources (i.e. information on household composition obtained from cohort member interview in 1991) was corrected (described in §2.4.1). The list of offspring that have been edited is as follows:

Serial	ID[†]	Sex[1]	Age[1]	H[1]	W[1]	Sex[2]	Age[2]	H[2]	W[2]
010168Y	4	1	4	.	.	1	4	106.0	19.2
041022T	6	1	2	.	.	2	2	.	.
041030S	4	1	2	131	30.5	2	9	131.0	30.5
041030S	5	2	9	.	.	1	2	.	.
042011T	3	2	0	162	52.8	2	13	162.0	52.8
042011T	4	2	0	154	50.0	2	12	154.0	50.0
042011T	5	1	0	145	36.5	1	9	145.0	36.5
044006M	3	1	7	130	.	1	7	130.0	28.6
044026T	3	1	11	133	.	1	11	133.0	28.6
046036H	2	2	6	117	21.0	1	6	117.0	21.0
051005Z	3	2	7	.	.	2	7	124.0	21.6
053005L	4	2	4	.	.	2	4	107.0	19.1
071020J	3	2	7	123	2.5	2	7	123.0	25.0
083049B	3	2	10	141	.	2	10	141.0	31.8
083054U	3	2	17	170	.	2	17	170.0	58.1
083091A	3	1	8	122	.	1	8	122.0	23.6
086022W	3	1	9	122	.	1	9	122.0	27.2
086053J	3	1	6	133	.	1	6	133.0	31.8
089022N	3	1	0	.	.	1	10	140.0	29.3
089022N	4	2	0	.	.	2	8	124.0	22.5
089022N	5	2	0	.	.	2	6	114.0	19.1
089022N	6	2	0	.	.	2	4	97.0	14.9

Serial	ID[1]	Sex[1]	Age[1]	H[1]	W[1]	Sex[2]	Age[2]	H[2]	W[2]
089023Q	3	2	14	.	.	2	14	157.0	59.9
089023Q	4	2	9	.	.	2	9	136.0	45.5
089023Q	5	1	8	.	.	1	8	129.0	28.7
091020W	3	1	0	166	56.5	1	15	166.0	56.5
091020W	4	1	0	134	30.9	1	8	134.0	30.9
092033M	3	1	7	130	25.6	1	8	130.0	25.6
093009V	3	1	10	.	.	1	10	140.7	37.0
093235E	3	1	9	143	35.4	1	10	143.0	35.4
093249S	3	2	15	167	.	2	15	167.0	54.5
095019K	3	2	0	132	30.1	2	8	132.0	30.1
096017L	4	2	10	48	42.5	2	10	148.0	42.5
096017L	5	2	8	47	32.2	2	8	147.0	32.2
099046K	3	2	4	111	.	2	4	111.0	19.1
100045H	5	1	11	126	26.5	2	9	126.0	26.5
120077K	4	1	7	125	26.2	2	7	125.0	26.2
188077S	5	.	0	.	.	1	3	.	.
200028Q	3	1	11	26	27.3	1	11	126.0	27.3
280022D	3	1	0	.	.	1	1	.	.
280048Y	3	1	11	46	36.0	1	11	146.0	36.0
280068E	3	2	8	.	.	2	8	136.0	38.1
280080U	4	1	8	28	24.0	1	8	128.0	24.0
340043U	3	1	0	.	.	1	8	.	.
340043U	4	2	0	.	.	2	6	.	.
350034Z	3	.	0	.	.	2	7	125.0	24.7
350034Z	4	.	0	.	.	1	4	105.0	18.1
360003U	4	1	12	144	34.0	1	13	144.0	34.0
380049J	3	2	16	52	48.4	2	16	152.0	48.4
382009F	3	.	0	.	.	1	5	109.0	19.2
382009F	4	.	0	.	.	1	1	.	.
410008E	3	2	8	129	25.1	2	9	129.0	25.1
423061H	3	1	0	.	.	1	11	148.0	36.6
423061H	4	1	0	.	.	1	9	139.0	30.4
425032L	6	2	11	.	.	2	1	.	.
433012Z	3	.	0	.	.	1	7	123.0	26.9
433012Z	4	.	0	.	.	2	5	117.0	27.4
440010L	3	2	0	124	24.4	2	5	124.0	24.4
440010L	4	1	0	107	17.8	1	3	107.0	17.8
460016M	2	2	0	.	.	2	13	156.0	60.0
460016M	3	2	0	135	15.3	2	8	135.0	15.3
460045U	4	2	9	137	28.6	2	10	137.0	28.6
483011E	4	1	5	114	20.1	1	6	114.0	20.1
500322N	3	2	0	.	.	2	4	107.0	19.6
500322N	4	2	0	.	.	2	1	.	.

Serial	ID[1]	Sex[1]	Age[1]	H[1]	W[1]	Sex[2]	Age[2]	H[2]	W[2]
500487X	3	1	9	.	.	1	9	129.0	25.5
500494U	4	1	5	111	18.8	1	6	111.0	18.8
511125X	3	2	3	.	.	2	4	.	.
511125X	4	2	4	.	.	2	3	.	.
514106K	3	2	9	132	28.2	1	9	132.0	28.2
514153U	3	1	0	124	25.3	1	6	124.0	25.3
517216J	3	1	5	.	.	1	5	103.0	16.7
517218N	3	2	0	.	.	2	3	.	.
517218N	4	1	0	.	.	1	2	.	.
520001D	3	1	0	149	38.2	1	11	149.0	38.2
520001D	4	2	0	139	37.9	2	10	139.0	37.9
520001D	5	2	0	115	21.4	2	6	115.0	21.4
520022N	3	1	2	.	.	2	2	.	.
520022N	4	2	1	.	.	1	1	.	.
523033K	3	2	0	.	.	2	1	.	.
525027A	3	1	13	163	5.8	1	13	163.0	58.0
525055F	4	1	0	154	39.4	1	12	154.0	39.4
550284Q	3	1	11	.	.	1	11	152.0	36.0
550284Q	4	1	9	.	.	1	9	140.0	30.0
550284Q	5	1	5	.	.	1	5	109.0	17.2
581007M	2	2	6	125	2.7	2	6	125.0	27.0
581069L	3	1	9	133	24.9	1	10	133.0	24.9
582003J	5	2	8	130	29.5	2	9	130.0	29.5
591005P	2	2	13	.	.	2	13	147.0	48.9
620119M	4	1	9	134	.	1	9	134.0	25.9
650003L	3	1	0	161	51.6	1	13	161.0	51.6
650003L	4	1	0	149	36.2	1	11	149.0	36.2
650048K	3	2	5	115	18.3	2	6	115.0	18.3
650054D	2	2	11	163	45.2	2	12	163.0	45.2
650149R	2	1	0	140	39.2	1	10	140.0	39.2
650149R	3	1	0	131	28.9	1	8	131.0	28.9
684053T	3	1	7	.	.	1	7	125.0	24.7
684053T	4	2	4	.	.	2	4	106.0	17.5
720046T	3	1	0	138	25.4	1	8	138.0	25.4
730131Q	3	2	6	.	.	2	6	118.0	22.7
730160X	3	2	6	117	.	2	6	117.0	19.1
740004P	3	1	0	146	34.7	1	13	146.0	34.7
740004P	4	1	0	139	27.2	1	11	139.0	27.2
740015U	3	2	0	.	.	2	1	.	.
782156A	4	2	5	110	19.6	2	6	110.0	19.6
815028U	3	.	0	.	.	1	7	132.0	30.7
815028U	4	.	0	.	.	1	5	117.0	24.4

Serial	ID[1]	Sex[1]	Age[1]	H[1]	W[1]	Sex[2]	Age[2]	H[2]	W[2]
815035R	3	1	13	134	20.5	1	14	151.0	37.4
815035R	4	1	9	151	37.4	1	9	134.0	20.5
820011E	3	1	0	154	41.9	1	11	154.0	41.9
820011E	4	1	0	142	34.3	1	10	142.0	34.3
820011E	5	1	0	118	25.1	1	5	118.0	25.1
823010U	3	2	0	.	.	2	10	145.0	39.3
823010U	4	2	0	.	.	2	8	129.0	26.3
823010U	5	2	0	.	.	2	1	.	.
823513X	4	2	11	57	70.2	2	11	157.0	70.2
824511Y	3	1	12	155	44.4	1	13	155.0	44.4
850025M	3	2	10	140	5.5	2	10	140.0	55.0
850025M	4	2	7	115	3.0	2	7	115.0	30.0
880037P	3	2	0	.	.	2	2	.	.
882013K	3	2	4	.	15.8	2	4	99.5	15.8
882054Z	3	.	0	.	.	1	6	108.0	24.6
882054Z	4	.	0	.	.	2	5	95.0	19.4
910017U	3	1	5	.	.	1	5	112.0	19.4
937028A	3	1	6	.	.	1	6	92.0	18.8
937058L	3	2	2	.	.	1	2	.	.
960085V	3	1	6	121	2.3	1	6	121.0	23.0
962009P	3	2	0	145	34.9	2	11	145.0	34.9
985009T	3	1	6	113	19.5	1	5	113.0	19.5
985037Y	3	2	4	100	19.4	2	5	100.0	19.4
986232B	5	1	3	97	16.9	1	4	97.0	16.9
987031W	3	2	0	147	44.1	2	11	147.0	44.1
987031W	4	1	0	140	34.8	1	9	140.0	34.8
989002Z	2	2	0	168	23.3	2	12	168.0	23.3
989002Z	3	2	0	158	53.7	2	11	158.0	53.7
X46042L	3	2	14	162	10.3	2	14	162.0	103.1
X77025L	3	2	13	141	31.3	2	14	141.0	31.3
X80058V	3	.	11	147	35.7	2	11	147.0	35.7
X80058V	4	.	10	143	38.7	2	10	143.0	38.7
X80058V	5	.	6	119	21.6	2	6	119.0	21.6
X82203N	3	2	12	55	53.8	2	12	155.0	53.8
X82301N	3	2	0	163	50.5	2	12	163.0	50.5
X82332Z	4	2	10	46	40.6	2	10	146.0	40.6
X82340Y	4	1	5	112	12.0	1	5	112.0	19.6
X82381P	4	1	10	138	30.9	1	11	138.0	30.9
X82381P	5	2	8	125	22.0	2	9	125.0	22.0
X85013Y	4	2	6	172	25.2	2	6	122.0	25.2

Serial	ID†	Sex[1]	Age[1]	H[1]	W[1]	Sex[2]	Age[2]	H[2]	W[2]
Y01176P	3	1	0	146	41.5	1	12	146.0	41.5
Y01176P	4	2	0	137	31.8	2	12	137.0	31.8
Y01176P	5	1	0	127	24.4	1	10	127.0	24.4
Y01176P	6	2	0	118	19.6	2	8	118.0	19.6
Y01176P	7	1	0	111	19.0	1	6	111.0	19.0
Y01176P	8	2	0	93	14.2	2	4	93.0	14.2
Y30154S	3	2	0	.	.	2	4	.	.
Y30154S	4	2	0	.	.	2	3	.	.
Y30154S	5	1	0	.	.	1	1	.	.

† identification of an individual in the cohort family

[1] sex, age, height and weight before editing

[2] sex, age, height and weight after editing

Chapter 3

Statistical methods in life-course studies

Life-course epidemiology concerns complicated associations such as how biological and social factors throughout life, independently, cumulatively, or interactively influence health and disease [9]. A life-course approach typically requires information collected from different life stages, including before birth and from previous generations.

There is a wide range of statistical techniques that may be applied to life-course analyses. Sometimes a traditional method is adequate, whereas in other situations more complex statistical models may be necessary, depending on the data structure and the life-course hypothesis proposed. For example, a simple relationship between an early exposure and later disease can be examined using a traditional model, whereas a study of the relationship between the trajectory of a disease risk and factors that may affect the trajectory requires a more complicated model. However, each method suits for the specific purposes and has its advantages and limitations.

Table 3.1 includes some statistical methods that are commonly applied to life-course analyses. Given that the main response variable in this study is height, which is known to have a Normal distribution, methods discussed in this chapter are mainly suitable for continuous response variables. Methods designed for categorical or other non-Normal variables are included in Table 3.1, but are not considered in subsequent sections. In §3.1, two types of study design and data structure are described. While the methodology

presented in §3.2 requires independent samples, models described in §3.3 are suitable for (1) longitudinal repeated measures and (2) data with a clustered nature, and are applied in subsequent analyses. Some techniques included may not be directly relevant to the current study objectives, but are however widely applied for investigating life-course relationships. In §3.4, causal modelling in path analysis is briefly discussed.

3.1 Study design and data structure

3.1.1 Cross-sectional and longitudinal studies

A *cross-sectional* study examines the relationship between a response variable and exposure variables at one point in time. The exposure variable can be fixed (e.g. sex) or variable (e.g. current smoking or recalled smoking history). Thus a cross-sectional study is not suitable for determining the temporal sequence of events since it only deals with the relationship at one time point, and therefore cannot provide enough evidence for a causal relationship. In general, the statistical techniques for dealing with cross-sectional studies are easier than those required by longitudinal studies. When the response variable is continuous (i.e. height), the analysis can include testing the difference in mean height between two groups using a *t*-test, or between three or more groups using ANOVA. A bivariate relationship between two continuous variables (e.g. height and BMI) may be assessed using correlation and regression analyses. Multiple regression models can be used to adjust for potential confounding factors (§3.2).

Table 3.1 General overview of statistical methods that may be applied in life-course analyses

Method	Data	Assumptions	Advantages	Limitations
Linear regression or generalised linear models [216;217]	Cross-sectional Longitudinal	Underlying distribution of the response. Observations are independent	Available in all statistical packages	Not practical when the path diagram is complicated
Multilevel/ random effect models [139;218;219]	Cross-sectional Longitudinal	Underlying distribution of the response. Observations are clustered in a higher level or subjects are measured on more than one occasion	The correlation structure is accounted for. Estimate fixed parameters and variance components at multiple levels. All data is incorporated	
Generalized Estimating Equations (GEE) [140;219-221]	Longitudinal	Underlying distribution of the response. Subjects are measured on more than one occasion	The correlation structure is accounted for. All data is incorporated. Useful for estimating fixed parameters	
Growth models [222;223]	Longitudinal	Underlying distribution of the response. Subjects are measured on more than one occasion. Time is assumed to be continuous	The correlation structure is accounted for. All data is incorporated. Trend can be tested. Timing and spacing of time points may vary	Not practical when time intervals are large
Multivariate response models [139]	Cross-sectional Longitudinal	Underlying distributions of the responses. Subjects are measured on more than one occasion, or on several response measures. Time is considered as fixed occasions	Repeated or multiple response measures are examined simultaneously. Correlation structure is accounted for. Effect can be directly compared between occasions or responses. All data is incorporated	Not practical when the number of repeated measures is large
Structural equations [142-145]	Cross-sectional Longitudinal	Response and intermediate variables are Normally distributed. For path analysis latent variables are involved. Assumption for causal directions	Estimate direct and indirect effects. Can be used when there is more than one response variable in system	Can't determine the underlying causal structure
G-estimation [141]	Longitudinal (event data)	Time-dependent covariates are both confounders and intermediate variables	Can be used when time-dependent exposure variables are also measured repeatedly	Not available in statistical packages

In a *longitudinal* study, a sample of individuals is observed prospectively over a specified time interval. Exposure variables or response variables are observed on several occasions, where the response variable is observed after the exposure variable [224]. For example, a longitudinal study of coronary heart disease (CHD) may define a sample at baseline, and follow the individuals to observe risk factors and morbidity through time. However, longitudinal data could also be obtained retrospectively by reviewing health records or by asking individuals to recall past events. The longitudinal study of the Office of Population Censuses and Surveys (OPCS) follows a 1% sample of the British population that was initially identified at the 1971 Census. Outcomes such as mortality and incidence of cancer have been related to socio-economic factors measured at successive censuses [225;226]. Thus longitudinal designs are uniquely suited to investigate the temporal sequence of events, the relationship between changes of an outcome over time and factors that have affected those changes, or the relationship between the outcome and the accumulation of the exposures. Longitudinal studies therefore provide more evidence of causality than cross-sectional studies.

Prospective longitudinal studies have been referred to as cohort studies. The 1958 cohort provides responses and exposures collected at different life stages, from before birth to adulthood. The Mother and Child Study was conducted only once in 1991 and therefore is a cross-sectional design. However, a cross-generational comparison of cohort members and their offspring is considered as a longitudinal design. Common issues of longitudinal studies include the loss in follow-ups for a variety of reasons and may be a source of bias. Details for testing the missing patterns are given in §3.3.1. In addition, the correlation of the repeated measures within individuals needs to be accounted for in the analyses. These issues are also discussed in §3.3.1.

3.1.2 Independent and hierarchical data structures

An independent data structure is characterized by the fact that the value of one observation does not affect that of the others. Whereas, a hierarchical structure is characterized by the fact that individuals can be treated as members of groups. Units at one level are grouped within units at a higher level and data observed from the same group are related. For example, children from the same family share similar genes as well as environment; measurements taken from the same individuals are more alike than those taken from different individuals.

Data of the 1958 cohort have a unique hierarchical structure. *First,* height and other variables of interest were measured at several occasions for cohort members (G2) (i.e. at ages 7, 11, 16, 23, and 33 years). The variation in height between individuals is greater than the variation between measurements within individuals once age is adjusted for. *Second,* cohort members and their offspring (G3) are nested within families; subjects from same families are correlated. Therefore, statistical methods that take account of the data structure are essential in order to make inferences of the data.

Statistical models that are suitable for independent data are briefly described in §3.2. In §3.3 more complicated models for data with a hierarchical structure are discussed in detail.

3.2 Statistical models for independent data

Linear regression models

Simple *linear regression* can be used to establish the relationship between a continuous response variable and one or more explanatory variables, where the response variable follows an independent identical Normal distribution [216]. The regression parameters (i.e. intercept and slope) can be estimated using Ordinary Least Squares (OLS), which minimizes the sum of squares of the residuals. The association between an explanatory variable of interest and the response can be assessed by using a *t*-test for the null hypothesis of the true slope of the regression line being zero.

In a multiple regression model, where more than one explanatory variable is considered, the parameter for a specific explanatory variable is a partial regression coefficient representing the increase in the expected response for every unit increase in the explanatory variable when other variables are held fixed (or adjusted). Curvilinear relationships can be explored by adding quadratic, cubic terms, or higher order terms to the model [216].

Test for the linear trend in means for ordered categorical variables

Some explanatory variables are ordered categorical rather than continuous. In the simplest case, the order of the category can be treated as a continuous variable. A linear regression model can be applied to test for a linear trend of a continuous response variable according to the ordered categories, assuming that they are equally spaced. For a response variable height and an explanatory variable social class, the slope indicates the height increment for

every category increase in social class variable. A non-zero slope of the regression line indicates significant social class gradients in height.

Confounding factors and effect modifiers

The association between a particular exposure variable and a response variable can sometimes be altered after accounting or controlling for a third variable--- known as a confounding variable, which is associated with both the response and the exposure variable of interest. In general, a confounder cannot be an intermediate step in the causal path between the exposure and the outcome. A confounding factor may partially or wholly account for the apparent association between the explanatory variable and the outcome variable [227]. The distortion introduced by the confounder may lead to the over- or under-estimation of an effect, depending on the direction of the associations between the confounding factor and both the exposure and response variables. Failure to take account of confounding effects may lead to the conclusion that a relationship exists when in fact it does not, or there may be a failure to detect a relationship when one truly exists. For example, consider an association between family size and height, with children from larger families tending to be shorter than children from smaller families. It is known that social class is positively associated with height and negatively associated with family size. If the association between family size and height is different, depending on whether we ignore the proportion of individuals in each social class or control it by studying the association separately for each social class, then social class is an example of a confounding factor for the relationship between family size and height, as family size is unlikely to be a causal factor for social class.

The strength of the association between the exposure and the response variable (i.e. the value of the regression coefficient) may sometimes vary with the level of a third variable, known as an effect modifier. In the same example, if the estimated association between family size and height is significantly different from one social class to another, then social class is an example of an effect modifier. As another example, consider an association between size at birth and adult disease, where children with retarded fetal growth tend to have a higher risk of a disease. It is known that childhood growth may play a role as an effect modifier of the associations between small size at birth and risks of adult diseases [2-4;228]. In particular, it has been shown that the relationship between birthweight and high blood pressure appears to be modified by adult BMI [2].

The distinction between a confounder and an effect modifier in statistical terms is that a confounder is normally treated as a covariate in a model, while effect modification is assessed by modelling the interaction between the exposure and the modifier. For example, an effect modifier can be used to identify a subgroup with a lower (or higher) risk for a disease. Thus confounding is a bias that needs to be controlled for, whereas effect modification should be described and reported [227].

One way to remove the confounding effect and to evaluate and describe effect modification is splitting the third variable into subgroups or strata and obtaining a separate effect estimate of the exposure from each stratum. Strata are usually defined by levels of a confounder or a combination of confounders. When the association estimated from the crude analysis (without stratification) has a different magnitude (or even a different direction) from the estimated association within strata, suggesting the existence of a confounding effect, the single crude estimate of the effect should be replaced with a set of

effect estimates from all strata. The effect estimated within each stratum according to the confounding variable is not confounded. When the effect estimates differ across strata, suggesting the existence of an effect modifier, the findings should be presented separately for each of the strata.

When there is a large number of strata involved, the data will be dispersed too thinly over the strata and the estimate of an effect will be imprecise. Multiple regression models are commonly used for the adjustment of confounders when a stratified analysis becomes impractical. The coefficient for any explanatory variable is conditioned on the remaining explanatory variables in the model. Multiple regression models provide an efficient way to obtain precise estimates, while controlling for potential confounding factors. The magnitude of the confounding effect is assessed by comparing the effect estimates obtained from models before and after the adjustment of the potential confounder. The presence of a modifier can be assessed by testing the interaction term of the third variable and the exposure variable. In an epidemiological study involving many confounding variables, all the confounding factors can be controlled simultaneously in a single multiple regression model, and the adjusted effect of each factor can be estimated.

The potential confounding factors were examined throughout this study and the adjustment was made when necessary. In Chapters 4 and 5, the unadjusted relationship between each early life factor of interest and height (SDS) was first examined; the relationship was then adjusted by adding parental height, fetal and early life factors into the model to establish whether the relationship under investigation was in part related to influences of other factors.

It becomes more complicated when the confounding factor is also an intermediate variable. It occurs when an exposure in some way causes the change in the confounding variable [229]. For example, smokers may have higher blood pressure, which may in turn increase the risk of death. However, those with higher blood pressure may have increased motivation to quit smoking, which may in turn reduce the risk of death. Thus higher blood pressure may be a confounder for the effect of smoking, and also an intermediate variable on the causal pathway of smoking on mortality. Longitudinal data are needed to assess such relationships. Conventional methods, i.e. survival models with time-varying covariates [230] may be biased when this form of time-varying confounders exist. Statistical approaches that are suitable for time-varying confounders are discussed in §3.4.2.

This current study focuses on early influences on height. The exposure and confounding variables used were all measured at one age in early life. Therefore the issue of a confounding factor also being an intermediate variable does not arise in our analyses. However, it is an important issue in life-course study and is discussed briefly in §3.4.2.

3.3 Statistical models for data with a hierarchical structure

Statistical approaches described in §3.2 require the assumption of an independent sample, where observations are not related to one another. As mentioned in Chapter 1, testing life-course hypotheses requires information collected over time or even across generations. For example, repeated measures are needed to assess a longitudinal relationship. Samples can sometimes be naturally clustered due to the study design. For example, a cross-generational

comparison may involve two generations that are likely to be correlated within families. Statistical models that take into account the covariance structure of these samples are important.

In the following sections, methods for hierarchical data are described. They are divided into two parts: §3.3.1 describes approaches that can be applied for repeated measurements, including simple models for two measurement occasions and more complicated models for multiple occasions, and §3.3.2 describes models for data that are grouped by nature and correlated within each group. For example, cohort members and offspring from the same family, or offspring from the same family are naturally clustered. Approaches concerning causal and pathway relationships or time dependent exposures are included in §3.4, although they are not used in subsequent analyses.

3.3.1 Models for repeated height measurements

There are two types of approach for analysing longitudinal data. *First*, earlier measurements are treated as covariates rather than responses. This approach is more appropriate when there are only a small number of discrete occasions (i.e. two occasions). *Second*, all measurements are treated as response variables and models that take into account the covariance structure are required. In the latter approach, the repeatedly measured response variables are commonly converted to standard deviation scores (SDS) so that they can be compared directly.

Models for measurements on two-occasions

Although our analyses of longitudinal data involve responses measured on more than two occasions (i.e. height at ages 7, 11, 16, and 33 years), we start from the simplest case of two measurements of the response variable.

Assume x_i and y_i are the response variable measured for the ith individual on the first and second occasions, e.g., childhood height and adult height (SDS). A linear relationship between the two measurements can be written as

$$y_i = \alpha + \beta\, x_i + \varepsilon_i . \qquad (3.1)$$

Algebraically, (3.1) is equivalent to a model for the change adjusted for the first measurement:

$$y_i - x_i = \alpha + (\beta - 1)x_i + \varepsilon_i . \qquad (3.2)$$

In regression model (3.1), βrepresents the linear relationship between childhood height and adult height, while in model (3.2) β-1 represents the linear relationship between childhood height and change in height from childhood to adulthood (i.e. change in relative position in the sample if measures are SDS). Examination of the association between the change in a variable and its initial value in a longitudinal study is complicated by the presence of measurement errors and variability within subjects [231;232]. These two factors contribute to the statistical phenomenon known as *regression towards the mean* (RTM). Because of the presence of such variation, subjects who were short (or tall) in childhood tend to be closer

to the sample mean in adulthood than they were in childhood. In the situations where RTM is present, the observed correlation is expected to consist partly of true correlation and partly of RTM effect [231;232]. Regression towards the mean occurs unless there is a perfect correlation ($r = 1$). The weaker the correlation between the two measurements is, the bigger the effect will be.

The RTM effect can be reduced by using alternative measures as the initial value, for example, using the average of two height measures in childhood (i.e. height SDS at ages 7 and 11 years) as initial values. For the special case where $\beta = 1$, (3.2) can be written as

$$y_i - x_i = \alpha + \varepsilon_i, \qquad (3.3)$$

which models the simple change without the adjustment of initial value; i.e. ignoring the RTM effect. These models may include further covariates (i.e. early life factors) to investigate the early influences on growth.

In the current study, all height measures on cohort members are considered as response variables (Chapter 4). The inter-correlations between measurements are accounted for by using more complicated models, which are described in this section.

Studying the associations between early life factors and growth trajectory in the 1958 cohort is one of the main objectives of the study. The main statistical approaches for growth data include growth models (treating age as a continuous variable) and multivariate response models (treating age as fixed discrete occasions).

Growth model

Growth models are often used when there are a sufficient number of observations for each individual. Data are considered as a two-level hierarchy in growth models, where measurement occasions (level-1 units) are clustered within individuals (level-2 units). The variation of a measurement can be separated into two components: within-individual variation and between-individual variation.

Growth modelling incorporates random effects, as well as conventional fixed regression coefficients. Assume that Y is a response variable (i.e. height), X is a level-2 explanatory variable, (y_{it}, x_i) are observations taken from the ith individual at the tth occasion, and z_{it} is the age of the ith individual at the tth occasion, a growth model can be written as

$$y_{it} = \beta_{0i} + \beta_1 z_{it} + \alpha\, x_i + \nu\, z_{it} x_i + \varepsilon_{it} \quad t=1,2,\ldots, n_i \text{ and } i=1,2,\ldots, n \qquad (3.4)$$

$$\beta_{0i} = \beta_0 + \mu_{0i}$$

where n_i is the number of height measures for the ith individual. Model (3.4) assumes that height (Y) is linearly related to age (Z) with each individual having their own intercept (random intercept with $E(\beta_{0i}) = \beta_0$ and $Var(\beta_{0i}) = \sigma_0^2$) but a common slope β_1. It also assumes that $E(\varepsilon_{it}) = 0$, $Var(\varepsilon_{it}) = \sigma_e^2$, $cov(\varepsilon_{it}, \varepsilon_{it'}) = 0$, and $cov(\varepsilon_{it}, \mu_{0i}) = 0$ (t and t' are two separate occasions). Random terms μ_{0i} and ε_{it} are both Normally distributed with mean 0 and variance σ_0^2 and σ_e^2, respectively.

The variable X can be a level-2 covariate (constant over occasions, such as gender or birthweight) or a level-1 covariate (measured on each occasion). A non-zero coefficient (ν) for the interaction term of X and age (Z) indicates that the effect of X on the response variable changes linearly with age.

Repeated observations y_{it} and $y_{it'}$ from the same individual (at occasions t and t') are usually positively correlated and observations from distinct individuals are assumed to be independent. Model (3.4) can be extended to include further explanatory variables measured at either level, or extend the linear function of age to include higher order terms to describe the relationship between age and height [222]. The common slope β_1 can also be assumed to be random, so that each individual has its own growth trajectory.

Model (3.4) requires the estimation of fixed parameters (β_0, β_1, α, and ν) and random parameters (σ_0^2 and σ_e^2). The iterative generalized least squares procedure (IGLS) is used in this study to estimate the fixed and random parameters (incorporated in MLwiN) [222]. When the errors are Normally distributed, the procedure is equivalent to maximum likelihood estimation (MLE).

A key feature of a growth model is that the response variable is measured on the same scale at every occasion of interest, or otherwise making inferences on quantitative change or growth is meaningless. Growth models have flexibility for varied timing and spacing of time points. They do not require balanced data to obtain efficient estimates for the parameters if we can assume that data are missing at random (MAR) with regard to

variables in the model. The issue of missing patterns of response variables is discussed later in this section.

In this current study, height measurements on cohort members are widely spaced, with four measures for each person throughout childhood to adulthood. Moreover, the age when final adult height was achieved is unknown. Thus a growth model may not be a practical approach for such data. Therefore, a model that can be applied to repeated measures with large time intervals is needed for the study of the growth trajectory of the 1958 cohort.

Multivariate response model

In life-course analyses, some health outcomes are naturally multi-dimensional with more than one response variable of interest. For example, systolic and diastolic blood pressures, or leg and trunk lengths. The degree of the correlation between these response variables may itself be important.

Repeated measures with a small number of measurements can also be considered as multi-dimensional outcomes, for example height or BMI measured on several occasions. A simple approach to data with multiple response variables is to carry out a univariate analysis for each response, and ignore the fact that measures made on the same individual are likely to be correlated (i.e. linear regression models described in §3.2). However, such an approach can only establish the association between the exposure and each response variable separately. Results (i.e. the strength of the association) cannot be compared directly across models.

A *multivariate response model* models several response variables simultaneously [139]. Let y_{ij} be the jth response for ith individual (i=1,2,...n and j=1,2,...p), then the p response variables can be modelled simultaneously as a function of explanatory variables. A simple multivariate response model with one common explanatory variable X may be formulated as

$$y_{ij} = \sum_{l=1}^{p} (\beta_{0il} + \beta_l x_i) d_{lij} \qquad (3.5)$$

$$\beta_{0ij} = \mu_{0j} + \varepsilon_{ij},$$

where dummy variables d indicate which response variable is present: d_{lij} =1 if l=j (ith individual has a measurement on jth response) or d_{lij} =0 otherwise.

The fixed parameters μ_{0j} and β_j (j=1, 2, ..., p) represent the intercept and the regression coefficient for the covariate with respect to the jth response variable.

The random effect ε_{ij} is the residual of observed data around the mean of the jth response, which follows a multivariate Normal distribution, with E(ε_{ij})=0, Var (ε_{ij})= σ_j^2, and Cov (ε_{ij}, $\varepsilon_{ij'}$)= $\sigma_{jj'}$ (i=1, 2, ..., n and j, j' =1, 2, ..., p). Therefore the correlation coefficient between the jth and j'th responses is $\rho_{jj'}=\sigma_{jj'}/(\sigma_j \times \sigma_{j'})$. The covariance matrix is assumed to be constant across the whole sample (for all i). However, a multivariate response model also allows us to explore non-constant covariance matrices, which can be specified in the model.

Hypotheses concerning the equality of subsets of parameters can be tested by constructing the appropriate contrasts or linear functions of the parameters. For example, the null hypothesis of similar effects of a level-2 factor on four response variables (p=4) can be expressed as H_0: $\mathbf{H}^T\boldsymbol{\beta} = \mathbf{0}$, where $\boldsymbol{\beta} = (\beta_1, \beta_2, \beta_3, \beta_4)^T$ and the corresponding contrast for testing H_0 is

$$\mathbf{H}=\begin{bmatrix} 1 & 0 & 0 \\ -1 & 1 & 0 \\ 0 & -1 & 1 \\ 0 & 0 & -1 \end{bmatrix}.$$

The null hypothesis H_0 is equivalent to testing $\beta_1 = \beta_2$, $\beta_2 = \beta_3$, and $\beta_3 = \beta_4$, simultaneously (or jointly).

Like a growth model, a multivariate response model can been considered as a multilevel model, where measurements (level-1) are nested within individuals (level-2). There is no level-1 variation specified in (3.5), as level-1 is used only to define the multivariate structure. However there is level-2 variation in the residual ε_{ij} (between individuals). Model (3.5) can be extended to include further covariates at either level-1 or level-2.

In Chapters 4 and 6, multivariate response models are applied to examine the influences of early life factors on the height of cohort members (G2) at different ages, from childhood to adulthood. The four response variables are height SDS at ages 7, 11, 16, 33 years, internally standardised (§2.4.2) and are assumed to follow a multivariate Normal distribution $N(\boldsymbol{\mu}, \boldsymbol{\Sigma})$, where $\boldsymbol{\mu} = (0,0,0,0)^T$ and

$$\Sigma = \begin{bmatrix} 1 & \sigma_{7,11} & \sigma_{7,16} & \sigma_{7,33} \\ \sigma_{7,11} & 1 & \sigma_{11,16} & \sigma_{11,33} \\ \sigma_{7,16} & \sigma_{11,16} & 1 & \sigma_{16,33} \\ \sigma_{7,33} & \sigma_{11,33} & \sigma_{16,33} & 1 \end{bmatrix}.$$

Assuming that individuals are the level-2 (i) units and the within-individual measurements are the level-1 (j) units, equation (3.5) with height measured at four occasions and one explanatory variable, X (e.g. individual level variable birthweight) can be expressed as:

$$y_{ij} = (\beta_{0i1} + \beta_1 x_i)d_{1ij} + (\beta_{0i2} + \beta_2 x_i)d_{2ij} + (\beta_{0i3} + \beta_3 x_i)d_{3ij} + (\beta_{0i4} + \beta_4 x_i)d_{4ij} \quad (3.6)$$

$$\beta_{0ij} = \mu_{0j} + \varepsilon_{ij}, \quad i=1, 2, \ldots, n \text{ and } j=1, 2, 3, 4.$$

The fixed parameters μ_{0j} and β_j (j=1, 2, 3, 4) represent the intercept and the regression coefficient of the relationship between birthweight and the jth height measure. Since the response variables are on the same scale, differences in the effect of birthweight on height at all ages can be tested using a joint contrast test. If the null hypothesis of similar effects of birthweight on height at all four ages (β_j=constant) is rejected, then a further test of the difference between every two successive ages (e.g. height at 7 and 11) may be used to assess the height gain (or growth rate) over two occasions.

Model (3.6) assumes that the variance at each age is 1 (between-individual variance). The covariance between height SDS measured at any two ages is Cov ($\varepsilon_{ij}, \varepsilon_{ij'}$) = $\sigma_{jj'}$, which is the same as the correlation coefficient between height SDS at two ages j and j'. Additional

covariates, measured at the individual level (level-2) or occasion level (level-1), can be easily incorporated into (3.6).

Like growth models, multivariate response models do not require complete data on response variables. The individual is included in the analysis even if height is missing on one or more occasions. Thus the number of observations per individual may vary. The estimated parameters are unbiased when data are missing at random (MAR) [139], in which case the association between individuals with missing responses is on average similar to that observed for individuals with complete responses.

Multivariate response models can also be applied when response variables have different distributions, or when they are a combination of continuous and discrete variables. For example, we can examine three response variables, age of menarche (early, intermediate, late), height and weight (continuous) and their relationships with other covariates simultaneously, taking into account the inter-relationship between the response variables. Further extensions can be made when response variables are also measured repeatedly, e.g., height and weight are repeatedly measured.

Although the linear age trend of an effect can be tested directly using a growth model, a multivariate response model provides more detailed information on the change of an effect over time. For example, when there are three time points involved, non-existence of a linear trend shown in a growth model could actually be an increasing trend between the first two occasions and a decreasing trend between the last two occasions and this can be detected by a multivariate model.

For a growth model where β is the slope of the linear trend of an effect (the change in the effect for an increase of one year in age), the null hypothesis for testing a linear trend is H_0: $\beta=0$ versus the alternative hypothesis H_a: $\beta \neq 0$. In a multivariate response model, where there are three response variables (height SDS at age 7, 11, and 16 years), the slope between the first two measures is $\beta_1= (\beta_{11} -\beta_7) /4$, where β_7 and β_{11} are the effect of an early life factor on height at age 7 and 11 years, the slope between the next two measures is $\beta_2= (\beta_{16} -\beta_{11}) /5$, where β_{16} is the effect at age 16 years. Testing for a linear trend requires first testing for H_0: $\beta_1 = \beta_2 = 0$ versus H_a: $\beta_1 \neq 0$ or $\beta_2 \neq 0$. If we fail to reject H_0, then we can conclude that there is no significant linear trend. However, if H_0 is rejected, we need to further test for (1) H_0: $\beta_1 = 0$ versus H_a: $\beta_1 \neq 0$ (equivalent to $\beta_7 =\beta_{11}$) and (2) $\beta_2 = 0$ (equivalent to $\beta_{11} =\beta_{16}$) versus H_a: $\beta_2 \neq 0$. If results show that $\beta_1 > 0$ and $\beta_2 > 0$ are both true, then we can conclude that there is a significant positive linear trend. If results show that $\beta_1 < 0$ and $\beta_2 < 0$ are both true, then we can conclude that there is a significant negative linear trend. If results show that one slope is positive, and the other one is negative, or at least one is not significantly different from zero, then the tests are inconclusive.

For example, in the 1958 cohort, consider a test for the linear trend of an early life effect on growth trajectory, it is equivalent to testing for H_0: the effect is 0 at all occasions, or in other words, the effect of the early life factor on every two successive occasions are the same and are all zero (i.e. $(\beta_{11} -\beta_7)/4 = (\beta_{16}-\beta_{11})/5 =0$). The contrast for testing the null hypothesis can be written as

$$\begin{bmatrix} 1 & 0 & 5 \\ -1 & 1 & -9 \\ 0 & -1 & 4 \end{bmatrix}.$$

If the null hypothesis is rejected, the contrasts for further tests can be written as

$$\begin{bmatrix} 1 \\ -1 \\ 0 \end{bmatrix} \text{ and } \begin{bmatrix} 0 \\ 1 \\ -1 \end{bmatrix}.$$

Strictly speaking, the height of each cohort member was not measured at exactly the same time. As mentioned in §2.4.2, the relationships between several key variables and height were similar when using growth models with fixed ages of 7, 11, and 16 years and exact ages at measurement (data not presented). A multivariate response model, which requires age to be a fixed occasion, is therefore reasonable.

Multivariate response models (3.6) are applied to explore the influence of each early life factor (Chapter 4) or social class (Chapter 6) on height at different life stages simultaneously. These associations are further adjusted for potential confounding factors. In these analyses, the response variables are the internally derived height standard deviation scores (SDS) at ages 7, 11, 16 and 33 years (§2.4.2). Particularly, in Chapter 6, differences in height (SDS) among all social classes and between extreme groups at all ages, and social class differences in height at successive occasions (i.e. between 7 and 11 years; 11 and 16 years, and 16 and 33 years etc) are tested using contrast tests.

Limitations for the multivariate response models applied in this study include (1) it is not practical when the number of repeated measures is large and (2) the length of time between two measurements is not accounted for. Thus inferences made from the model are related to the relationship at particular ages, no inference can be made between any two occasions.

Missing at random

As described in §2.5.3, the achieved sample of the 1958 cohort reduced from 17,415 subjects at birth to 11,407 subjects at age 33. In particular, not all cohort members had their height measured at all four occasions (7, 11, 16, and 33 years). Out of 16835 cohort members who had at least one height measure, 7430 (44.1%) individuals were measured at four occasions. Among those with incomplete measures, 1512 (9.0%), 2842 (16.9%), and 5051 (30.0%) had one, two, or three measurements, respectively. The loss of response at each sweep may introduce selection bias.

Although statistical models for repeated measures used in subsequent analyses do not require complete data for the response variables, they however require the assumption that the response variables are missing at random (MAR), that is, the probability of missing response does not depend on the unobserved response, in order to obtain unbiased estimates [139].

For data with a multivariate Normal distribution, Dixon (1983) proposed a multiple *t*-tests approach to multivariate data (i.e. *p* variables) [233]. For each response variable with missing values, the sample is split into two groups, which contain cases with that variable observed and cases with that variable missing, respectively. The means of the observed values of the other variables in the two groups are then compared by two sample *t*-tests, with non-

significant differences in the two means indicating that missing is completely at random (MCAR), that is, the probability of a missing response depends on neither the observed nor the unobserved response [233;234]. This procedure yields up to (p-1) t-tests for each variable.

Dixon's multiple t-tests are applied here to test for the assumption that response variables (height at four ages) are MCAR. Table 3.2 provides differences in mean height SDS between non-missing and missing groups defined for each height measure and p-values for the t-tests. Results show that children with missing height measures were consistently shorter at all ages and some differences are significant at levels between 0.01 and 0.03.

Table 3.2 Comparing mean height by missing pattern at each age: difference (p-value)

	7 years		**11 years**		**16 years**		**33 years**	
	d	*p*	d	*p*	d	*p*	d	*p*
Missing/non-missing at 7			-0.041	0.19	-0.011	0.72	-0.005	0.87
Missing/non-missing at 11	-0.027	0.42			-0.074	0.02	-0.051	0.09
Missing/non-missing at 16	-0.051	0.02	-0.049	0.03			-0.021	0.35
Missing/non-missing at 33	-0.103	0.03	-0.109	0.03	-0.132	0.01		

We further examine whether the missing patterns have an impact on the relationships between some early life factors (i.e. social class) and height at each age. We adopted a pattern-mixture model proposed by Park and Lee (1997) [235] and applied it to the multivariate response models.

We first fit a multivariate response model including only an explanatory variable of interest. The relationship between the explanatory variable and the response variable sometimes may be affected by the missing patterns; since the pattern of missing data can be related to the explanatory variable.

Assume that there are p response variables. Let y_{ij} be the jth response for the ith individual (i=1,2,...n and j=1,2,...p), l be the index for the p measurements, K be the number of distinct missing patterns, and S_k be a set of observations with missing data pattern k (k=1, 2, 3, ..., K). To take account of the missing data mechanism, we consider the following extended model with one common explanatory variable x (i.e. social class)

$$y_{ij} = \sum_{l=1}^{p} (\sum_{k=1}^{K} I_{ik}\alpha_{lk} + \beta_{0il} + \beta_l x_i) d_{lij} \qquad (3.7)$$

$$\beta_{0ij} = \mu_{0j} + \varepsilon_{ij},$$

where dummy variables d indicate which response variable is present: d_{lij} =1 if l=j (ith individual has a measurement on jth response) or d_{lij} =0 otherwise. I s are also dummy variables with I_{ik}=1 if the ith subject is in S_k and I_{ik}=0 otherwise. If the effect estimated from (3.7) differs from the one estimated from the model without the indicator for missing patterns, we might conclude that the relationship is affected by the missing patterns.

We first define an indicator variable for each missing data pattern. For four height measures there are a total of 14 distinct types of missing pattern. Denoting "A" as a response that is available and "M" as a missing response, Table 3.3 illustrates all the possible missing patterns. To classify the 14 missing patterns, we define 14 indicator variables for the ith

cohort member with kth missing pattern as: I_{ik}=1 or I_{ik}=0 otherwise (i=1, 2, ..., n and k=1, 2, ..., K).

Because of the large number of missing patterns with four response variables, we first consider a simple model including only the intercept and 14 indicators to the data, assuming the assumption of equal covariance between height measures at any two ages. Based on the equalities of parameter estimators for the 14 indicators, the 14 missing patterns are combined into three broader groups, also shown in Table 3.3.

Table 3.3 Missing data patterns

Missing patterns*	N (%)	Occasion				N (%)
		7y	11y	16y	33y	
Group 1	6741 (40.04)	M	A	A	A	1086 (6.45)
		A	M	A	A	1185 (7.04)
		A	A	M	A	2344 (13.92)
		A	M	M	A	886 (5.26)
		A	A	M	M	607 (3.61)
		A	M	M	M	633 (3.76)
Group 2	1093 (6.49)	M	M	A	A	662 (3.93)
		A	M	A	M	112 (0.67)
		M	M	A	M	109 (0.65)
		M	A	M	M	210 (1.25)
Group 3	1571 (9.33)	A	A	A	M	436 (2.59)
		M	A	M	A	467 (2.77)
		M	A	A	M	108 (0.64)
		M	M	M	A	560 (3.33)
Total missing†						9405 (55.87)
All cohort members‡						16835 (100)

A=available M=missing
* Group 1-Group 3 are defined based on parameter estimators for 14 missing patterns
† any individuals with at least one height missing
‡ individuals with at least one height measure (included in the analysis)

We fit the multivariate response models to the data with unstructured correlations, first including only social class variable (without indicators for missing patterns). Next we use Model (3.7) including the social class and also indicators for three broader groups of missing patterns (k=3). As shown in Table 3.4, both models show a strong influence of social class on height of cohort members at all ages. Moreover, the differences in the estimates for the social class effect on height at all ages between the two models are small. Therefore, there is no evidence that the missing patterns have affected the relationship between social class and height at any ages.

Table 3.4 Summary of models 1&2: estimates and their standard errors for social class at age 7

		Model 1 †			Model 2 ‡			
	Response at	β*	s.e	p-value	β' *	s.e	p-value	β-β'
Non-manual	7y	0.330	0.018	<0.001	0.324	0.018	<0.001	0.006
Non-manual	11y	0.313	0.018	<0.001	0.306	0.018	<0.001	0.009
Non-manual	16y	0.315	0.018	<0.001	0.308	0.018	<0.001	0.007
Non-manual	33y	0.278	0.018	<0.001	0.271	0.018	<0.001	0.007

† Model 1 includes social class only (unadjusted)
‡ Model 2 includes social class and indicators for three groups of missing patterns (adjusted)
* Baseline is manual social class

Although results from Dixon's tests show some evidence against the assumption of MCAR in our data, the significance levels are not conservative enough for a sample of this size and the large number of tests. Furthermore, the pattern-mixture model does not show a strong effect of the missing patterns on relationships between early life factors (i.e. social class) and height at all ages. Therefore there is no reason to suspect that missing patterns are not at random. Estimates are unlikely to be biased for the unbalanced data using multivariate response modelling to establish early influences on growth trajectory in Chapters 4 and 6.

3.3.2 Models for clustered data

In life-course studies, data are sometimes clustered within groups. For example, offspring of the 1958 cohort (G3) are naturally clustered within families.

Consider the sample has a 2 level hierarchical structure, where the offspring (G3) are "level 1 (*i*)" units and "level 2" (*j*) units are the families (i.e. cohort members). Let y_{ij} be the height SDS of the *i*th child from family *j*. A simple two level model for the offspring (G3) with one level-1 explanatory variable X can be formulated as

$$y_{ij} = \beta_0 + \beta_1 x_{ij} + \mu_j + \varepsilon_{ij}. \qquad (3.8)$$

There are two fixed parameters: β_0 is the intercept and β_1 is the regression coefficient for the explanatory variable. There are two random parameters: μ_j is the family-specific part of the intercept, which indicates the unexplained difference between families controlling for the effect of the explanatory variable, and ε_{ij} is the random error of the *i*th child in the *j*th family, which indicates the unexplained variation among individuals within a family. Model (3.8) assumes that random terms (μ_j and ε_{ij}) are independently Normally distributed with mean 0 and variance σ_u^2 and σ_e^2, respectively. It also assumes that $\text{Cov}(\mu_j, \varepsilon_{ij}) = 0$. Model (3.8) requires the estimation of fixed parameters β_0 and β_1, and random parameters σ_u^2 and σ_e^2. The variance of the response y_{ij}, given the fixed parameters and the predictor, is

$$\text{Var}(y_{ij} \mid \beta_0, \beta_1, x_{ij}) = \text{Var}(\mu_j + \varepsilon_{ij}) = \sigma_u^2 + \sigma_e^2,$$

which is the sum of the level-1 variance and the level-2 variance. Model (3.8) implies that the total variance for height SDS of each child is constant and that the covariance between two children in the same family is σ_u^2. The conditional covariance between response measurements of two children in the same family is given by

$$\text{Cov}\,(\mu_j + \varepsilon_{ij},\ \mu_j + \varepsilon_{i'j}) = \text{Cov}\,(\mu_j, \mu_j) = \sigma_u^2.$$

Therefore the correlation coefficient of height SDS between two children within a family is

$$\rho = \frac{\sigma_\mu^2}{\sigma_\mu^2 + \sigma_e^2}.$$

This correlation (ρ) measures the proportion of total variance that is between children in the same family. Model (3.8) can be extended to include further covariates measured at both levels to examine the relationship between X and Y adjusting for other characteristics.

Response variable y_{ij} is expressed as the sum of a fixed part $(\beta_0+\beta_1 x_{ij})$ and a random part $(\mu_j + \varepsilon_{ij})$. Unlike the standard linear regression model, or analysis of variance (ANOVA) [236], the multilevel model includes more than one residual term. Thus iterative Generalized Least Squares (IGLS) is applied to estimate fixed and random parameters [139].

In Chapter 6, height gain of the offspring with respect to their parents in relation to social class of origin is assessed using a two-level model (3.8), where X is the social class of origin and age of the child is an additional covariate.

3.3.3 Models for comparing height across two generations

Consider the two generations of the 1958 cohort (G2 and G3), where individuals are clustered within the family (i.e. one parent and several offspring). *Firstly*, heights of parent and offspring from the same family are correlated, with a correlation coefficient of 0.43. *Secondly* heights of offspring within the same family are correlated, with a correlation coefficient of 0.39. We define family members (G2 or G3) as level-1 units, and families as level-2 units. Within level 1, indexed by i, the parent (G2) is i=1 and the offspring (G3) are i=2, 3, …, n_j for n_j -1 children. Therefore, level-1 units are clustered within level-2.

Assume that the response variable follows a Normal distribution. Let y_{ij} be the response of individual i in family j (i=1, 2, …, n_j and j=1, 2, …, m), then the response variable can be modelled as a function of an explanatory variable (at either level). A single two-level model with one level-1 explanatory variable X can be formulated as

$$y_{ij} = (\beta_{0j} + \beta_1 x_{ij})d_{2ij} + (\gamma_{0ij} + \gamma_1 x_{ij})d_{3ij} \qquad (3.9)$$

$$\beta_{0j} = \beta_0 + \mu_{2j}$$

$$\gamma_{0ij} = \gamma_0 + \mu_{3j} + \varepsilon_{ij},$$

where d_{2ij} =1 if i=1 (subject is G2) or d_{2ij} =0 otherwise and d_{3ij} =1 if i>1 (subject is G3) or d_{3ij} =0 otherwise (i.e. $d_{2ij} + d_{3ij}$ =1).

The fixed parameters β_0 and γ_0 represent the mean intercepts, and β_1 and γ_1 represent the regression coefficients for the explanatory variable, for cohort members and their offspring respectively.

The parameters μ_{2j} and μ_{3j} are random effects (between-families) for G2 and G3 with mean E(μ_{2j}) = 0 and E(μ_{3j}) = 0, respectively. The parameter ε_{ij} is the level-1 residual for the offspring with ε_{ij}~N(0, σ_e^2).

Model (3.9) assumes that there is no level-1 variance (variance between subjects within a family) specified for G2 as there is only one cohort member in a family. The level-2 variation is the between family variance

Var (μ_{2j}) = σ_2^2.

For the offspring (G3), the level-1 variance (within-family variance) and the level-2 variance (between-family variance) are Var (e_{ij}) = σ_e^2 and Var (μ_{3j}) = σ_3^2 respectively. Thus the total offspring variance is $\sigma_e^2 + \sigma_3^2$. Assuming that the covariance between cohort members and their offspring is Cov (μ_{2j}, μ_{3j}) = σ_{23} and also Cov ($\mu_{3j}, \varepsilon_{ij}$) = 0, the correlation between cohort members and their offspring is therefore

$$\rho_{23} = \frac{\sigma_{23}}{(\sigma_2^2(\sigma_3^2 + \sigma_e^2))^{1/2}}$$

and the correlation between children (G3) from the same family is

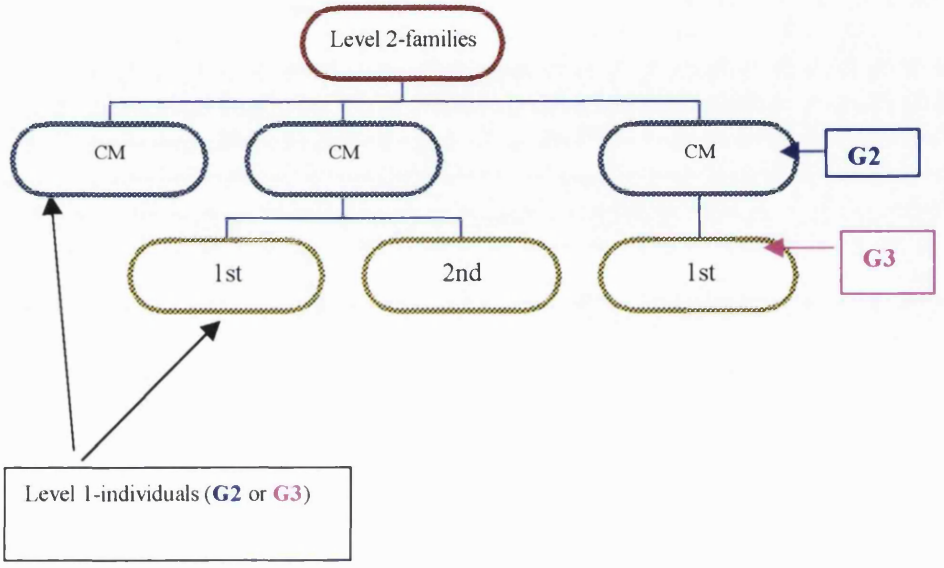
$$\rho_{33} = \frac{\sigma_3^2}{\sigma_3^2 + \sigma_e^2}.$$

Suppose there are m and k individuals in G2 and G3, respectively ($k = \sum_{j=1}^{m} n_j - m$). The response variables for G2 and G3 are donated by column vectors $\mathbf{y}_2 = (y_{21},..., y_{2m})^T$ and $\mathbf{y}_3 = (y_{31},..., y_{3k})^T$. The sets of covariates or explanatory variables are arranged as $m \times p$ and $k \times p$ matrices $\mathbf{X}_2$ and $\mathbf{X}_3$. The sets of parameters are vectors of dimension p, denoted by $\boldsymbol{\beta}_2 = (\beta_{21},..., \beta_{2p})$ and $\boldsymbol{\beta}_3 = (\beta_{31},..., \beta_{3p})$. Model (3.9) can also be expressed in the form

$$\begin{pmatrix} \mathbf{y}_2 \\ \mathbf{y}_3 \end{pmatrix} = \begin{pmatrix} \mathbf{X}_2 & \vec{\mathbf{0}} \\ \vec{\mathbf{0}} & \mathbf{X}_3 \end{pmatrix} \begin{pmatrix} \boldsymbol{\beta}_2 \\ \boldsymbol{\beta}_3 \end{pmatrix} + \begin{pmatrix} \boldsymbol{\mu}_2 \\ \boldsymbol{\mu}_3 + \mathbf{e} \end{pmatrix}.$$

Figure 3.1 illustrates an example of two generations from three families; "Family 1" has a cohort member but no children, either he/she had no children by age 33 years or they were not selected for the offspring sample, "Family 2" includes a cohort member and two children, and "Family 3" includes a cohort member and one child.

Figure 3.1 An example of two generations from three families



If we re-organize the individuals so that those from the same family are adjacent, the covariance matrix **V** of the response variable for the six individuals from three families given in Figure 3.1 can be written as

$$\mathbf{V} = \begin{pmatrix} \sigma_2^2 & & & & & \\ & \sigma_2^2 & \sigma_{23} & \sigma_{23} & & \\ & \sigma_{23} & \sigma_3^2 + \sigma_e^2 & \sigma_3^2 & & \\ & \sigma_{23} & \sigma_3^2 & \sigma_3^2 + \sigma_e^2 & & \\ & & & & \sigma_2^2 & \sigma_{23} \\ & & & & \sigma_{23} & \sigma_3^2 + \sigma_e^2 \end{pmatrix}$$

The "block diagonal" structure reflects the fact that the covariance between individuals in different families is zero. It can be extended to any number of families.

The generalized least square estimation (GLS) for the fixed parameters is

$$\hat{\boldsymbol{\beta}} = (\mathbf{X}^{\mathrm{T}}\mathbf{V}^{-1}\mathbf{X})^{-1}\mathbf{X}^{\mathrm{T}}\mathbf{V}^{-1}\mathbf{Y},$$

where $\mathbf{V}$ is the "block diagonal" covariance matrix for height as defined above for all families.

When subjects in the sample are independent of each other, the matrix $\mathbf{V}$ then becomes the identity matrix (I), and $\hat{\boldsymbol{\beta}}$ is the OLS estimator: $\hat{\boldsymbol{\beta}} = (\mathbf{X}^{\mathrm{T}}\mathbf{X})^{-1}\mathbf{X}^{\mathrm{T}}\mathbf{Y}$.

The OLS estimator can be calculated directly. But for the GLS estimator where subjects are not independent, the matrix V is dependent on random parameters (σ_2^2, σ_3^2, σ_{23}, and σ_e^2). The estimation procedure for both fixed and random parameters has to be iterative (IGLS).

Model (3.9) not only takes into account the correlation between offspring, but also between children and parents (cohort members). Because cohort members and offspring are in the same model as well as at the same level, the fixed parameters can be compared across the two generations and the statistical significance of the differences in the effects of early life factors on height can be tested using contrast tests.

In Chapters 5 and 6, we make comparison of early life influences on childhood height in two generations (G2 and G3). In both analyses, external height standard deviation scores (SDS) for G3 and G2 based on the 1990 British growth reference are used [201]. Social class

gradients in height are assessed by testing the linear trend of the effect of social class, which is treated as a continuous variable.

To illustrate, Table 3.5 displays regression coefficients (s.e.) for the univariate associations between each of two covariates: birthweight and maternal age and height SDS of G2 and G3. Results in Table 3.5 are estimated from (1) separate linear regression models for both generations (ignoring the correlation structure completely), (2) linear regression models for G2 and a two-level model for G3 (ignoring the correlation between G2 and G3), and (3) a single model (3.9) for both generations.

As shown in Table 3.5, the estimated effects of birthweight and maternal age on height of G3 is largely reduced once the correlation between G2 and G3 is accounted for. Table 3.5 also suggests that the estimated effects of both factors are only slightly over-estimated in G2 by using separate models. This is because about 20% of families had children. Although the estimated effects change little in G2 by including the offspring in the model, differences in estimated effects in G3 are pronounced. This is due to the fact that most offspring had their parent (i.e. cohort members) in the study sample. Therefore including both generations in the same model has a greater effect on results for G3 than for G2.

Table 3.5 Regression coefficient β(se) of height on birthweight and maternal age using a single model and separate models for G2 and G3

Covariate	Separate models†		Separate models‡		Model (3.9)	
	G2	G3	G2	G3	G2	G3
Birthweight (kg)	0.53(0.02)	0.39(0.04)	0.53(0.02)	0.37(0.04)	0.51(0.02)	0.32(0.04)
Maternal age (year)	0.009(0.002)	0.018(0.007)	0.009(0.002)	0.013(0.006)	0.008(0.002)	0.004(0.006)

† linear regression models for G2 and G3, separately

‡ a linear regression model for G2 and a multilevel model for G3

This example indicates the importance of choosing an appropriate model which takes account of the underlying covariance structure. Therefore, in Chapter 5, model (3.9) is applied to compare early life influences on childhood height in two generations (G2 and G3). Additional covariates are added to the model to make adjustment for first parental height, then fetal and infant factors, and finally early environmental factors. Model (3.9) is also used in Chapter 6 to compare the social inequalities in height in two generations.

Most models discussed in §3.2 and §3.3 have been applied to the analyses in subsequent chapters. Statistical methods described below (also listed in Table 3.1) have not been applied here, but are useful in life-course analyses.

3.4 Causal modelling in path analyses

Examining the relationship between two variables sometimes requires assumptions about which is the "*cause*" and which is the "*effect*". Variable X is a cause of variable Y when a change in X leads to a change in Y. The "cause" must happen before the "effect". For example, consider the relationship between maternal smoking and birthweight, we might assume that maternal smoking is the "cause" and birthweight is the "effect", because maternal smoking might influence birthweight, but not the other way around.

There are two types of effect in causal relationships: a *direct effect* occurs when a variable has an effect on another variable without a third variable intervening between them, and an *indirect effect* occurs when a third variable (intermediate variable) intervenes in the relationship. Thus *intermediate* variables serve as responses to some variables, which in turn are explanatory variables to the others:

Exposure → Intermediate Variable→ Response.

For example, birthweight is a response to maternal smoking during pregnancy, but it is also an explanatory variable for height.

A collection of variables may be viewed as a *system* in which a directional assumption for each pair of variables is made. The response variables may affect each other and be affected by the explanatory variables.

Ordinary regression models or generalized linear models have been used in a life-course study for the relationships between one dependent variable and several explanatory variables from different stage of the life-course [216;217;237]. Variables are grouped within a conceptual framework according to the stage of the life-course [238]. These conventional methods can estimate the relative impact of variables within a causal structure by adding exposures from different life stages, separately, into the model. However, these methods have their limitations when the path structure is complicated or there are a number of dependent variables in a system of interest, as they do not provide estimates of the correlation structure between variables.

Causal modelling is usually used in path analysis. It involves estimating of the parameters in a system of simultaneous equations relating dependent and explanatory variables. Causal modelling not only examines the relationship between explanatory and response variables, but also the correlation structure between variables in the system.

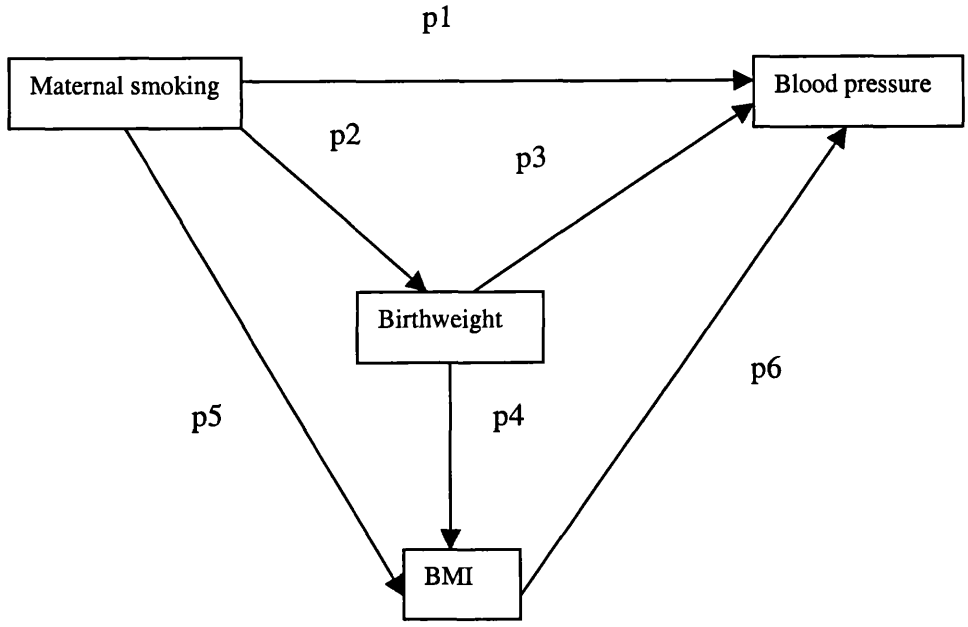
Path diagrams give the explicit causal connections between variables and play an important role in path analysis. They are frequently used to describe the causal relationships and are particularly useful for testing life-course hypotheses such as how the biological and early life factors directly and indirectly affecting the adult health outcome. A one-way arrow between two variables indicates the expected causal connection. For example, early life circumstances are associated with growth. As shown in Chapter 1 (Figure 1.2), a two-way arrow indicates that the variables may be correlated. Prepubertal growth is associated with age of maturation, which in turn is associated with post-pubertal growth trajectory. Since the cause must precede the effect, the time order should be considered in the path diagram.

3.4.1 Path analysis

Path analysis examines patterns of relationships between a number of response and explanatory variables and provides quantitative estimates of the likely causal connections between sets of variables. In a path analysis, there are two kinds of variables: exogenous variables, which are not influenced by other variables, and endogenous variables, which are affected by other variables.

Figure 3.2 illustrates the path relationships involving four variables: maternal smoking during pregnancy, birthweight, body mass index (BMI), and blood pressure [239]. The direct effect of one variable on another variable is given in the diagram as p1-p6. Maternal smoking may have a direct effect on blood pressure (p1). There may also be an indirect effect of maternal smoking on blood pressure: maternal smoking affects offspring BMI (p5), which in turn affects blood pressure (p6); maternal smoking affects birthweight of the offspring (p2), which in turn affects blood pressure (p3); and maternal smoking affects birthweight (p2) again, but this time it affects offspring BMI (p4), which in turn affects blood pressure (p6). In addition, birthweight may have a direct effect on blood pressure (p3) and an indirect effect through BMI (p4), which in turn affects blood pressure (p6). Finally, BMI may have a direct effect on blood pressure (p6) but no indirect effect.

Figure 3.2 Path diagram for blood pressure



In the case of Figure 3.2, three structural equations can be written, one for each endogenous variable. Included in each equation are those variables that directly affect the endogenous variables. A path coefficient is a standardized regression coefficient which can be estimated from the following *structural equations*

(1) Birthweight $=\beta_2$ Smoking + e_1

(2) Blood pressure $=\beta_1$ Smoking $+\beta_3$ Birthweight $+\beta_6$ BMI + e_2

(3) BMI $=\beta_5$ Smoking $+\beta_4$ Birthweight + e_3

where e_1 is the amount of variation in birthweight that is not accounted for by maternal smoking, e_2 is the amount of error arising from the variation in blood pressure that is not explained by maternal smoking, birthweight, and e_3 is the amount of variation in BMI that is not explained by maternal smoking and birthweight.

The path coefficients are estimated from the structural equations, which are treated as multiple regression models ignoring the intercept terms. The intercept term can be omitted if we assume variables and residual terms are all standardized with mean zero and variance one. The standardized coefficient for maternal smoking (β_1) in (1) provides p2. The coefficients for maternal smoking, birthweight, and BMI in (2) will provide p1, p3, and p6, respectively. The coefficients for maternal smoking and birthweight in (3) will provide p5 and p4.

The path coefficients are comparable because they are standardized. The total causal effect of one variable X on the other variable Y is the sum of the values of all the direct or indirect paths from X to Y. The total causal effect of maternal smoking on blood pressure is the direct effect of the maternal smoking plus the indirect effects, which equals

p1 + (p2*p3) + (p5*p6) + (p2*p4*p6).

As indicated in Table 3.1, one of the main advantages of structural equations is that they enable us to examine the causal process underlying the observed relationship and to estimate the relative importance of alternative paths of influence. Structural equations can also be used when there is more than one response variable in a system. However, path analysis does not establish causality and can't determine the underlying causal structure as

described in Table 3.1. It depends on our own view about the likely causal links among groups of variables. It also requires variables to be Normally distributed. Structural equations are not used in the current analyses, as the objectives are to investigate the influences of early life factors on growth, rather than the causal connection between variables.

Variables are sometimes divided into (1) variables that can be directly observed (*manifest variables*) and (2) variables that are hypothetically constructed, such as social class and social support (*latent variables*). Latent variables are usually not directly observable [143]. For example, a linear growth model (3.4) described in §3.3.1 can be considered as a latent growth model, because the trajectory or the growth curve is unobservable depending on the unobserved latent variables (i.e. random intercept).

In a life-course study, interest usually centres on examining the pattern of relationships between three or more variables simultaneously. For example, we consider whether the observed relationships between more than two variables can be explained in terms of one or more other variables. If the possible explanatory variables are actually observed (as in the given example on birthweight and BMI), then the conventional methods described so far are adequate to determine whether they account for the relationships amongst the other variables [240]. When the possible explanatory variables or dependent variables cannot be directly observed, common methods of analysis include structural equation models [142;241]. The Linear Structural Relationships (LISREL) model may be used in path analysis involving continuous latent variables. Latent class analysis is sometimes used in causal modelling when both manifest and latent variables are categorical [242].

3.4.2 Event data

Most statistical approaches described so far (except for growth models) are based on a set of well-defined occasions when individuals are measured. An alternative way is to follow individuals through time to record the time at which a specified event takes place, for example death, where the main interest of a study is the survival time after an event.

In life-course studies, we sometimes want to assess how much a time-dependent exposure variable affects the response variable. Including time in the study may help strengthen the inference we make (i.e. growth models). A new challenge arises when there are time-dependent covariates involved, which may not be pure confounders since the effect of the exposure on the outcome can be mediated through the effect of the intermediate variable, which in turn is a risk factor for the outcome [227]. A factor that is both a confounder and an intermediate variable is only possible when the exposure is itself time varying. As shown in the earlier example in §3.2, higher blood pressure may be a confounder for the effect of smoking and an intermediate variable on the causal pathway of smoking on mortality. As another example, consider the association between the socio-economic status (time-dependent exposure) and offspring height at each age. However, those from lower socio-economic groups are more likely to live in overcrowded accommodation and have poorer nutrition; both of which are associated with a high infection rate, which in turn relates to poor growth. Thus crowding and nutrition in childhood may be confounders for the effect of socio-economic status, and also intermediate variables in the causal pathway from socio-economic status to offspring height. Special techniques are required when a variable is both a confounder, which should be controlled for in the analysis, and an intermediate variable, which should not be controlled for. In the presence of such covariates, standard approaches for the adjustment for confounding factors are inappropriate.

Event history modelling [141;243] generalizes the confounder-intermediate variable to the time-dependent exposure variable. G-estimation, proposed by Robins [141], estimates the causal effect of a time-dependent exposure on the outcome variable in the presence of time-dependent covariates that may be simultaneously confounders and intermediate variables. It estimates the parameters of a new class of causal models, the structural nested failure time models [141].

3.5 Summary

The 1958 birth cohort has a longitudinal structure in the cohort generation (G2) and a nested structure in the offspring generation (G3). Furthermore, cohort members and offspring are clustered within families. These data structures have implications for the statistical appropriateness of different methods. Height is mainly influenced by genetic and environmental factors, the latter acting mainly in childhood, rather than by accumulation over long periods of life. Therefore multiple regression models are appropriate to examine the effects of early life factors on height of cohort members (G2) at a specific age, adjusting for confounding factors where appropriate.

Analysing growth trajectories of cohort members (G2) involving repeated height measures and this requires methods that take account of the covariance structure, in order to obtain efficient estimates of the parameters and to assess both within-individual and between-individual variation. Although the heights of cohort members were not measured at exactly the same time, a growth model relating height at each age and some key variables (i.e.

parental height and social class) using exact ages and fixed ages showed only small differences. Therefore, multivariate response models were adopted to describe the growth trajectories, where ages were treated as fixed occasions (Chapters 4 and 6).

For analyses involving the offspring, the nested nature of the data requires methods that deal with the correlation of children from the same family. A two-level model was applied in Chapter 6 to examine the social class differences in height increment between two generations. Furthermore, height is also correlated across the two generations, with more variation in height among individuals from different families than those from the same family. Thus a single two-level model is applied to G2 and G3 simultaneously to make comparisons of early life influences on growth of two generations. All statistical analyses in this study are carried out using statistical packages SAS for UNIX and MLwiN.

Chapter 4

Influences on childhood growth, pubertal development, and final height

4.1 Introduction

As mentioned earlier (§1.1.2), adverse early circumstances are associated with adult disease risks [5;12]. Recent evidence has suggested that impaired early growth is also linked to increased blood pressure [26-29] and cardiovascular disease [30]. Poor growth in childhood resulting from unfavourable early conditions may underlie the relationships between early exposures and later diseases. Therefore, the associations between early life circumstances and growth in height are of great interest in relation to a wide range of health outcomes in adulthood.

It has been well accepted that height is largely determined by genetic factors, and partly by early environmental factors (§1.2.2). However, the long-term impact of early environmental conditions on growth in height is not well understood, though it is believed that their influences on height are affected by their influences on tempo of growth. For example, children from less favourable backgrounds tend to grow slower in early life, mature later and catch up at a later stage compared to those from a more favourable background [151].

Socio-economic conditions, such as early nutrition, family size, maternal age at childbirth, social class, parental educational level, and housing conditions are found to be associated with height. Another group of environmental factors that might influence growth are conditions associated with fetal development. Although smoking during pregnancy is known to have a strong influence on birthweight and birth length, which are both in turn strongly associated with childhood and final height [244], evidence on whether maternal smoking represents a lasting effect on growth is not consistent [70;159;160]. It has also been recognized that childhood stress and illness are associated with slow growth and short adult stature [92;95-97].

Early circumstances that affect growth may also have an impact on the age of maturation. Early influences on final height start in early childhood and are mitigated by the extension of growth period. Therefore examining the influence of early life factors on growth trajectories and pubertal development rather than height at a given age may help us to identify "critical periods" of early life exposures for future disease.

Objectives

A wide range of factors have been identified to be associated with height of the 1958 birth cohort in previous studies [57;68;70;84;92;94;153-158]. Pubertal development has been explored in relatively few studies of the cohort so far. Within the cohort, early maturation was found to be associated with high BMI at ages 7-33 years [122], although early menarche was also reported for girls who were under or average weight [245]. An association between region and age of menarche has been reported, which was not attributed to social class [246]. The distribution of age at menarche was not influenced by social class [245]. There was little

evidence on the associations between a wider range of early life conditions and age of maturation in the 1958 cohort.

Methodologically, results reported on the cohort were all based on relationships between early life factors and height at one age. Statistical methods used have ignored the fact that measures made on the same individual were correlated. Little is known about the longitudinal influences of early conditions on growth trajectories. This chapter examines the early life influences on height at four different ages simultaneously, from early childhood until the achievement of final adult height, in order to make comparison of the early influences on growth at different life stages, to establish their impact on growth trajectories. The specific aims are:

i) to investigate growth trajectories and early life factors in relation to pubertal development; and

ii) to examine early life influences on height of cohort members at ages 7, 11, 16, and 33 years simultaneously to establish their roles at each growth phase and the extent to which associations remain with adult height.

Influences investigated included: (a) parental height, an indicator of genetic potential, (b) maternal smoking during pregnancy and birthweight, indicators of fetal environment, (c) early circumstances of cohort members in terms of family size and level of crowding, indicators of social disadvantage and the standard of living [158;247], (d) parental separation or divorce, a major contribution to family conflict and psychosocial influence related to slow growth in childhood [94], and (e) childhood disability, an indicator of health status in early life, on growth and final height. This current analysis was extended to assess the effect of

the timing of parental divorce in order to establish the "critical period" of the exposure that resulted in the reduction of growth and whether that reduction was attributable to the stress, or to the socio-economic hardship following the divorce. Social class was adjusted for in order to understand the different aspects of socio-economic circumstances in early life. The influence of social class on growth of cohort members is further investigated in detail in Chapter 6.

4.2 Methods and measures

Detailed descriptions of height and pubertal development, and information of early environment and childhood health used in the current analyses are given in §2.3. A summary of main variables is shown in Table 4.1.

Response variables, internally derived height SDS at all ages (§2.4.2), stage of pubertal development at 16 years for boys, and age of menarche for girls were all investigated. In this analysis, three categories, "early", "average", and "later" were used for both sexes as indicators of pubertal development of cohort members (§2.3.2)

Table 4.1 Summary of variables used in Chapter 4

Factors	*n*	Mean (s.d.)
Height at 7 (cm)		
Boys	7036	122.8 (5.8)
Girls	6598	121.9 (6.1)
Height at 11 (cm)		
Boys	6494	143.9 (6.9)
Girls	6195	144.7 (7.5)
Height at 16 (cm)		
Boys	5746	170.2 (7.9)
Girls	5382	160.9 (6.2)
Height at 33 (cm)		
Men	7105	176.8 (6.9)
Women	7515	162.4 (6.5)
Maternal height (cm)	17812	161.0 (6.4)
Paternal height (cm)	13133	174.5 (7.4)
Birthweight (g)	16052	3332 (524)
Maternal age (y)	17397	27.5 (5.7)
	n	Percent %
Stage of pubertal development at 16 in boys		
Early	1361	23.9%
Average	3723	65.3%
Late	618	10.8%
Age of menarche in girls		
Early (9-11y)	695	15.4%
Average (12-14y)	3505	77.5%
Late (15y+)	324	7.2%
Maternal smoking	17186	33.6%
Family size at 7	14590	
3+		56.3%
Over-crowding at 7	13945	
1.5+ persons/room		19.5%
Parental divorce	11278	
0-7y		3.5%
Disability	14627	5.1%

Growth trajectories of early, average, and late developers were examined. The associations between early life factors and pubertal development were analysed using analysis of variance (ANOVA) for continuous variables (§3.2) and *chi*-squared tests for discrete variables.

As explained in §3.3.1, multivariate response modelling was used here to explore the relationship between early life factors and response variables, height at 7, 11, 16, and 33 years simultaneously, with ages as fixed occasions. The model not only takes account of the correlation in height measures within the individual, but also allows the inclusion of cohort members who did not have all four measurements.

The unadjusted relationships between height at all ages and each factor were examined simultaneously. They were then adjusted for parental height, birthweight, and finally socio-economic factors of family size and social class. Analyses were restricted to cohort members (G2) with at least one height measurement and complete information on each specific factor of interest and confounding variables in order to include as many subjects as possible. It has been shown in Chapter 3 (§3.3.1) that response variable (height) is missing at random (MAR) and the missing patterns do not affect the relationships under investigation. The influence of each factor on growth trajectories was first examined using the joint contrast test for the hypothesis concerning the equality of the parameters at four occasions. If the null hypothesis of similar effects on height at all ages was rejected, we further tested the difference between pairs of parameters (e.g. height at 7 and 11). The difference in height gain (or rate of growth) over two ages between sub-groups (e.g. children of large and small families, smoker and non-smoker mothers) was also tested using contrast tests.

Additional analyses were carried out to examine (1) the growth patterns for children of low birthweight for premature and term infants, separately, and (2) the association between family size and height at all ages for manual and non-manual social classes, separately, to determine whether the association is modified by social class. As boys and girls have different growth patterns due to their different growth tempo, each sex was analysed separately throughout the chapter. Age 20 years was used for final achieved height in all figures (Figures 4.1-4.9) to avoid the large time interval from 16 to 33 years, which might underestimate the rate of growth after age 16.

4.3 Results

As described in Chapter 3, a total of 16835 cohort members had at least one height measure, with 1512, 2842, 5051, and 7430 members having one, two, three, or all four measurements, respectively.

4.3.1 Childhood and final adult height

Table 4.2 illustrates the strength of correlations between height measures within individuals. The strong positive correlations confirm the importance of using multivariate response models. As expected, correlations were generally greater over shorter intervals than longer ones, except for girls, where the correlation with adult height (16 and 33 years) was greater for height at 7 than height at 11. The correlation between height at 7 years and final adult height was the same (0.70) for boys and girls. Boys had a higher correlation with adult height at age 11 years, but a lower correlation at 16 years compared to girls, reflecting

their later pubertal growth spurt compared to girls. The correlation between height at ages 16 and 33 was much stronger among girls since most girls had achieved final adult height by age 16 whereas many boys had not (Table 4.2).

Table 4.2 Correlation coefficients between height measures (G2) at different ages

	Boys				Girls			
Age (y)	7	11	16	33	7	11	16	33
7	1.00				1.00			
11	0.87	1.00			0.83	1.00		
16	0.76	0.84	1.00		0.74	0.72	1.00	
33	0.70	0.72	0.77	1.00	0.70	0.66	0.92	1.00

4.3.2 Growth of early, average, and late developers

Far from parallel lines, there were marked differences in growth trajectories between early and late developers as illustrated in Figure 4.1. Early developers were taller throughout childhood than late developers, but late developers caught up in later puberty.

Among boys, early developers, defined as top 23.9% ratings based on Tanner's stages (§2.3.2) were on average 1.7 cm taller, while late developers (bottom 10.8% ratings) were 2.7 cm shorter than the average developers at age 7 (Figure 4.1-a). The differences increased to 3.1 cm and 3.8 cm at 11 years, respectively. By age 16 the difference was 2.7 cm between early and average developers and had reached 8.3 cm between late and average developers. After age 16, the difference between early and average developers disappeared, and only a smaller difference of 1.1 cm ($p<0.001$) remained in adult height between

average and late developers. Thus, pubertal rating at age 16 provided an indication of residual growth potential in boys.

Girls demonstrated a different growth pattern and were normally ahead of boys at all stages of puberty. At age 7, girls who matured early (menarche 9-11y) were on average 2 cm taller, while girls who matured late (>14y) were 2.6 cm shorter than the average developers (menarche 12-14y). The difference was the greatest at 11 years, as girls who matured earlier had started their pubertal growth spurt earlier than other girls. In particular, girls who matured early were on average 5.3 cm taller, while girls who matured later were 5.5 cm shorter than average developers. By age 16, early and average developers had reached the same average height, but the late developers remained to be 2.5 cm shorter than other girls. Late maturing girls continued to grow after age 16 and by adulthood, they caught up with normal maturing girls, whereas early maturing girls who achieved final height earlier were on average 1 cm shorter than other girls in adulthood (p=0.001).

Table 4.3 Stage of pubertal development at age of 16 in boys in relation to biological and early life factors (G2)

Factors	*N*	Early	Average	Late
		23.9%	65.3%	10.8%
Mean			†	
Maternal height (cm)*	5487	161.5	161.1	160.7
Paternal height (cm)*	4665	174.8	174.7	173.6
Birthweight (g)	5110	3408	3408	3358
Maternal age (y)*	5290	27.5	27.4	26.8
%			‡	
Maternal smoking	5222	30.8	33.3	30.5
Large family (3+)*	4889	51.4	55.9	64.0
Over-crowding (1.5+)*	4746	15.7	19.0	23.9
Social class IV&V*	5370	22.0	24.1	27.8
Parental divorce at 0-7y	3785	2.7	3.2	2.3
Disability at 7y	4912	5.6	5.4	5.7

† differences between early and late with respect to average developers are tested using ANOVA
‡ differences are tested using chi-squared test
* $p<0.05$

Table 4.4 Age of menarche in girls in relation to biological and early life factors (G2)

Factors	*N*	Early (9-11y)	Average (12-14y)	Late (15y+)
		15.4%	77.5%	7.2%
Mean			†	
Maternal height (cm)	3786	161.1	161.0	161.2
Paternal height (cm)	3746	174.7	174.6	173.8
Birthweight (g)	4117	3273	3261	3260
Maternal age (y)	4229	27.5	27.4	27.5
%			‡	
Maternal smoking	4182	30.8	31.6	29.5
Large family (3+)*	3957	48.3	56.5	64.7
Over-crowding (1.5+)*	3831	14.0	19.1	28.9
Social class IV&V*	4313	25.3	23.1	32.9
Parental divorce at 0-7y	3366	4.2	3.4	3.9
Disability at 7y*	3967	3.0	3.6	7.1

† differences between early and late with respect to average developers are tested using ANOVA
‡ differences are tested using chi-squared test
* $p< 0.05$

4.3.3 Factors influencing onset of puberty

Among boys, parental height, maternal age at childbirth, family size, household crowding, and social class were significantly associated with pubertal development at age 16 years (Table 4.3). Early developers were linked to taller mothers and less crowding, while late developers were linked to shorter parents, younger mothers, more over-crowding, larger families, and lower social class (IV&V).

Among girls, paternal height, family size, household crowding, social class, and childhood disability were all significantly associated with age of menarche (Table 4.4). Early maturation was linked to smaller family size and less crowding, while late maturation was linked to more over-crowding, larger families, lower social class (IV&V) and childhood disability.

4.3.4 Factors influencing childhood growth and final adult height

As shown in Tables 4.5 and 4.6, the effects of parental height, birthweight, maternal smoking during pregnancy, family size, household crowding, parental divorce (females) and disability in early childhood were significantly associated with height in childhood and adulthood. Their influences were established by age 7, but the strength of these influences differed by growth stage due to their impact on pubertal development.

Parental height

From Table 4.7, it can be seen that parental height was positively associated with height of cohort members at all ages, with the relationship stronger for adult height than childhood height. For every SD increase in maternal height, height at age 7 increased by 0.37 SD in

boys and 0.38 SD in girls, and adult height increased by 0.45 SD. Similarly, for every SD increase in paternal height, height at 7 increased by 0.35 SD, and adult height increased by 0.42 SD in men and 0.40 SD in women. The effect of maternal height attenuated after simultaneous adjustment for paternal height, but substantial effects remained and likewise, for paternal height (Tables 4.5 and 4.6). The association of mid-parental height SDS with cohort member growth was affected little by adjustment of other factors (Figure 4.2). Accordingly, mid-parental height captures the joint effects of both parents and shows stronger effects (0.55-0.72) than that for one parent (0.31-0.46) (Figure 4.2).

Table 4.5 Estimated effects (s.e.) of parental height (G1) and early life factors on height (SDS) of male cohort members (G2)

	Model (1)				Model (2)				Model (3)				Model (4)			
Height SDS at	7	11	16	33	7	11	16	33	7	11	16	33	7	11	16	33
Maternal height SDS	0.366*	0.386*	0.379*	0.452*	0.295*	0.315*	0.305*	0.368*	0.269*	0.289*	0.279*	0.341*	0.261*	0.281*	0.274*	0.339*
n=5633	(0.013)	(0.012)	(0.013)	(0.012)	(0.012)	(0.012)	(0.013)	(0.012)	(0.012)	(0.012)	(0.013)	(0.012)	(0.012)	(0.012)	(0.013)	(0.012)
Paternal height SDS	0.352*	0.356*	0.364*	0.423*	0.273*	0.272*	0.282*	0.325*	0.261*	0.261*	0.271*	0.314*	0.244*	0.245*	0.260*	0.309*
n=5633	(0.013)	(0.013)	(0.013)	(0.013)	(0.013)	(0.013)	(0.013)	(0.012)	(0.012)	(0.012)	(0.013)	(0.012)	(0.012)	(0.012)	(0.013)	(0.012)
Birthweight (kg)	0.493*	0.494*	0.489*	0.526*	0.367*	0.362*	0.366*	0.358*					0.367*	0.363*	0.366*	0.360*
n=5633	(0.025)	(0.025)	(0.026)	(0.026)	(0.024)	(0.024)	(0.026)	(0.023)					(0.023)	(0.023)	(0.025)	(0.023)
Maternal smoking	-0.192*	-0.168*	-0.151*	-0.136*	-0.152*	-0.127*	-0.110*	-0.091*	-0.109*	-0.085*	-0.068*	-0.048*	-0.083*	-0.061*	-0.052*	-0.043
n=5576	(0.029)	(0.029)	(0.030)	(0.030)	(0.026)	(0.026)	(0.028)	(0.027)	(0.026)	(0.026)	(0.028)	(0.027)	(0.026)	(0.026)	(0.027)	(0.027)
Social class *n*=5633																
I&II	0.468*	0.443*	0.363*	0.338*	0.303*	0.279*	0.233*	0.111*	0.287*	0.264*	0.217*	0.096*	0.245*	0.220*	0.180*	0.074*
	(0.040)	(0.040)	(0.042)	(0.042)	0.037)	(0.037)	(0.040)	(0.036)	(0.037)	(0.036)	(0.039)	(0.035)	(0.037)	(0.036)	(0.039)	(0.036)
IIINM	0.362*	0.352*	0.297*	0.268*	0.229*	0.221*	0.199*	0.083	0.211*	0.203*	0.180*	0.064	0.150*	0.138*	0.127*	0.031
	(0.050)	(0.050)	(0.052)	(0.052)	(0.046)	(0.046)	(0.049)	(0.044)	(0.045)	(0.045)	(0.048)	(0.043)	(0.045)	(0.045)	(0.048)	(0.044)
IIIM	0.143*	0.141*	0.101*	0.191*	0.090*	0.088*	0.060	0.027	0.093*	0.091*	0.062	0.029	0.067*	0.065*	0.040	0.016
	(0.034)	(0.033)	(0.035)	0.035)	(0.031)	(0.031)	(0.033)	0.030)	(0.030)	(0.030)	(0.033)	(0.029)	(0.030)	(0.030)	(0.032)	(0.029)
Large families (3+)	-0.326*	-0.336*	-0.271*	-0.199*	-0.254*	-0.262*	-0.197*	-0.114*	-0.266*	-0.273*	-0.208*	-0.125*	-0.254*	-0.264*	-0.202*	-0.124*
n=5633	(0.027)	(0.027)	(0.028)	(0.028)	(0.024)	(0.024)	(0.025)	(0.023)	(0.024)	(0.023)	(0.025)	(0.023)	(0.024)	(0.024)	(0.025)	(0.023)

Table 4.5 (cont.)

	Model (1)				Model (2)				Model (3)				Model (4)			
Height SDS at	7	11	16	33	7	11	16	33	7	11	16	33	7	11	16	33
Over-crowding(1.5+)	-0.488*	-0.469*	-0.385*	-0.275*	-0.303*	-0.276*	-0.186*	-0.041	-0.319*	-0.291*	-0.201*	-0.056	-0.231*	-0.200*	-0.140*	-0.029
n=5633	(0.034)	(0.034)	(0.036)	(0.036)	(0.031)	(0.031)	(0.033)	(0.033)	(0.030)	(0.030)	(0.032)	(0.030)	(0.035)	(0.035)	(0.037)	(0.035)
Parental divorce 0-7y	-0.195*	-0.228*	-0.144	-0.112	-0.229*	-0.263*	-0.180*	-0.156*	-0.213*	-0.246*	-0.164	-0.138	-0.154*	-0.195*	-0.128	-0.120
n=3765	(0.101)	(0.101)	(0.106)	(0.100)	(0.091)	(0.090)	(0.096)	(0.084)	(0.089)	(0.088)	(0.095)	(0.082)	(0.088)	(0.088)	(0.094)	(0.082)
Disability	-0.172*	-0.167*	-0.124*	-0.119*	-0.157*	-0.155*	-0.110*	-0.104*	-0.125*	-0.123*	-0.078	-0.072	-0.111*	-0.109*	-0.069	-0.069
n=5618	(0.059)	(0.059)	(0.061)	(0.060)	(0.052)	(0.052)	(0.055)	(0.051)	(0.051)	(0.051)	(0.054)	(0.050)	(0.051)	(0.050)	(0.053)	(0.050)

* $p< 0.05$

Model (1) unadjusted, Model (2) adjusted for maternal and paternal height, for maternal or paternal height themselves, each adjusted for height of the other parent, Model (3) adjusted for maternal and paternal height, and birthweight, and Model (4) adjusted for maternal and paternal height, birthweight, family size and social class

Note: (1) different sample size, which includes subjects with one or more height measures, complete information on parental height, birthweight, family size, social class and the factor of interest, was used for each row to achieve the maximum sample size. (2) Baseline groups are 'non-smokers', 'social class IV&V', 'small families', 'uncrowded', 'no divorce by age 7y', or 'no disability'.

Table 4.6 Estimated effects (s.e.) of parental height (G1) and early life factors on height (SDS) of female cohort members (G2)

	Model (1)				Model (2)				Model (3)				Model (4)			
Height SDS at	7	11	16	33	7	11	16	33	7	11	16	33	7	11	16	33
Maternal height SDS	0.379*	0.349*	0.461*	0.454*	0.309*	0.285*	0.376*	0.374*	0.282*	0.261*	0.347*	0.346*	0.274*	0.354*	0.342*	0.343*
n=5385	(0.013)	(0.013)	(0.013)	(0.013)	(0.013)	(0.013)	(0.013)	(0.012)	(0.013)	(0.013)	(0.013)	(0.012)	(0.013)	(0.013)	(0.012)	(0.012)
Paternal height SDS	0.346*	0.314*	0.414*	0.398*	0.267*	0.241*	0.318*	0.304*	0.255*	0.231*	0.306*	0.292*	0.238*	0.215*	0.293*	0.283*
n=5385	(0.013)	(0.013)	(0.013)	(0.013)	(0.013)	(0.013)	(0.012)	(0.012)	(0.013)	(0.013)	(0.012)	(0.012)	(0.013)	(0.013)	(0.012)	(0.012)
Birthweight (kg)	0.487*	0.444*	0.549*	0.527*	0.327*	0.294*	0.351*	0.332*					0.330*	0.296*	0.344*	0.325*
n=5385	(0.026)	(0.027)	(0.027)	(0.026)	(0.024)	(0.025)	(0.024)	(0.023)					(0.024)	(0.025)	(0.023)	(0.023)
Maternal smoking	-0.181*	-0.193*	-0.149*	-0.152*	-0.126*	-0.142*	-0.081*	-0.085*	-0.078*	-0.099*	-0.027	-0.034	-0.048	-0.073*	-0.007	-0.021
n=5326	(0.029)	(0.030)	(0.030)	(0.030)	(0.026)	(0.027)	(0.025)	(0.025)	(0.026)	(0.027)	(0.025)	(0.025)	(0.026)	(0.027)	(0.025)	(0.025)
Social class *n*=5385																
I&II	0.423*	0.371*	0.416*	0.359*	0.206*	0.170*	0.151*	0.099*	0.195*	0.160*	0.140*	0.088*	0.161*	0.127*	0.123*	0.076*
	(0.041)	(0.042)	(0.042)	(0.042)	(0.038)	(0.039)	(0.036)	(0.036)	(0.037)	(0.038)	(0.036)	(0.035)	(0.037)	(0.038)	(0.036)	(0.035)
IIINM	0.352*	0.333*	0.414*	0.350*	0.171*	0.164*	0.190*	0.127*	0.161*	0.156*	0.181*	0.118*	0.110*	0.105*	0.156*	0.099*
	(0.050)	(0.051)	(0.052)	(0.051)	(0.046)	(0.047)	(0.044)	(0.043)	(0.045)	(0.046)	(0.043)	(0.042)	(0.045)	(0.046)	(0.044)	(0.042)
IIIM	0.108*	0.104*	0.117*	0.097*	0.061*	0.059	0.060*	0.039	0.057	0.056	0.057*	0.036	0.034	0.034	0.046	0.028
	(0.034)	(0.035)	(0.035)	(0.035)	(0.031)	(0.032)	(0.030)	(0.029)	(0.030)	(0.031)	(0.029)	(0.029)	(0.030)	(0.031)	0.029	(0.029)
Large families (3+)	-0.305*	-0.293*	-0.183*	-0.145*	-0.249*	-0.242*	-0.118*	-0.081*	-0.266*	-0.256*	-0.135*	-0.097*	-0.255*	-0.248*	-0.126*	-0.091*
n=5385	(0.027)	(0.028)	(0.028)	(0.028)	(0.025)	(0.025)	(0.024)	(0.023)	(0.024)	(0.025)	(0.023)	(0.023)	(0.024)	(0.025)	(0.024)	(0.023)

Table 4.6 (cont.)

	Model (1)				Model (2)				Model (3)				Model (4)			
Height SDS at	7	11	16	33	7	11	16	33	7	11	16	33	7	11	16	33
Over-crowding (1.5+)	-0.535*	-0.504*	-0.363*	-0.318*	-0.394*	-0.373*	-0.188*	-0.146*	-0.408*	-0.385*	-0.204*	-0.160*	-0.310*	-0.294*	-0.145*	-0.119*
n=5194	(0.035)	(0.035)	(0.037)	(0.036)	(0.031)	(0.033)	(0.031)	(0.030)	(0.031)	(0.032)	(0.030)	(0.030)	(0.033)	(0.035)	(0.033)	(0.032)
Parental divorce 0-7y	-0.170*	-0.175*	-0.202*	-0.206*	-0.090	-0.099	-0.100	-0.110	-0.050	-0.064	-0.060	-0.070	-0.033	-0.051	-0.050	-0.064
n=3932	(0.094)	(0.094)	(0.094)	(0.092)	(0.084)	(0.085)	(0.080)	(0.077)	(0.082)	(0.084)	(0.078)	(0.076)	(0.081)	(0.083)	(0.078)	(0.075)
Disability	-0.422*	-0.442*	-0.436*	-0.402*	-0.411*	-0.434*	-0.420*	-0.387*	-0.383*	-0.408*	-0.391*	-0.360*	-0.375*	-0.401*	-0.385*	-0.356*
n=5370	(0.070)	(0.071)	(0.073)	(0.071)	(0.062)	(0.064)	(0.061)	(0.059)	(0.061)	(0.064)	(0.060)	(0.058)	(0.061)	(0.064)	(0.060)	(0.058)

* $p < 0.05$

Model (1) unadjusted, Model (2) adjusted for maternal and paternal height, for maternal or paternal height themselves, each adjusted for height of the other parent, Model (3) adjusted for maternal and paternal height, and birthweight, and Model (4) adjusted for maternal and paternal height, birthweight, family size and social class

Note: (1) different sample size, which includes subjects with one or more height measures, complete information on parental height, birthweight, family size, social class and the factor of interest, was used for each row to achieve the maximum sample size. (2) Baseline groups are 'non-smokers', 'social class IV&V', 'small families', 'uncrowded', 'no divorce by age 7y', or 'no disability'.

Table 4.7 Correlation coefficient between height of cohort members (G2) and their parents (G1)

Age (year)	Mother-son	Father-son	d†	Mother-daughter	Father-daughter	d‡
7	0.37	0.35	0.02	0.38	0.35	0.03
11	0.39	0.36	0.03	0.35	0.31	0.04
16	0.38	0.36	0.02	0.46	0.41	0.05
33	0.45	0.42	0.03	0.45	0.40	0.05

† difference between maternal and paternal correlation with the son
‡ difference between maternal and paternal correlation with the daughter

Birthweight

As shown in Tables 4.5 and 4.6, birthweight was significantly associated with height of cohort members at all ages, with the association persisting through to adulthood. Each 1kg increase in birthweight resulted in an average increase of approximatly 0.4-0.5 SD in mean height for boys and girls. The effect of birthweight on height reduced but remained strong at all ages after parental height was accounted for. Further adjusting for family size and social class did not alter the relationship (Tables 4.5 and 4.6).

Even though children of low birthweight appeared to be short compared to those with normal or high birthweight, there were considerable differences in growth pattern between premature and intrauterine growth retarded children. In particular, for those weighing 2000-2500g at birth, intrauterine growth retarded children (mean 2361g) were heavier than premature babies (mean 2294g) at birth, but were on average shorter by age 7. The two growth curves were nearly parallel, with a mean difference in height over 0.2 SD (1.2-1.6 cm), which persisted to adulthood (Figure 4.3).

Maternal smoking

A significant association was found between maternal smoking during pregnancy and height at all ages (Tables 4.5 and 4.6). Boys whose mother smoked were shorter than those of non-smoking mothers by 0.19 SD (1.1 cm) at age 7, but they grew faster throughout childhood (Figure 4.4). Although the difference in height gain between pairs of successive ages (i.e. 7-11y, 11-16y, 16y-adulthood) was non-significant, the total growth from age 7 to adulthood was significantly greater for boys whose mother smoked compared to those of non-smoking mothers.

For girls, the effect of maternal smoking on height was at its strongest at age 11, with a difference of 0.19 SD (1.1 cm) between girls of non-smoking mothers and those whose mothers smoked (Table 4.6). Girls whose mothers smoked grew significantly faster between ages 11 and 16 years than those of non-smoking mothers (height increment 16.6 cm vs 16.1 cm). Thus the relationship became weaker at age 16. Maternal smoking did not affect growth after 16 as most girls had already achieved their final height (Figure 4.4).

The effect of maternal smoking was largely reduced once birthweight was adjusted for, with 34% and 43% of the maternal smoking effect on height at age 7, and 51% and 58% of the effect on adult height being mediated through birthweight, for males and females respectively. This suggests that birthweight was a pathway factor for the association between smoking and childhood growth. When adjusting for parental height, birthweight, family size and social class, there was only a small difference of 0.08 (0.5 cm) at 7 for boys and 0.07 (0.4 cm) at 11 for girls between those of non-smoking mothers and those whose mothers smoked, though still significant. The association with adult height (age 33 for

males, and ages 16 and 33 for females) was no longer significant after the adjustment (Tables 4.5 and 4.6).

Family size

There was a significant association between family size and height at all ages, which was stronger for childhood than for adult height (Figure 4.5). Children from large families (3+ children) had a slower growth rate in early childhood (before age 7) than those from small families (<3 children) and remained short until the age 11, with a difference of 0.34 SD in boys (2.3 cm) and 0.29 SD in girls (2.2 cm) between children from small and large families (Tables 4.5 and 4.6).

From the age 11, children from large families grew more, with girls gaining 1.1 cm more between ages 11 and 16 years ($p<0.001$) and boys growing for a longer period and gaining 0.8 cm more after the age of 16 ($p<0.001$) compared to those from small families (data not presented). As children from large families tended to mature later ($p<0.001$), the stronger association in boys than in girls at age 16 reflected the effect of family size on the stage of maturation in boys. The difference between children from small and large families reduced to 0.20 SD in men (1.4 cm) and 0.15 SD in women (1.0 cm) by adulthood (Tables 4.5 and 4.6).

As shown in Tables 4.5 and 4.6, the effect of family size on height reduced at all ages after parental height was accounted for, indicating that there are socio-economic components in parental height. But further adjustment for birthweight and social class did not alter the relationship (Tables 4.5 and 4.6). However, the effect of family size on height reduced

when social class was added to the univariate model (data not presented), indicating that part of the effect of family size was explained by social class.

Figure 4.6 shows that the association between family size and height was stronger in manual classes compared to non-manual classes, both for males and females. For example, at age 7, the difference between small and large families was 0.12 SD in boys (0.7 cm) and 0.18 SD in girls (1.1 cm) for non-manual classes, whereas the corresponding difference was 0.37 SD in boys (2.1 cm) and 0.32 SD in girls (1.9 cm) in manual social classes, suggesting that the impact of family size was in part due to socio-economic influence on height.

Household crowding

The relationship between the level of crowding and height was the strongest at age 7, with a significant difference between cohort members living in less crowded and over-crowded households (1.5+ persons/room) of 0.49 SD in boys (2.8 cm) and 0.54 SD in girls (3.2 cm) (Tables 4.5 and 4.6). As shown in Figure 4.7, the relationship weakened with increasing age.

Cohort members from over-crowded households grew consistently faster throughout childhood, with boys growing 1.2 cm more after age 16 years ($p<0.001$) and girls growing 1.5 cm more ($p<0.001$) between ages 11 and 16 years, compared to those from less crowded households. A weaker relationship therefore was observed between household crowding and adult height, with a difference of 0.28 SD in males (1.9 cm) and 0.32 SD in females (2.1 cm).

The effect of household crowding on height reduced after adjusting for parental height, particularly its effect on adult height, which became non-significant in men (Table 4.5). Thus parental height not only reflects a genetic influence, but also parents' own socio-economic background, which in turn is associated with their adult social position. The effect of household crowding reduced after further adjusting for social class and family size, as over-crowding is an indicator of social disadvantage.

Parental divorce

Parental divorce in early life was significantly associated with height in childhood. Boys whose parents divorced by age 7 were on average shorter than those whose parents did not by 0.23 SD (1.6 cm) at age 11, but they grew faster and gained more than those whose parents did not separate by 0.8 cm (non-significant) between ages 11 and 16 years. Thus in adulthood, the difference became non-significant. As illustrated in Figure 4.8, the impact of parental divorce on growth trajectories for boys changed little after adjusting for parental height, birthweight, family size and social class. Girls whose parents divorced by age 7 were shorter than those whose parents did not throughout the life-course, and remained shorter in adulthood by 0.21 SD (1.3 cm). However, the effect of parental divorce was weakened (Figure 4.8) and no longer significant after adjusting for genetic and early life factors (Table 4.6).

The influence of parental divorce on growth was found to be dependent on the age of the child when divorce took place in boys. Additional analysis for the timing of divorce showed that boys whose parents divorced before age 4 years had similar growth patterns as those whose parents did not divorce, while boys whose parents divorced at age between 4 and 7 years were significantly shorter than their counterparts at all ages, and were not only

short in childhood, but also in adulthood (data not presented). However, among girls, the association between parental divorce and height was independent of the age when divorce happened.

Childhood disability

More boys (5.5%) than girls (3.9%) were reported to have moderate or severe disability that limited their normal schooling or activity. Boys with disability were significantly shorter than those without by 0.17 SD (1 cm) at age 7 and 0.12 SD (0.8 cm) in adulthood. The effect of disability on height was no longer significant after the age 16 when allowance was made for parental height, birthweight, family size, and social class (Table 4.5). The impact of childhood disability on growth in height was much stronger in girls than in boys. Girls with disability were significantly shorter than those without throughout the life-course (Table 4.6). Although girls with disability tended to mature later than the others (p=0.007), childhood disability was not associated with the rate of growth and girls with disability did not catch up. The impact of disability on height was not affected by adjusting for parental height and socio-economic factors in childhood.

4.4 Discussion

As expected, all influences examined, parental height, prenatal factors (birthweight and maternal smoking during pregnancy) and postnatal factors (social class, family size, household crowding and parental separation or divorce) affected height in childhood. Even after compensatory growth either through a longer growth period or a faster rate of growth, most factors also influenced adult stature.

Within this cohort, four major patterns of influence can be identified. *First*, for parental separation or divorce, there appeared to be a short-term effect, at least in boys, characterised by delayed growth, followed by catch-up, thus the long-term effects was minimal. *Second*, for maternal smoking during pregnancy, deficits in childhood height were observed followed by rapid growth. No long-term effect on height persisted through to adulthood, after allowing for other factors. A persisting adverse effect of maternal smoking was seen to operate through its influence on birthweight. *Third*, socio-economic disadvantage as indicated by living in over-crowded homes and large families, was associated with substantial deficits in childhood height. Compensatory growth was substantial, though not sufficient to overcome the initial insult on growth. *Fourth*, for parental height and birthweight, associations were evident throughout, they were undiminished and even possibly strengthening by adulthood. There was only slight attenuation of effects with adjustment for other factors, suggesting a primarily genetic influence of parental height and birthweight.

Parental height, family size, household crowding and social class were also significantly associated with pubertal development in boys, with shorter parental stature, larger family size, over-crowding and lower social class being associated with later development in boys. Larger family size, over-crowding, lower social class and disability in early childhood were found to be associated with later menarche.

4.4.1 Methodological considerations

The long study period of a large population sample provides unique evidence on how early life circumstances influence growth at different life stages, pubertal development, and final adult height. In many previous studies, traditional multiple regression models were used to examine effects of the early life factors on height at each age separately and the strength of these associations could not be compared directly across different models. The application of multivariate response models to the 1958 cohort data allows these relationships at different ages to be tested simultaneously, and also allows the covariance structure to be accounted for. As explained in Chapter 3, such an approach is more appropriate than growth models because there are only a small number of measurements over the whole growth period (three childhood and one adult height measures). Moreover, the estimation from the multivariate response models should be efficient even with incomplete data on response variables, as there is no indication of any violation of the MAR assumption (Chapter 3).

However, there are several limitations mainly due to data restriction. *First*, we were unable to identify changes in growth patterns between two measurements as a result of the large time intervals. *Second*, unlike other studies (i.e. 1946 cohort), where age of menarche was

recorded to the nearest month [130;133], it was reported in years in the 1958 cohort. Thus the measurement error could be large and the estimates for group differences might not be accurate or informative.

4.4.2 Parental height and birthweight

Heights of parents are markers of genetic influence and are the most powerful predictors for height. Although parental height also mirrors parents' own childhood environment, it mainly reflects the parents' genotype in stature [57;58;61;62;248]. The impact of parental height was not affected by birthweight and early environmental factors. The stronger influence of parental height on final adult height compared to childhood height was due to the fact that childhood height is more sensitive to early environment, while adult height reflects the genetic potential.

The findings of a stronger effect of maternal height compared to paternal height are consistent with results from other studies [58-60]. Mothers influence offspring growth through their own height as well as through the birthweight of the baby. In the 1958 cohort, the effect of maternal height on birthweight was more than twice of that of paternal height (data not presented). Another possible explanation is that reported paternal height (G1), with a greater measurement error than measured maternal height due to reporting error, might have also attenuated its correlation with height of cohort members (G2).

Apart from parental height, birthweight, also a partly genetic and partly environmental influence, had a strong effect on height for the full range of birthweight, regardless of socio-economic factors, in this study or elsewhere [57;85]. Birthweight is an indicator of

prenatal development. Subjects who were small at birth remained, on average, small throughout the growth period, although there was evidence of catch-up growth [249]. A stronger association with adult height was explained by parental height, suggesting the stronger genetic influence on adult height than childhood height, which is more sensitive to environmental influences.

It has been suggested that intrauterine growth retardation is a stronger factor for short stature than is prematurity [244]. Our longitudinal analysis revealed that children of similar birthweight who were premature appeared to grow faster in early years and sustain less permanent growth impairment than those who were intrauterine growth retarded, although both remained smaller than their normal birthweight counterparts. Therefore growth trajectories are permanently affected by low birthweight, particularly by the intrauterine environment.

4.4.3 Maternal smoking

Children prenatally exposed to cigarettes are smaller at birth [149;250;251]. The growth deficits are maintained at subsequent ages [60;68], although it is suggested that the effect of maternal smoking weakens with increasing age [70;159;160]. Early analyses of the 1958 cohort showed a continuing effect of maternal smoking on physical growth up to 7 years in boys and 11 years in girls after its effect on birthweight was accounted for [68]. A weak relationship (p=0.05) between maternal smoking and self reported adult height at 23 was found only in females after adjusting for birthweight for gestational age and early environmental factors. It was suggested that smoking affected the rate of growth rather than total growth [70].

Our results showed that the growth deficits observed in early childhood occurred independently of fetal retardation. Thus maternal smoking influenced growth in height beyond birth, with the strongest impact on height in early childhood (age 7 in boys and 11 in girls). However, the fact that only a weak effect was found on childhood height after adjusting for early environmental factors suggested that early postnatal catch-up among children whose growth was impaired due to tobacco exposure in utero was dependent on early social conditions.

The current study of the longitudinal influence of maternal smoking on child-to-adult growth trajectory revealed a faster growth rate throughout growth period in boys and between ages 11 and 16 years in girls who were born to mothers who smoked during pregnancy compared to those of non-smoking mothers. Thus growth deficits due to maternal smoking did not persist to adulthood in the 1958 cohort. The rate of growth did not change after adjusting for genetic and early environmental factors, suggesting that the faster growth throughout childhood among children of mothers who smoked was independent of early social environment.

The exact reasons for a faster growth rate among children of mothers who smoked are unclear. Our data suggested that the rate of early growth was influenced by factors that operated during fetal development, independently of early environment. One possible explanation is that low leptin level at birth, reported to be associated with low birthweight, is linked to postnatal growth rate [252;253].

Maternal smoking influenced height of cohort members (G2) partly by reducing birthweight, which acted as a mediating factor. Unlike the prenatal findings, where the

relationship between maternal smoking and birthweight was independent of socio-economic conditions in early life [66], the relationship between maternal smoking and height was influenced by socio-economic background. Our results did not provide enough evidence of a direct causal relationship between maternal smoking and final height, yet a smoking related decrement in birthweight is still manifest in childhood. Although the effect of smoking during pregnancy was relatively small compared with the effects of other environmental factors, and children with retarded growth due to maternal smoking had complete catch-up in height by adulthood, the long-term impact of maternal smoking on later health remained to be seen.

There have been suggestions that reduced birthweight and height among children of mothers who smoked during pregnancy are attributable to higher consumption of alcohol, with studies showing that effects due to cigarette exposure are no longer significant after controlling for parental alcohol exposure [149;159;250;254-256]. On the other hand, other evidence showed that smoking and alcohol use during pregnancy had separate and additive effects on birthweight [257;258]. As we have no information on maternal alcohol consumption during pregnancy, we are unable to explore the inter-relationship between smoking and alcohol exposure and their association with postnatal growth.

4.4.4 Family size and household crowding

Family size and level of crowding at 7 are both indicators of socio-economic circumstances in childhood. In Sweden, a study based on samples of 10-year-old Stockholm children born between the 1930s-1960s showed that family size was consistently associated with height [162], with those from larger families tending to be shorter. A previous study of the 1958

cohort showed that boys of families with four or more children were taller than those of one-child families throughout childhood, whereas in girls the effect of family size peaked at age 11 and diminished at age 16. The current study comparing two broad groups (≤ 2 and >2 children per family) revealed a strong association of family size with childhood height and pubertal development; children from smaller families tended to have a faster prepubertal growth rate, matured earlier, and achieved final height earlier than those from larger families, both for boys and girls. Thus the effect of family size was weaker, though remained significant in adulthood.

The mechanism for the effect of family size on height is not clear. It has been suggested that economic factors are responsible [40] and the impact of family size on height is partly dependent on father's social class [259]. The present study showed that the effect of family size on height was marked among children from manual social classes, suggesting that poor growth among children from larger families was mainly the product of economic hardship. Family size operates on growth probably through income: a large family usually has less money available per family member [260]. However, our results showed that family size had an impact on height, independent of other environmental factors. Thus other than the material side of influence, there might be other explanations. For example, children in large families tend to get less individual care and attention, which might have an impact on growth.

Household crowding has a strong influence on growth in height [158]. Our results suggested that over-crowding was associated with slow growth in early childhood, which was in turn linked to late maturity. Subsequently, children lived in over-crowded conditions had a faster growth rate throughout adolescence and continued to grow after the age 16 years.

Thus the relationship was weaker in adulthood (non-significant) after adjusting for early environmental factors. Therefore over-crowding was a good indicator of poor socio-economic conditions in childhood. How over-crowding acts to reduce growth in height is not well understood. One possible explanation is that sleeping disturbance caused by over-crowded conditions may have acted as a mediate factor, which may reduce growth hormone secretion and result in slow growth [261]. It has been suggested that childhood housing conditions, including over-crowding, have an effect on health, distinguishable from the effect of socio-economic deprivation [262].

4.4.5 Parental divorce

A highly stressed environment can lead to growth retardation. Family conflict due to domestic tension, separation and divorce, or desertion during childhood was previously found to be associated with slow growth at 7 in this cohort, independent of socio-economic circumstances [94]. Psychosocial stress is related to slow growth, probably through hormonal disturbances. However, divorce not only causes stress in children, but also results in a sharp drop in household income after the divorce [263]. The current study focused on the impact of parental divorce on the child to adult growth trajectory and showed that among boys, the effect of parental divorce was significant only in childhood and was not affected by early social environment. In contrast, girls of parents who divorced or separated by the age of 7 were persistently shorter than those whose parents did not at all ages, with the relationship stronger in adulthood. The impact of parental divorce on height in girls was attributable to the early social environment. This is in agreement with another study suggesting that slow growth is an indicator of emotional disturbance and chronic stress in childhood only in boys [94]. In our study, for female cohort members whose growth reduction was due to parental

divorce in early life, catch-up growth did not occur, indicating a long-term impact of parental divorce on childhood growth and adult height in females.

Timing of divorce matters. Parental separation or divorce between ages 4 and 7 years was associated with slow growth in childhood and short stature in adulthood among boys, independent of genetic and early environmental factors. Height of boys whose parents divorced before the age of 4 was not affected. Possible explanations are that they were too young to be aware of the conflict or the normal growth resumed when the stress level was reduced after the divorce, which mirrored the evidence reported by the others that children with growth failure showed spontaneous catch-up growth after being removed from stressful home circumstances [264].

How emotion influences growth is not well understood. It is likely that stress or lack of sleeping caused by stress may affect the mount of growth hormone produced, which in turn links to slow growth in childhood [261].

4.4.6 Childhood health

Poor childhood health is associated with trunk length [34], which is a component of body height. Short stature in childhood is also an important indicator of organic disease [265].

A small difference was found at all ages between boys with disability due to illness and those without. There was no evidence of an impact of disability on pubertal development or rate of growth in boys. However, the current study showed that childhood disability had a strong and persistent influence on height of girls throughout the life-course, regardless of

genetic height potential and social environment. Although disability in girls was related to late menarche, it did not seem to have any impact on growth rate. Their growth impairment due to disability were established by age 7 and remained to be short as adults because catch-up growth did not occur. How childhood illness causes the slowing of growth is not clear, but several factors that might explain the mechanism include reduced food intake caused by poor appetite, long-term stress caused by disability, or suppression of normal activity. Furthermore, the inverse association of height and mortality in adulthood could partly be due to the short stature among children with illness in early life.

The reason for the stronger impact of disability in girls is unknown. It is suggested that growth in height is most retarded in the group of most severely disabled children [92]. However, we found no evidence that girls were more severely disabled than boys.

4.4.7 Timing of maturation

Our analyses showed that early maturers were taller at age 7, indicating a fast pre-pubertal growth, both in boys and girls, and were consistent with other studies [130;135]. A positive association between age at menarche and final attained height has been demonstrated by others [266;267]. Within the cohort, we found that although early maturing girls were 1 cm shorter on average than their contemporaries in adulthood, late maturing girls did not differ from average developers. In contrast, late maturing boys were 1 cm short on average than their contemporaries. It seems that age of menarche has altered subsequent growth trajectories in girls.

A positive association between birthweight and age of maturation has been reported [133;134]. dos Santos Silva et al (2002) has suggested that the timing of menarche may be set in utero or infancy, and modified by changes in body size and composition in childhood [135]. However, we did not find any evidence of an influence of fetal growth (i.e. maternal smoking during pregnancy or birthweight) on the timing of menarche in girls or pubertal development in boys. Because height of the cohort was first measured at the age of 7, we were unable to distinguish the association of growth in infancy or early childhood (before age 7), with the age of maturation.

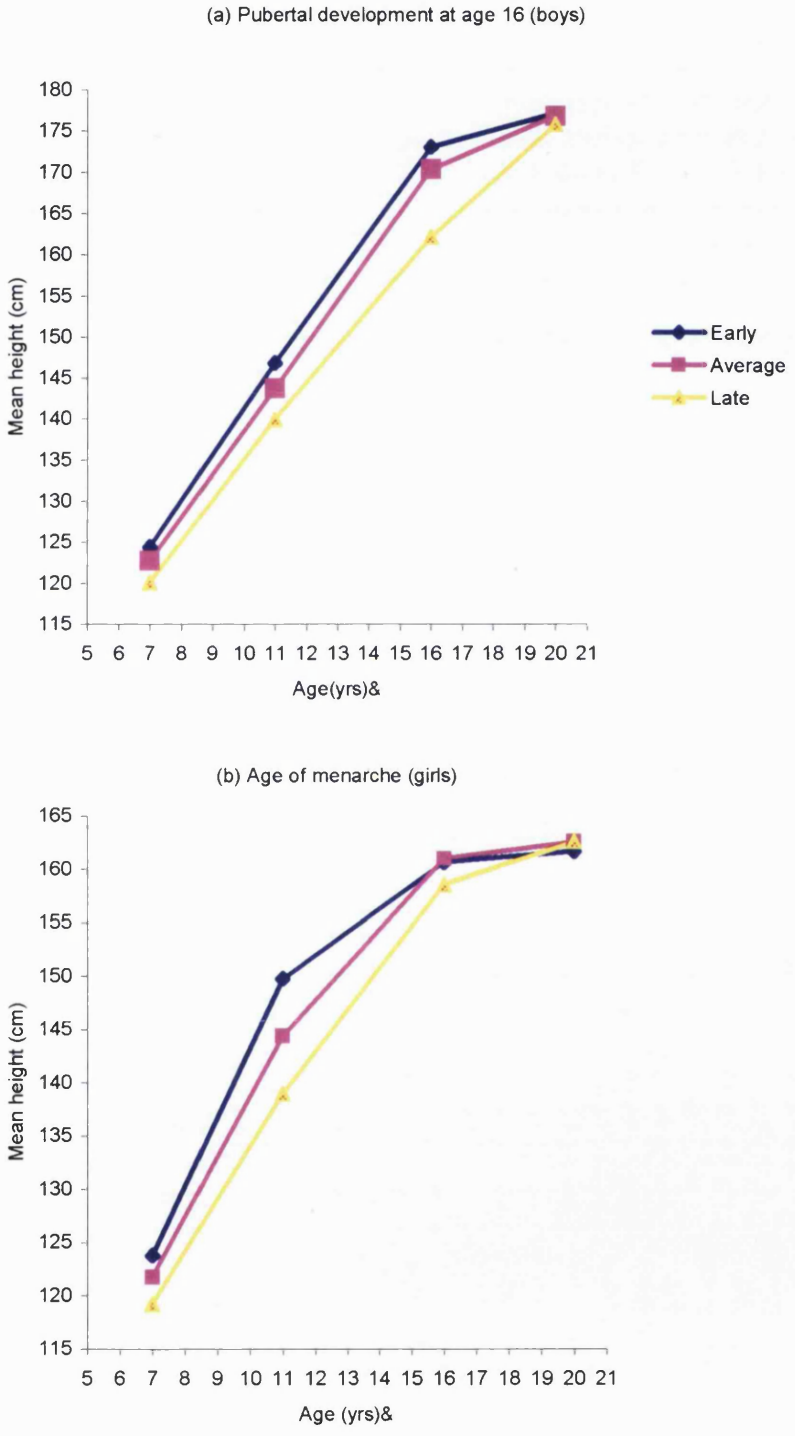
Similar to other studies [46], social class and family size were both found to be associated with age of menarche. Children from manual social class and over-crowded conditions were more likely to delay the onset of puberty than their respective counterparts. Their relationships with pubertal development at age 16 were also evident in boys.

4.5 Conclusions

The environment in which one grows up can have long-term consequences in growth and adult height. We found that genetic factors, early life circumstances (both prenatal and postnatal), and childhood health influenced growth in height, age of maturation and final adult stature. How much growth deficits remained in adult height seemed to depend on the duration and the severity of the insult and also the age at which it occurred [112]. A part of the socio-environmental effect on childhood height was due to differences in growth tempo. In adulthood, the effects of early life conditions on height were somewhat weaker, although

they may remain non-negligible. In particular, children who lived in less favourable conditions tended to have a slower growth rate before the pubertal spurt, matured later and grew for a longer period compared to their counterparts living in more favourable conditions. Thus childhood stature and rate of growth are better indicators for early environment than final adult stature [41]. However, height at a certain age may not be enough in studying the stature-disease relationship; it will be more informative if the growth trajectories and age of maturation are also included.

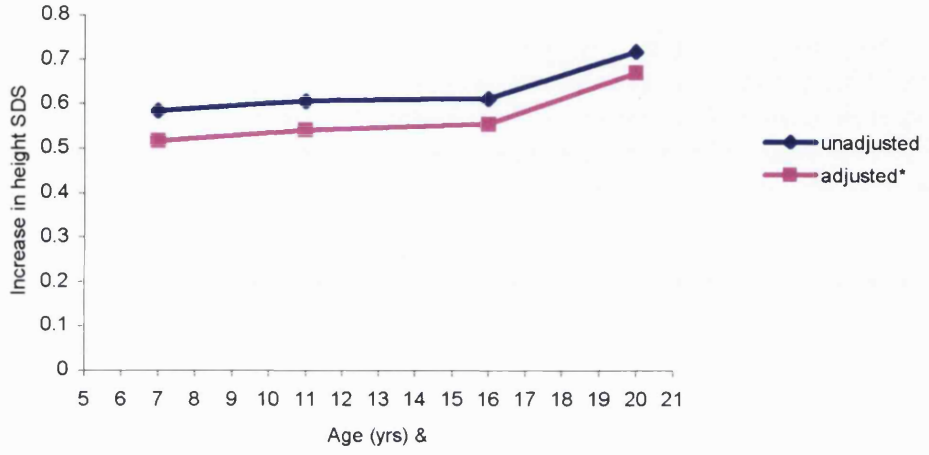
Figure 4.1 Growth trajectories for early, average, and late developers (G2)



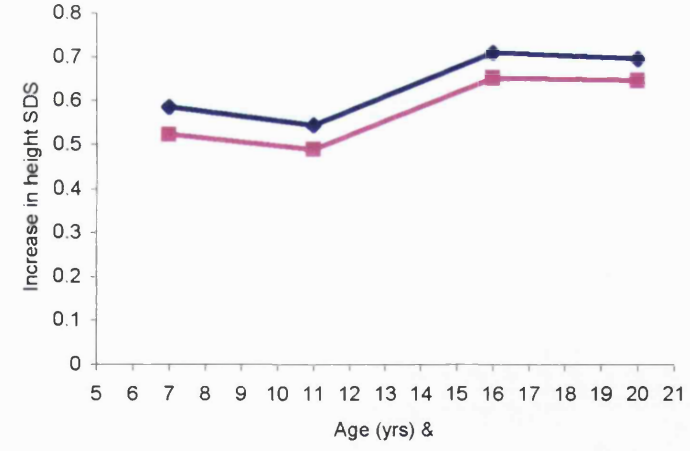
& adult height measured at age 33y and plotted at age 20

Figure 4.2 Change in G2 height SDS for every unit increase of mid-parental height SDS

(a) Boys

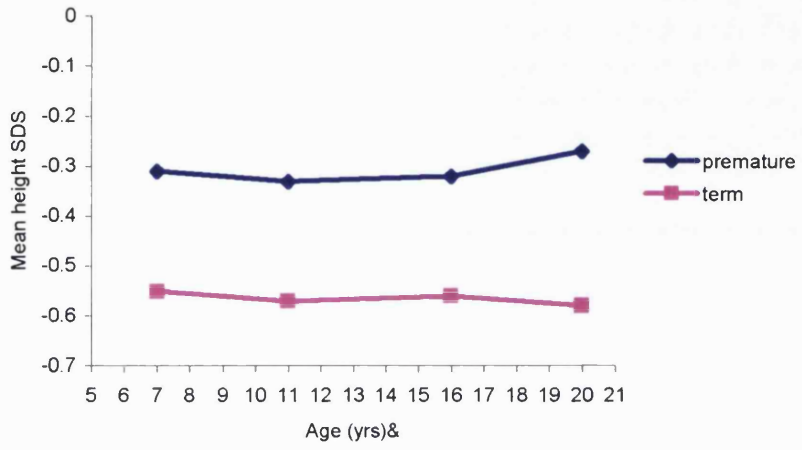


(b) Girls



* adjusted for birthweight, family size and social class
& adult height measured at age 33y and plotted at age 20

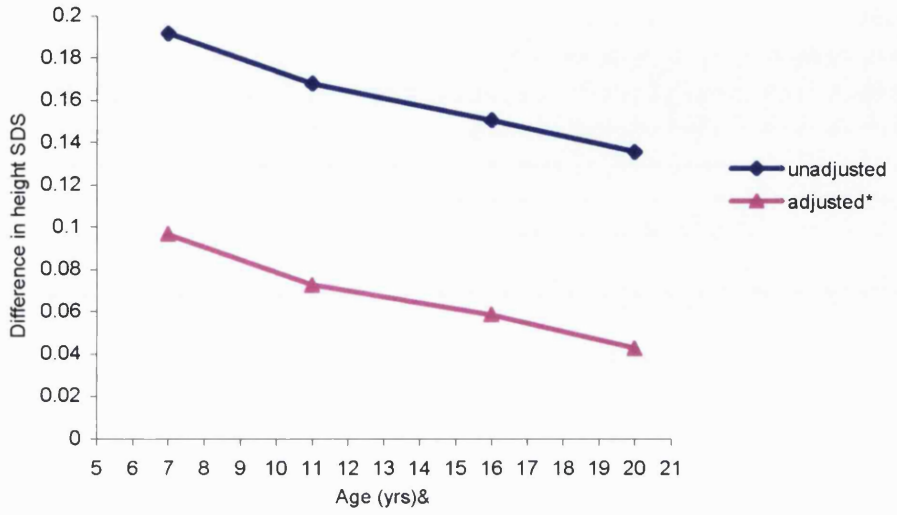
Figure 4.3 Growth for premature and term infants (2-2.5kg) (G2)



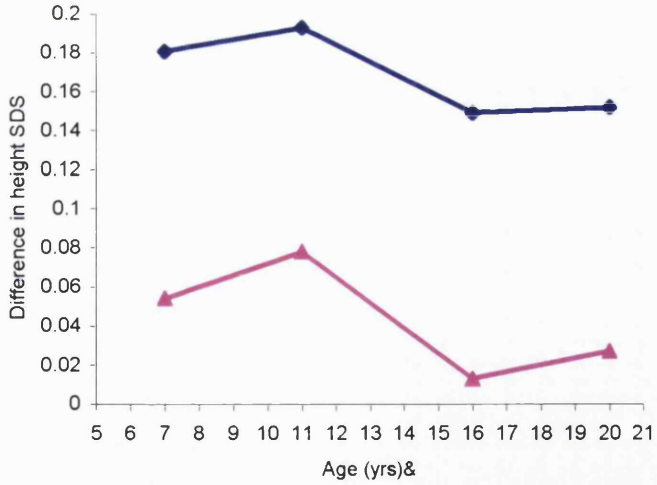
& adult height measured at age 33y and plotted at age 20

Figure 4.4 Difference in growth between children (G2) of non-smoker and smoker mothers

(a) Boys



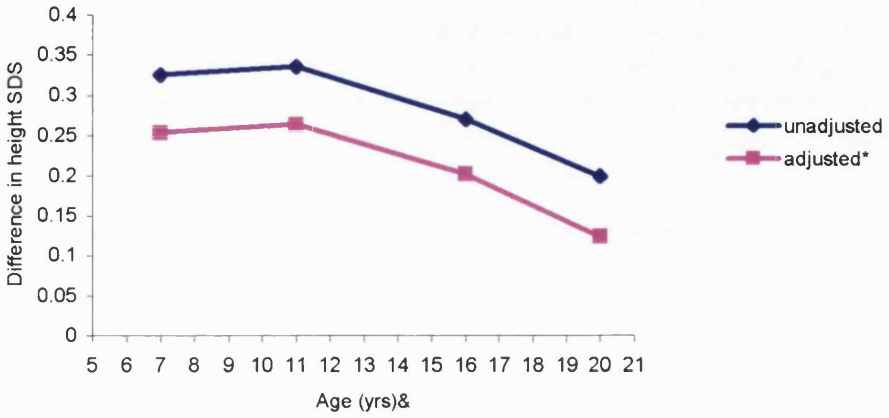
(b) Girls



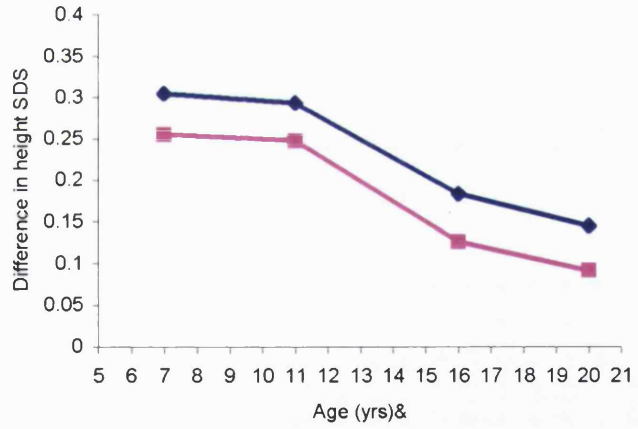
* adjusted for birthweight, family size and social class
& adult height measured at age 33y and plotted at age 20

Figure 4.5 Difference in growth between children (G2) from small (<3) and large (3+) families

(a) Boys

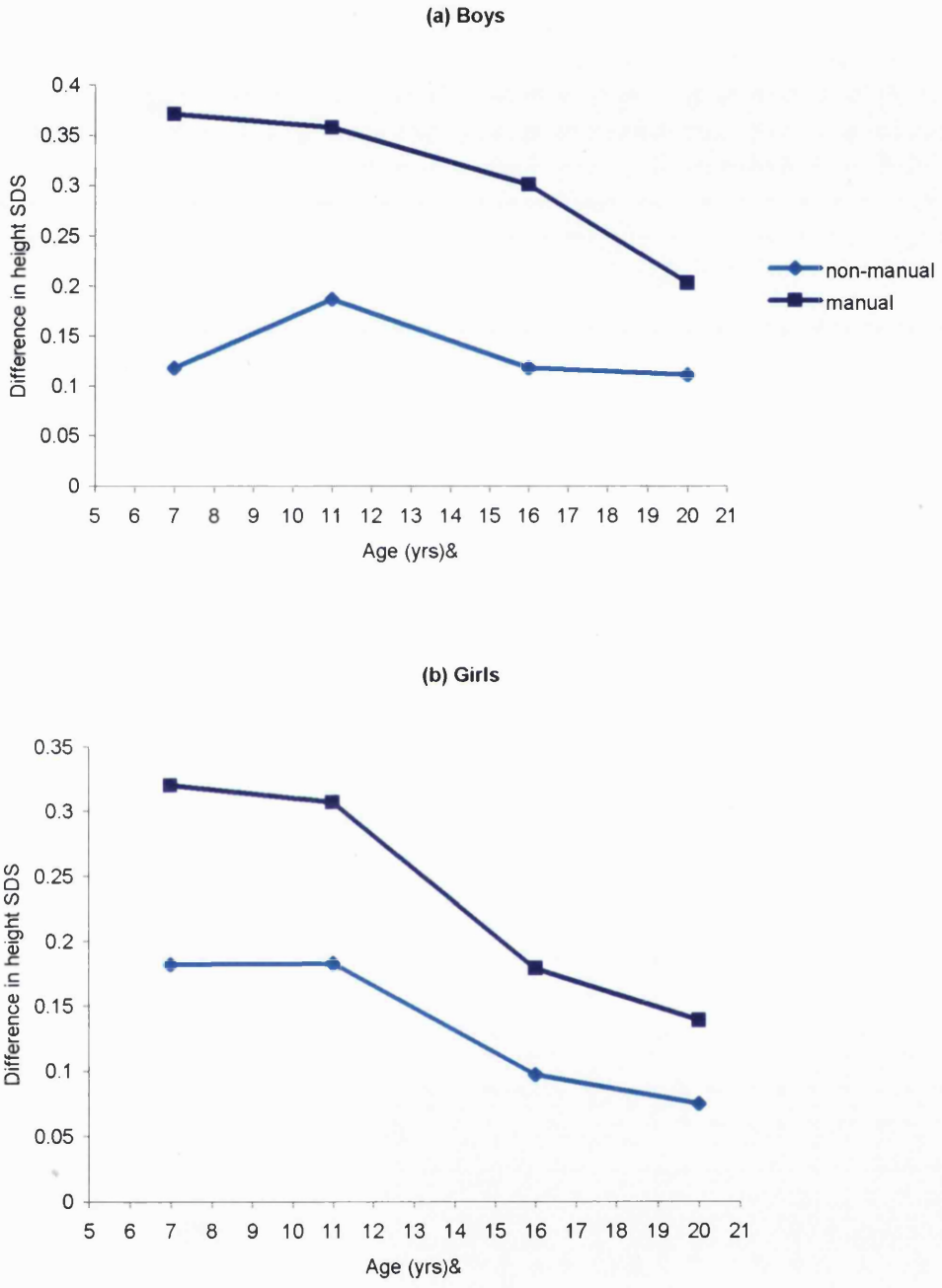


(b) Girls



* adjusted for parental height, birthweight and social class
& adult height measured at age 33y and plotted at age 20

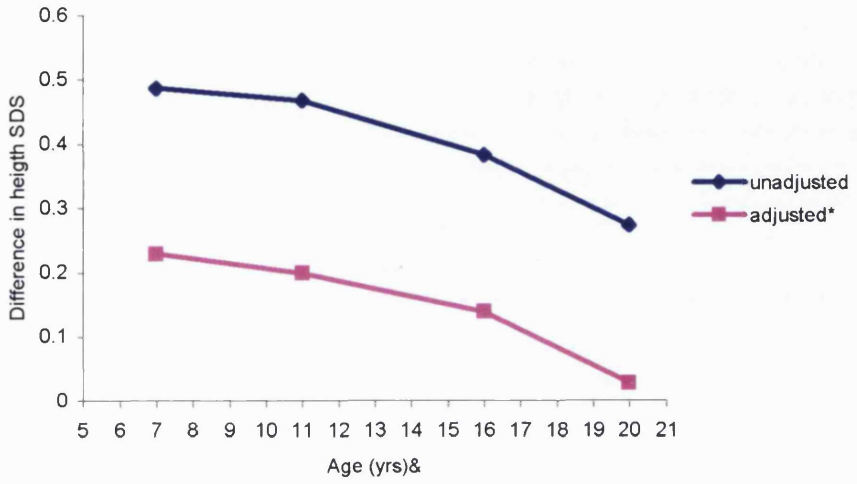
Figure 4.6 Difference in growth between children (G2) from small (<3) and large (3+) families by social class



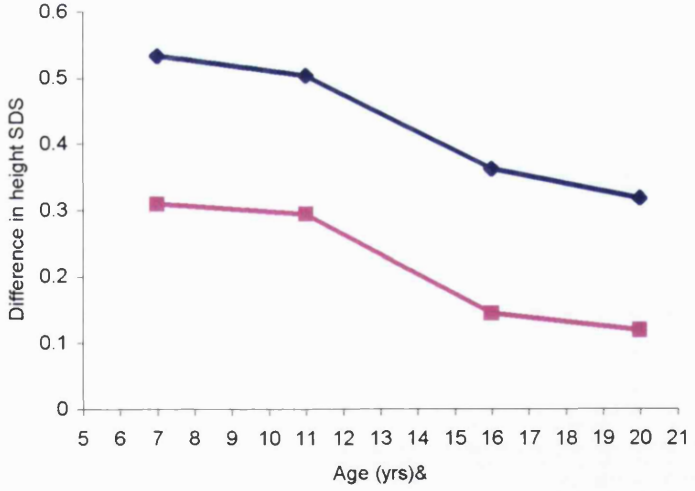
& adult height measured at age 33y and plotted at age 20

Figure 4.7 Difference in growth between children (G2) from uncrowded (<1.5 persons per room) and over-crowded households (1.5+ persons per room)

(a) Boys

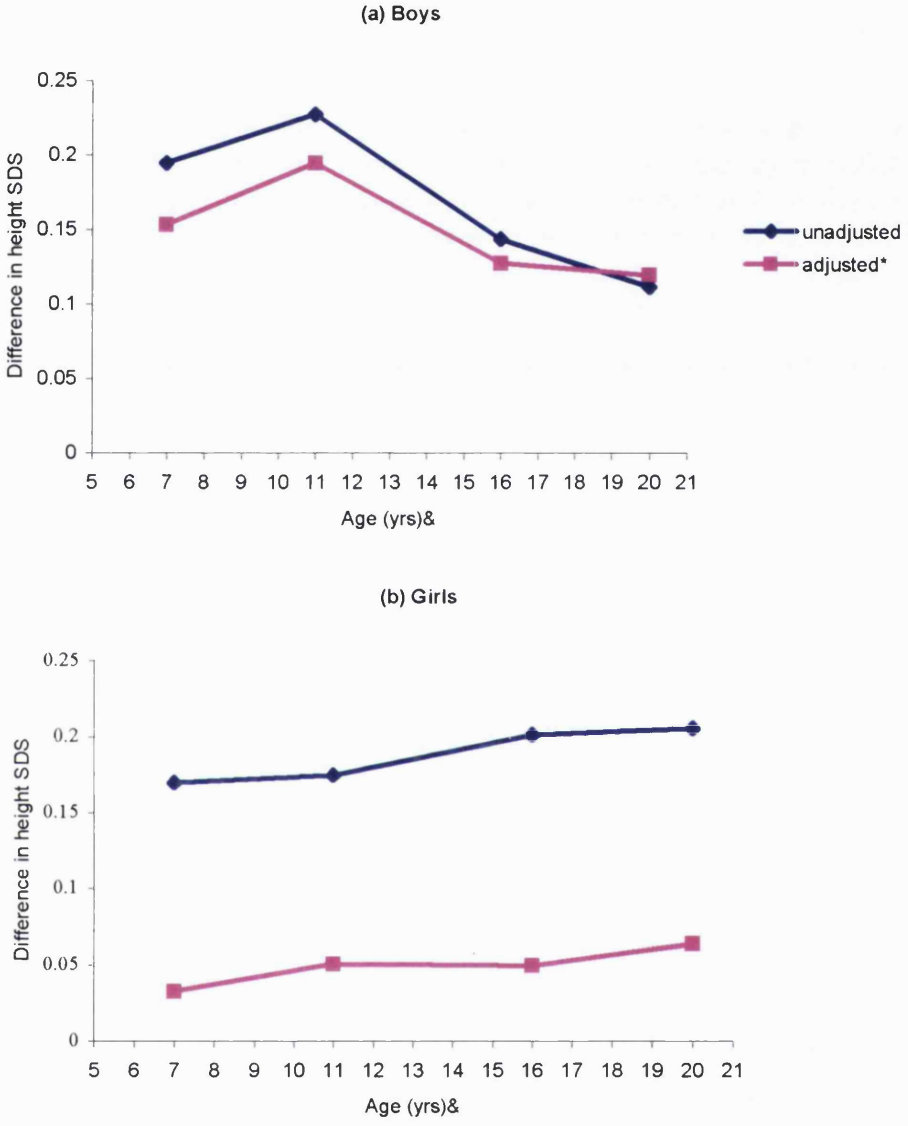


(b) Girls



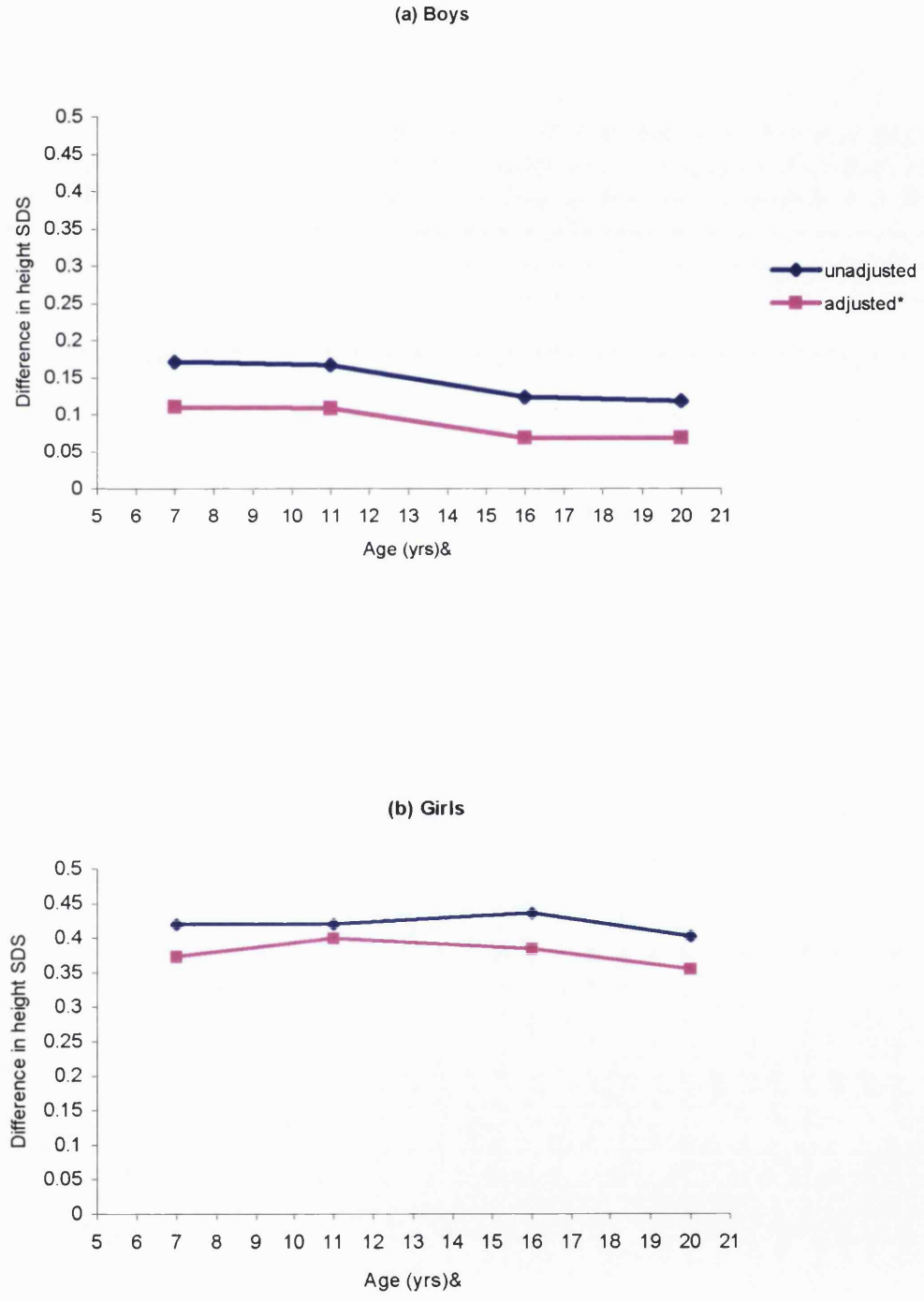
* adjusted for parental height, birthweight, family size and social class
& adult height measured at age 33y and plotted at age 20

Figure 4.8 Difference in growth between children (G2) whose parents did not divorce and children whose parents divorced by age 7



* adjusted for parental height, birthweight, family size and social class
& adult height measured at age 33y and plotted at age 20

Figure 4.9 Difference in growth between children (G2) without and with disability in childhood



* adjusted for parental height, birthweight, family size and social class
& adult height measured at age 33y and plotted at age 20

Chapter 5

A two generation comparison

5.1 Introduction

Height is influenced by a range of early life factors [57;61;85;259;268]. Results from Chapter 4 suggest that adverse conditions during early life have a long-term impact on height, starting in early childhood.

While many studies focus on adult height, it is now recognized that childhood height is a better indicator for early life conditions. Early life factors that influence growth in height may underlie the stature-disease association. Impaired linear growth is found to be associated with increased risk for mortality for coronary heart disease [30]. Study of the association between early life circumstances and childhood height is therefore important for identifying early exposures that may be associated with adult disease risks.

Almost all early life factors investigated in Chapter 4 were based on cohort members' circumstances up to 1965. Our findings on the cohort member generation may not reflect the extent of the early life influences on height in the current population [152]. In Britain, the secular trends in height continued [117], with an increase of more than 1 cm among English children and more than 2 cm among Scottish children between 1972 and 1994 [99], which are attributable to the increasing maternal age and the improvement of social and material

conditions [119]. Changes of early life influences on growth in height have been reported in several populations [162;269]. Greater secular trends among children from poorer socio-economic backgrounds have also been reported in some studies, which may be an indication of the improvement of health and welfare in recent years [87;151].

Evidence on the changes of associations between early environmental factors and height over time is sparse. The 1958 birth cohort including height and childhood conditions on their offspring provides a unique opportunity to evaluate the changing role of early life factors on height across two generations and the strength of the recent relationships. This information will provide insight of the risk factors for adult health outcomes for the future adult population.

Objectives

The aim of this chapter is to investigate influences of a range of factors such as parental height, maternal smoking during pregnancy, birthweight, breastfeeding, maternal age at childbirth, family size (divided into two components: birth order, number of younger siblings), social class, maternal education, housing tenure, household crowding, parental divorce, and disability in childhood on height in each generation to determine whether factors which affected the height of cohort members (G2) also influenced the height of their offspring (G3).

The specific aims are

i) to examine the association between each factor and height in cohort members (G2) and their offspring (G3) with and without taking account of other factors; and

ii) to explore whether these relationships have changed between two generations (G2 and G3).

5.2 Methods and measures

Detailed descriptions of response and explanatory variables used in this chapter are given in §2.3. A summary of these measures is shown in Table 5.1.

Externally derived height SDS based on the 1990 British growth reference (§2.4.2) was used for G2 and G3 to compare early life influences on height between two generations. These scores can easily be converted to height (cm) for a given age and sex using the formula (2.1) or for simplicity for 7 year or adult height using the conversion table (2.6) in §2.4.2.

Table 5.1 Summary of variables used in Chapter 5

Cohort members (G2)	Offspring (G3)
Outcome variables	
Height SDS at 7y	Height SDS (at 4-18y)
Parental factors	
Mid-parent height SDS	Parental height SDS (mother or father)
Fetal and early (infancy) factor	
Maternal smoking during pregnancy: non-smoker <1/day, medium smoker 1-9/day, variable smoker, and heavy smoker 10+/day	Maternal smoking during pregnancy: non-smoker <1/day, medium smoker 1-9/day, and heavy smoker 10+/day
Birthweight (kg)	Birthweight (kg)
Breastfeeding: never/ever	Breastfeeding: never/ever
Childhood environmental factors	
Birth order: 1^{st}, 2^{nd}, 3^{rd}+	Birth order: 1^{st}, 2^{nd}, 3^{rd}+
Number of younger siblings (at 7y): 0-1, 2, 3+	Number of younger siblings (4-18y): 0-1, 2, 3+
Maternal age at childbirth	Maternal age at childbirth
Social class based on father's occupation (at 7y): I&II, IIINM, IIIM, IV&V	Social class based on father's occupation (4-18): I&II, IIINM, IIIM, IV&V
Housing tenure (at 7y): Owner, private rental, council rental	Housing tenure (4-18y): Owner, private rental, council rental
Crowding (at 7y): <1, 1-1.5, >1.5 per room	Crowding (4-18y): <1, 1-1.5, >1.5 per room
Parental divorce/separation (by 7y): 0-3y, 4-7y, no divorce by 7y	Parental divorce/separation (4-18y): 0-3y, 4-7y, no divorce by 7y
Mother's education: did/did not stay after minimum school-leaving age	Mother's education: no education, <O-level, O-level, A-level or higher
Disability (at 7y): yes/no	Disability (4-18y): yes/no

Mid-parental height (SDS) was derived for each cohort member (G2) as the average of paternal and maternal height (SDS) based on the 1990 British growth reference (§2.4.2). Since height SDS is sex and age adjusted, and no marked difference was found between the father-child (0.44) and mother-child (0.42) correlation, the height SDS of the cohort member at age 33 based on the same reference was used as a parental height measure for the offspring (G3) because the other parent was not measured.

The interaction of sex with each of the explanatory variables was examined and found to be non-significant except for the interaction of sex with disability in G2 and with housing tenure in G3. Males and females were therefore combined and the sex of the subject was included as a covariate in all models. As relationships investigated were likely to be confounded by maternal age due to the selection of offspring, which was based on the age of cohort members, the age of the child was adjusted in all analyses concerning G3.

As described in Chapter 3, the height measures between individuals (G2 and G3) from the same family were correlated, two-level models described in §3.3.2, where individuals were defined as "level-1" units and families as "level-2" units, were applied here to explore the associations between early life factors and childhood height in two generations.

We fitted the data with model (3.9), containing age, sex, and one of the early life factors. The adjusted association between each factor and height SDS was also examined by first adding parental height, and then fetal and infant factors (maternal smoking, birthweight, and breastfeeding). Given that some of the early life factors were inter-correlated, in the final model we included all early life factors of interest to assess whether the influence of each factor on height was independent of other factors. The estimates of fixed parameters

from the two-level models (adjusted and unadjusted) that represent associations between early life factors and height (SDS) for each generation are shown in Tables 5.3 and 5.4, respectively. Using these models we further explored changes of these relationships between the two generations. The significance levels of these changes are given in Table 5.7.

Since height was only available for one parent of G3, maternal height and paternal height were also analysed separately to compare the genetic influences on height between the two generations.

The sample used in this chapter includes a total of 10455 subjects with complete information on the response variables and all the covariates. Among them 7993 subjects were cohort members (G2) and 2462 subjects were offspring (G3). Separate analyses have also been conducted using all subjects with information available (i.e. complete information on childhood height, confounding factors used in the model and the factor of interest) and the differences in results were found to be small (data not presented). Hence all the results presented here were based on the sample with complete data (study sample).

5.3 Results

As shown in Table 5.2, the offspring (G3) were taller on average than their parents generation (G2) by a height SDS of 0.19 (1.0 cm) in childhood, but they were not heavier at the time of birth. Maternal age at childbirth was younger for G3 (24.5 years) than for G2 (27.6 years). There has been a slight decrease in breastfeeding, from 70% in G2 to 65% in G3.

Housing conditions have shown an improvement in the offspring generation (G3), with 6% of G3 living in over-crowded accommodation (>1.5 persons per room) compared to 17.4% of G2. A majority (74.5%) of G3 were living in owner-occupied accommodation compared to 44.5% of G2. The social class distribution has also changed between 1965 and 1991, with the general trend of upward mobility. The proportion of children from classes I&II increased from 21.3% in G2 to 31.9% in G3. There were more first-borns children in G3 than in G2 (59.1% vs 37.3%), while the proportions of third or later born children (9.8% vs 30.4%) and children with three or more younger siblings (3.6% vs 7.1%) were smaller in G3 compared to G2, possibly as a product of the sample selection (i.e. cohort members had children at older ages were not included).

The proportion of children who experienced parental separation or divorce has increased dramatically over the two generations, from 2.8% in G2 to 13.6% in G3. Apart from an increase in divorce in recent years in Britain [185], some of the increase might be explained by the fact that the sample in G3 were on average older with a wider age range (4-18y) than

G2, even though parents were on average younger in G3. Therefore the length of the exposure period is different in the two generations.

Table 5.2 Descriptive characteristics for cohort members (G2) and their offspring (G3)

Variables	Category	G2 (*n*=7993)	G3 (*n*=2462)
Age at height measurement (mean (range))		7.3(7-8.5)	8.1(4-18)
Sex (%)	Males	48.9	49.1
Response-height SDS (mean (s.d.))		-0.19(1.07)	-0.003(1.05)
Maternal height SDS (mean (s.d.))		-0.42(1.04)	-0.25(1.03)†
Paternal height SDS (mean (s.d.))		-0.52(1.07)	-0.22(0.99)‡
Parental height SDS (mean (s.d.))			-0.24(1.02)
Mid-parental height SDS (mean (s.d.))		-0.47 (0.86)	
Maternal smoking (%)	None	68.3	70.8
	Median	14.7	8.7
	Variable	5.5	
	Heavy	11.5	20.4
Birthweight (mean in grams)	Boys	3420	3360
	Girls	3270	3260
Breastfeeding (%)	Ever	70.2	64.8
Maternal age (mean (range))		27.6(15-46)	24.5(15-38)
Birth order (%)	1st	37.3	59.1
	2nd	32.4	31.1
	3rd+	30.3	9.8
No. of younger siblings (%)	0-1	77.5	80.9
	2	15.5	15.5
	3+	7.1	3.6
Social class (%)	I&II	21.3	31.9
	IIINM	10.5	12.2
	IIIM	45.4	33.9
	IV&V	22.8	22.0
Maternal education (%)	Did not stay ©	73.8	
	Stayed ©	26.2	
	No education		13.4†
	<O-level		20.6†
	O-level		38.6†
	A-level		9.9†
	Higher (degree/equivalent)		17.5†
Housing tenure (%)	Owner	44.5	74.5
	Private rental	17.1	4.2
	Social housing	38.4	21.2
No. of inhabitants/room (mean (range))		1.11(0.2-5)	0.96(0.3-4)
Crowding (%)	< 1 person/room	34.8	45.3
	1-1.5 persons/room	47.8	48.7
	>1.5 person/room	17.4	6.0
Parental divorce/separation (%)	Yes	2.8	13.6
Childhood disability (%)	Yes	4.4	4.5

† children of female cohort members only (*n*=1580)
‡ children of male cohort members only (*n*=882)
© whether the mother stayed after minimum school-leaving age

Table 5.3 Estimated mean differences (s.e.) in height SDS at 7 (G2) by parental height and early life factors (*N*=7993)

	Height SDS at 7 (G2)							
	Model (1)		Model (2)		Model (3)		Model (4)	
	β(se)	*p*	*β*(se)	*p*	*β*(se)	*p*	*β*(se)	*p*
Sex male (3912)	0.04(0.02)	0.05	-0.01(0.02)	0.65	-0.01(0.02)	0.65	-0.01(0.02)	0.50
Parental height SDS†	0.56(0.01)	<0.001	-	-	0.51(0.01)	<0.001	0.48(0.01)	<0.001
Maternal height SDS‡	0.39(0.01)	<0.001	0.32(0.01)	<0.001	0.35(0.01)	<0.001	0.32(0.01)	<0.001
Paternal height SDS‡	0.35(0.01)	<0.001	0.28(0.01)	<0.001	0.33(0.01)	<0.001	0.29(0.01)	<0.001
Maternal smoking								
None (5461)	-	-	-	-	-	-	-	-
Median (1613)	-0.17(0.03)	<0.001	-0.13(0.03)	<0.001	-0.08(0.03)	<0.01	-0.03(0.03)	0.30
Heavy/variable (919)	-0.24(0.04)	<0.001	-0.21(0.03)	<0.001	-0.14(0.03)	<0.001	-0.06(0.03)	0.05
Birthweight (kg)	0.51(0.02)	<0.001	0.37(0.02)	<0.001	0.35(0.02)	<0.001	0.37(0.02)	<0.001
Breastfeeding								
Never breastfed (2383)	-0.15(0.03)	<0.001	-0.09(0.02)	<0.001	-0.06(0.02)	0.01	-0.04(0.02)	0.11
Breastfed (5610)	-	-	-	-	-	-	-	-
Maternal age (y)								
Age	0.008(0.002)	<0.001	0.010(0.002)	<0.001	0.009(0.002)	<0.001	0.015(0.002)	<0.001
Birth order								
Ist (2983)	0.32(0.03)	<0.001	0.23(0.03)	<0.001	0.28(0.03)	<0.001	0.32(0.03)	<0.001
2nd (2588)	0.27(0.03)	<0.001	0.16(0.03)	<0.001	0.17(0.03)	<0.001	0.17(0.03)	<0.001
3rd or more (2422)	-	-	-	-	-	-	-	-
Younger siblings								
No/One (6193)	-	-	-	-	-	-	-	-
Two (1235)	-0.17(0.03)	<0.001	-0.16(0.03)	<0.001	-0.15(0.05)	<0.001	-0.11(0.03)	<0.001
Three or more (565)	-0.37(0.05)	<0.001	-0.32(0.04)	<0.001	-0.31(0.04)	<0.001	-0.17(0.04)	<0.001
Social class								
I&II (1700)	0.39(0.04)	<0.001	0.20(0.03)	<0.001	0.17(0.03)	<0.001	0.03(0.03)	0.32
IIINM (837)	0.33(0.04)	<0.001	0.17(0.04)	<0.001	0.14(0.04)	<0.001	0.02(0.04)	0.68
IIIM (3633)	0.10(0.03)	<0.01	0.04(0.03)	0.11	0.04(0.03)	0.14	0.001(0.03)	0.99
IV&V (1823)	-	-	-	-	-	-	-	-
Housing tenure								
Owner (3558)	0.37(0.03)	<0.001	0.23(0.02)	<0.001	0.21(0.02)	<0.001	0.08(0.03)	<0.001
Private rental (1367)	0.19(0.03)	<0.001	0.12(0.03)	<0.001	0.12(0.03)	<0.001	0.07(0.03)	0.03
Social housing (3068)	-	-	-	-	-	-	-	-
Crowding								
<1 person/room (2781)	0.65(0.03)	<0.001	0.46(0.03)	<0.001	0.45(0.03)	<0.001	0.22(0.04)	<0.001
1-1.5(3823)	0.41(0.03)	<0.001	0.30(0.03)	<0.001	0.30(0.03)	<0.001	0.18(0.03)	<0.001
> 1.5 persons/room (1389)	-	-	-	-	-	-		-
Parental divorce								
Yes (220)	-0.20(0.07)	<0.01	-0.19(0.07)	<0.01	-0.15(0.06)	0.02	-0.08(0.06)	0.19
No (7773)	-	-	-	-	-	-	-	-
Maternal education								
Did not stay (5879)	-0.22(0.03)	<0.001	-0.08(0.02)	<0.01	-0.05(0.02)	0.03	0.03(0.03)	0.23
Stayed after minimum education (2086)	-	-	-	-	-	-	-	-
Disability at age 7								
Yes (348)	-0.24(0.06)	<0.001	-0.22(0.05)	<0.001	-0.19(0.05)	<0.001	-0.14(0.05)	<0.01
No (7645)	-	-	-	-	-	-	-	-

† the average of maternal and paternal height SDS

‡ Model (2) is adjusted for height of the other parent

Model adjustment

(1)adjusted only for sex

(2)adjusted for (1) and mid-parental height

(3)adjusted for (2) and fetal and infancy factors (maternal smoking, birthweight, breastfeeding)

(4)adjusted for (3) and all early life factors (maternal age, birth order, younger siblings, social class, housing tenure, crowding, maternal education, parental divorce, and childhood disability)

Table 5.3 (a) Estimated mean differences (s.e.) in height SDS at 7 (G2 males) by parental height and early life factors (*N*=3912)

	Height SDS at 7 (G2)							
	Model (1)		Model (2)		Model (3)		Model (4)	
	β(se)	*p*	β(se)	*p*	β(se)	*p*	β(se)	*p*
Parental height†	0.54(0.02)	<0.001	-	-	0.50(0.02)	<0.001	0.46(0.02)	<0.001
Maternal smoking								
None	-	-	-	-	-	-	-	-
Median	-0.22(0.04)	<0.001	-0.17(0.04)	<0.001	-0.12(0.04)	<0.001	-0.07(0.04)	0.05
Heavy/variable	-0.22(0.05)	<0.001	-0.22(0.05)	<0.001	-0.15(0.05)	<0.001	-0.07(0.05)	0.12
Birthweight (kg)	0.52(0.03)	<0.001	0.37(0.03)	<0.001	0.35(0.03)	<0.001	0.37(0.03)	<0.001
Breastfeeding								
Never breastfed	-0.17(0.05)	<0.001	-0.12(0.03)	<0.001	-0.09(0.03)	0.01	-0.06(0.03)	0.08
Breastfed	-	-	-	-	-	-	-	-
Maternal age (y)								
Age	0.008(0.003)	<0.001	0.010(0.003)	<0.001	0.008(0.003)	<0.001	0.014(0.003)	<0.001
Birth order								
Ist	0.48(0.05)	<0.001	0.36(0.04)	<0.001	0.39(0.04)	<0.001	0.28(0.05)	<0.001
2nd	0.37(0.04)	<0.001	0.25(0.04)	<0.001	0.23(0.04)	<0.001	0.14(0.04)	<0.001
3rd or more	-	-	-	-	-	-	-	-
Younger siblings								
No/One	-	-	-	-	-	-	-	-
Two	-0.19(0.05)	<0.001	-0.17(0.04)	<0.001	-0.16(0.04)	<0.001	-0.12(0.04)	<0.001
Three or more	-0.47(0.07)	<0.001	-0.41(0.06)	<0.001	-0.40(0.06)	<0.001	-0.27(0.06)	<0.001
Social class								
I&II	0.42(0.05)	<0.001	0.21(0.05)	<0.001	0.18(0.05)	<0.001	0.05(0.05)	0.28
IIINM	0.35(0.06)	<0.001	0.18(0.06)	<0.001	0.14(0.06)	<0.001	0.03(0.06)	0.58
IIIM	0.11(0.04)	<0.01	0.06(0.04)	0.13	0.05(0.04)	0.16	0.02(0.04)	0.65
IV&V	-	-	-	-	-	-	-	-
Housing tenure								
Owner	0.38(0.04)	<0.001	0.25(0.03)	<0.001	0.22(0.03)	<0.001	0.10(0.04)	0.01
Private rental	0.24(0.05)	<0.001	0.16(0.04)	<0.001	0.15(0.04)	<0.001	0.10(0.04)	0.02
Social housing	-	-	-	-	-	-	-	-
Crowding								
<1 person/room	0.68(0.05)	<0.001	0.46(0.04)	<0.001	0.45(0.04)	<0.001	0.19(0.06)	<0.001
1-1.5	0.43(0.05)	<0.001	0.29(0.04)	<0.001	0.29(0.04)	<0.001	0.15(0.05)	<0.001
> 1.5 persons/room	-	-	-	-	-	-		-
Parental divorce								
Yes	-0.21(0.10)	0.04	-0.21(0.09)	0.03	-0.17(0.09)	0.06	-0.11(0.09)	0.21
No	-	-	-	-	-	-	-	-
Disability at age 7								
Yes	-0.20(0.08)	0.01	-0.15(0.07)	0.03	-0.11(0.07)	0.11	-0.08(0.07)	0.25
No	-	-	-	-	-	-	-	-

† the average of maternal and paternal height SDS

Model adjustment

(1)unadjusted

(2)adjusted for (1) and mid-parental height

(3)adjusted for (2) and fetal and infancy factors (maternal smoking, birthweight, breastfeeding)

(4)adjusted for (3) and all early life factors (maternal age, birth order, younger siblings, social class, housing tenure, crowding, maternal education, parental divorce, and childhood disability)

Table 5.3 (b) Estimated mean differences (s.e.) in height SDS at 7 (G2 females) by parental height and early life factors (*N*=4081)

	Height SDS at 7 (G2)							
	Model (1)		Model (2)		Model (3)		Model (4)	
	β(se)	*p*	*β*(se)	*p*	*β*(se)	*p*	*β*(se)	*p*
Parental height†	0.57(0.02)	<0.001	-	-	0.53(0.01)	<0.001	0.50(0.02)	<0.001
Maternal smoking								
None	-	-	-	-	-	-	-	-
Median	-0.14(0.04)	<0.001	-0.09(0.04)	0.02	-0.03(0.04)	0.36	0.02(0.04)	0.62
Heavy/variable	-0.27(0.05)	<0.001	-0.20(0.05)	<0.001	-0.13(0.05)	<0.01	-0.06(0.05)	0.21
Birthweight (kg)	0.52(0.03)	<0.001	0.36(0.03)	<0.001	0.34(0.03)	<0.001	0.39(0.03)	<0.001
Breastfeeding								
Never breastfed	-0.14(0.04)	<0.001	-0.08(0.03)	0.02	-0.05(0.03)	0.11	-0.02(0.03)	0.53
Breastfed	-	-	-	-	-	-	-	-
Maternal age (y)								
Age	0.008(0.003)	<0.001	0.009(0.003)	<0.001	0.008(0.003)	<0.001	0.017(0.003)	<0.001
Birth order								
Ist	0.49(0.05)	<0.001	0.39(0.04)	<0.001	0.46(0.04)	<0.001	0.36(0.04)	<0.001
2nd	0.36(0.04)	<0.001	0.24(0.04)	<0.001	0.27(0.04)	<0.001	0.20(0.04)	<0.001
3rd or more	-	-	-	-	-	-	-	-
Younger siblings								
No/One	-	-	-	-	-	-	-	-
Two	-0.17(0.05)	<0.001	-0.15(0.04)	<0.001	-0.14(0.04)	<0.001	-0.09(0.04)	0.04
Three or more	-0.29(0.07)	<0.001	-0.24(0.06)	<0.001	-0.22(0.06)	<0.001	-0.08(0.06)	0.20
Social class								
I&II	0.37(0.05)	<0.001	0.17(0.05)	<0.001	0.15(0.05)	<0.001	0.02(0.05)	0.70
IIINM	0.31(0.06)	<0.001	0.16(0.06)	<0.01	0.13(0.05)	0.02	0.01(0.05)	0.92
IIIM	0.09(0.04)	0.03	0.04(0.04)	0.31	0.03(0.04)	0.41	-0.02(0.04)	0.68
IV&V	-	-	-	-	-	-	-	-
Housing tenure								
Owner	0.36(0.04)	<0.001	0.21(0.03)	<0.001	0.20(0.03)	<0.001	0.06(0.04)	0.08
Private rental	0.15(0.05)	<0.001	0.09(0.04)	0.03	0.10(0.04)	<0.01	0.03(0.04)	0.46
Social housing	-	-	-	-	-	-	-	-
Crowding								
<1 person/room	0.63(0.05)	<0.001	0.45(0.04)	<0.001	0.45(0.04)	<0.001	0.25(0.05)	<0.001
1-1.5	0.41(0.05)	<0.001	0.33(0.04)	<0.001	0.33(0.04)	<0.001	0.22(0.04)	<0.001
> 1.5 persons/room	-	-	-	-	-	-	-	-
Parental divorce								
Yes	-0.15(0.10)	0.13	-0.12(0.09)	0.18	-0.08(0.09)	0.37	-0.04(0.09)	0.63
No	-	-	-	-	-	-	-	-
Disability at age 7								
Yes	-0.31(0.09)	<0.001	-0.30(0.08)	<0.001	-0.29(0.08)	<0.001	-0.24(0.08)	<0.01
No	-	-	-	-	-	-	-	-

† the average of maternal and paternal height SDS

Model adjustment

(1)unadjusted

(2)adjusted for (1) and mid-parental height

(3)adjusted for (2) and fetal and infancy factors (maternal smoking, birthweight, breastfeeding)

(4)adjusted for (3) and all early life factors (maternal age, birth order, younger siblings, social class, housing tenure, crowding, maternal education, parental divorce, and childhood disability)

Table 5.4 Estimated mean differences (s.e.) in height SDS (G3) by parental height and early life factors (*N*=2462)

	Height SDS (G3)							
	Model (1)		Model (2)		Model (3)		Model (4)	
	β (se)	p	*β* (se)	p	*β* (se)	P	*β* (se)	*p*
Sex male (1210)	-0.04(0.04)	0.35	-0.06(0.04)	0.11	-0.06(0.04)	0.10	-0.06(0.04)	0.17
Parental height*	0.44(0.02)	<0.001	-	-	0.42(0.02)	<0.001	0.42(0.02)	<0.001
Maternal height SDS†	0.43(0.02)	<0.001			0.41(0.02)	<0.001	0.40(0.02)	<0.001
Paternal height SDS‡	0.47(0.03)	<0.001			0.44(0.03)	<0.001	0.46(0.03)	<0.001
Maternal smoking								
None (1744)	-	-	-	-	-	-	-	-
Median (215)	0.03(0.07)	0.68	0.05(0.07)	0.51	0.08(0.07)	0.26	0.09(0.07)	0.21
Heavy (503)	-0.08(0.06)	0.14	-0.08(0.05)	0.15	-0.04(0.05)	0.47	-0.01(0.05)	0.84
Birthweight(kg)	0.32(0.04)	<0.001	0.27(0.04)	<0.001	0.27(0.04)	<0.001	0.28(0.04)	<0.001
Breastfeeding								
Never breastfed (867)	-0.03(0.04)	0.55	-0.02(0.04)	0.61	0.00(0.04)	0.96	0.02(0.03)	0.56
Ever breastfed (1594)	-	-	-	-	-	-	-	-
Maternal age (y)	0.004(0.006)	0.52	0.001(0.006)	0.82	0.001(0.006)	0.87	0.003(0.006)	0.68
Birth order								
Ist (1454)	0.24(0.07)	<0.001	0.21(0.07)	<0.01	0.24(0.07)	<0.001	0.26(0.07)	<0.001
2nd (767)	0.19(0.07)	<0.01	0.16(0.07)	0.02	0.17(0.07)	0.01	0.17(0.07)	0.01
3rd or more (241)	-	-	-	-	-	-	-	-
Younger siblings								
No/one (1992)	-	-	-	-	-	-	-	-
Two (381)	-0.09(0.05)	0.10	-0.07(0.05)	0.16	-0.07(0.05)	0.19	-0.12(0.06)	0.04
Three or more (89)	-0.12(0.11)	0.26	-0.11(0.10)	0.28	-0.09(0.10)	0.39	-0.14(0.11)	0.21
Social class								
I&II (785)	0.05(0.06)	0.43	0.01(0.06)	0.87	-0.01(0.06)	0.88	-0.05(0.06)	0.40
IIINM (301)	0.09(0.08)	0.27	0.03(0.07)	0.73	-0.02(0.07)	0.74	-0.04(0.07)	0.58
IIIM (835)	0.003(0.06)	0.96	-0.02(0.06)	0.69	-0.04(0.06)	0.52	-0.05(0.06)	0.39
IV&V (541)	-	-	-	-	-	-	-	-
Housing tenure								
Owner (1835)	0.15(0.06)	<0.01	0.15(0.05)	<0.001	0.14(0.05)	<0.01	0.13(0.06)	0.02
Private rental (104)	0.33(0.12)	<0.01	0.26(0.11)	0.01	0.25(0.11)	0.02	0.24(0.11)	0.03
Social housing (523)	-	-	-	-	-	-	-	-
Crowding								
< 1 person/room (1115)	0.30(0.10)	<0.01	0.19(0.10)	0.06	0.17(0.10)	0.08	-0.02(0.11)	0.80
1-1.5 persons/room (1199)	0.22(0.10)	0.04	0.12(0.10)	0.21	0.12(0.10)	0.22	-0.02(0.10)	0.84
> 1.5 persons/room (148)	-	-	-	-	-	-	-	-
Parental divorce								
Yes (334)	0.05(0.06)	0.65	0.05(0.06)	0.41	0.07(0.06)	0.26	0.08(0.06)	0.21
No (2128)	-	-	-	-	-	-	-	-
Maternal education†								
<A-level (1124)	-0.05(0.07)	0.11	0.03(0.06)	0.75	0.06(0.06)	0.99	0.12(0.06)	0.05
A-level+ (424)	-	-	-	-	-	-	-	-
Disability (4-18y)								
Yes (111)	-0.22(0.09)	0.01	-0.19(0.09)	0.02	-0.16(0.09)	0.08	-0.16(0.09)	0.07
No (2351)	-	-	-	-	-	-	-	-

* the height SDS of cohort members at age 33, either the father or the mother
† children of female cohort members only (*n*=1580)
‡ children of male cohort members only (*n*=882)
Model adjustment
(1)adjusted only for age and sex
(2)adjusted for (1) and parental height
(3)adjusted for (2) and fetal and infancy factors (maternal smoking, birthweight, breastfeeding)
(4)adjusted for (3) and all early life factors (maternal age, birth order, younger siblings, social class, housing tenure, crowding, maternal education, parental divorce, and childhood disability)

5.3.1 Factors influencing height at age 7 in cohort members (G2)

All factors examined were significantly associated with height of G2 at age 7 (Table 5.3). Their influences on height were reduced but remained significant after adjusting first for mid-parental height, and then for fetal and infant factors. After allowing for all childhood factors, the influences of breastfeeding, father's social class, parental divorce and maternal education on height were no longer significant, suggesting that their impact on childhood height was explained by other early life factors.

Mid-parental height

Parental height was the strongest predictor for height of children; for every unit increase in mid-parental height SDS, the mean height SDS for cohort members increased by 0.56 (2.9 cm) at age 7. The relationship remained strong after allowing for all other factors (Table 5.3).

Maternal smoking

Maternal smoking during pregnancy was significantly associated with childhood height in G2. Variable and heavy smokers were combined as the strength of their effects was similar. Table 5.3 shows that children of heavy/variable smokers were shorter than those of non-smoking mothers by a height SDS of 0.24 (1.2 cm) at age 7. The difference reduced to 0.13 (0.7 cm), but was still significant after adjusting for birthweight, indicating that birthweight was a pathway factor in the relationship between smoking and childhood growth as shown in Chapter 4. The difference further reduced to 0.06 (0.3 cm), though it remained significant after adjusting for other factors. Therefore, maternal smoking had only a weak effect on height in G2 once birthweight and all other factors were taken into account.

Birthweight

A significant linear relationship was found between birthweight and height in G2 in childhood (Table 5.3). For every 1kg increase in birthweight, the mean height SDS increased by 0.51 (2.6 cm) at age 7. The relationship was weakened but remained highly significant after adjusting for parental height. However, further adjusting for fetal, infant, and childhood factors did not affect the linear relationship.

Breastfeeding

Breastfeeding had a significant effect on childhood height in G2. Cohort members who were breastfed were taller on average than those who were never breastfed by a height SDS of 0.15 (0.8 cm) at age 7. The difference reduced by 40% to 0.09 once mid-parental height was accounted for. The relationship was no longer significant after adjusting for early life factors, suggesting that the influence of breastfeeding on height was explained by parental height and other early life factors.

Maternal age

A weak but significant linear relationship between maternal age at childbirth and height was seen at 7 years in G2. The relationship strengthened after allowing for early life factors, possibly due to the negative confounding effect of birth order; later-born children were more likely to be born to older mothers and were shorter on average than early born children.

Birth order and number of younger siblings

Birth order and number of younger siblings were both associated with G2 height, with first-born children being taller on average than third or later born children, by a height SDS of

0.32 (1.7 cm). The effect of birth order on height changed little after adjusting for other early life factors, suggesting that its impact on height was independent of other early life factors. However, the difference reduced to 0.08 (0.4 cm) after adjusting for family size (data not presented). Cohort members with few younger siblings (none or one) were taller on average than those with three or more, by a height SDS of 0.37 (2.0 cm). The difference reduced to 0.07 (0.4 cm) and was no longer significant after adjusting for family size (data not presented). Therefore, effects of birth order and number of younger siblings were mainly explained by the effect of family size in G2; later-born children and those with more siblings were shorter because they came from larger families.

Social class

Social class was significantly associated with height of G2 at age 7, with clear social class gradients (Table 5.3). The difference in height SDS between classes I&II and classes IV&V was pronounced (0.39) and was reduced but remained significant after adjusting for mid-parental height, suggesting that some of the social class effect on height was explained by parental height, a combined genetic and environmental factor. The relationship between social class and childhood height was no longer significant after further allowing for other childhood factors.

Housing tenure and household crowding

The association between housing tenure and height was significant in G2, with children from owner occupied properties being the tallest, followed by children from private rental accommodation (Table 5.3). Children from council/housing association rental accommodation were the shortest, with a difference in height SDS between the two extreme groups of 0.37 (1.9 cm). Only a weak relationship existed with a much smaller difference of

0.08 (0.4 cm) after allowing for all other early life factors, including social class and crowding (although still significant).

As shown in Table 5.3, the effect of crowding on height was also significant in G2, with a clear trend according to level of crowding. The difference in height SDS between children from households with less than one person per room and households with more than 1.5 persons per room was 0.65 (3.4 cm). It was reduced to 0.22 (1.1 m) but remained significant after allowing for other early life factors.

Parental divorce/separation

Cohort members who had experienced parental separation or divorce were on average shorter than those who had not, by a height SDS of 0.20 (1.0 cm). The relationship was not affected by fetal and infant factors, but became non-significant after allowing for other early life factors. As shown in Chapter 4, the age of the child when the separation or divorce took place was found to have an impact on growth. Cohort members whose parents divorced between ages 4 and 7 years were not only significantly shorter on average than children whose parents were not divorced by a height SDS of 0.35 (1.8 cm), but also shorter than children whose parents divorced before the age of 4 years by 0.27 (1.4 cm), though borderline significant (p=0.06). The association remained with a significant difference of 0.22 (1.1 cm) after allowing for all other early life factors (data not presented).

Maternal education

Mother's education was significantly associated with G2 childhood height, with children whose mother stayed at school after the minimum school-leaving age being taller on average than those whose mother did not stay, by a height SDS of 0.22 (1.1 cm). The

difference reduced by 64% after the adjustment of mid-parental height, and disappeared after all other factors were accounted for. Therefore the influence of maternal education on height was explained by parental height and other early life factors in G2.

Childhood disability

Childhood disability was significantly associated with G2 height. Children with disability were shorter on average than those without by a height SDS of 0.24 (1.2 cm) at age 7. The difference remained (0.14) after adjusting for all other factors. Childhood disability therefore influenced G2 growth independently of other early life factors.

Summary

Within the cohort, all factors, except breastfeeding, social class, maternal education, and parental divorce, were significantly associated with height at age 7 after taking into account parental height and other early life factors. Mid-parental height SDS was the most powerful variable in terms of the percentage of the variance in height explained, accounting for 20.4%, followed by birthweight (6.6%). Other early life factors together accounted for 7.1% of variation in height. The total variation attributable to all these factors was 27.2% (Table 5.5).

Table 5.5 Percentage of variance in height SDS (G2 and G3) explained by biological and early life factors

Factors	G2	G3
Mid-parental height	20.4%	
Parental height (either parent)		18.2%
Maternal height	14.2%	
Paternal height	13.1%	
Birthweight	6.6%	3.8%
Early life factors †	7.1%	2.2%
All factors	27.2%	21.6%

† all factors except parental height and birthweight

5.3.2 Factors influencing childhood height in the offspring (G3)

Several factors, including parental height, birthweight, birth order, housing tenure, crowding, and childhood disability were found to be significantly associated with the height of G3, whereas the effects of maternal smoking, breastfeeding, maternal age, number of younger siblings, social class, parental divorce and maternal education on height were no longer significant (Table 5.4).

Parental height (father's or mother's) was significantly associated with height of G3, with the mean height SDS increasing by 0.44 (2.3 cm) for every unit increase in parental height SDS. The relationship remained strong (β =0.42) after adjusting for all other factors.

A significant linear relationship was also found between *birthweight* and height of G3, for every 1kg increase in birthweight, the mean height SDS increased by 0.32 (1.7 cm). The

relationship was weakened but remained highly significant after allowing for parental height, and was not affected by further adjustment for other fetal, infant, and childhood factors.

Birth order was significantly associated with height of G3, with first-born children being taller on average than third or later-born children by a height SDS of 0.24 (1.2 cm). A difference of 0.21 remained (1.1 cm) after adjusting for family size. Thus the influence of birth order on height was independent of family size among G3. The association of the *number of younger siblings* and height was not significant in G3, although a small difference in height SDS of 0.12 (0.6 cm) was seen between children with none or one sibling and children with three or more siblings. Effects of birth order and number of younger siblings on height remained after adjusting for each other and early life factors.

Housing tenure was significantly associated with height of G3. Children from private rental properties were the tallest, followed by children from owner occupied accommodation. Children from council/housing association rental accommodation were the shortest. The difference in height SDS between the two extreme groups was 0.33 (1.7 cm), while children from owner occupied properties were taller on average than those from council/housing association rental accommodation by a height SDS of 0.15 (0.8 cm). After allowing for other factors, the difference between the two extreme groups reduced to 0.24 (1.2 cm), but remained significant.

Childhood disability was significantly associated with height of the offspring. Children with disability were shorter on average than children without by a height SDS of 0.22 (1.1

cm). The difference remained high (0.16) after adjusting for all other factors, although it was borderline significant (p=0.07).

Other factors: The associations of maternal smoking during pregnancy, breastfeeding, father's social class, and maternal education with height found in G2 were not significant in G3. The linear relationship between maternal age and height was no longer significant in G3. However, further analysis (data not presented) showed that offspring of young (<25y) and lone-mothers were shorter on average than the others by 1 cm, although the difference was borderline significant (p=0.08).

There was a clear trend of reducing mean height SDS with increasing level of crowding in G3, with a difference between children from households with less than one person per room and more than 1.5 persons per room of 0.30 (1.6 cm). The difference was no longer significant after allowing for other early life factors.

No difference was found between offspring who experienced parental separation or divorce and those who did not by the age 7. As the offspring (G3) had a large age range, a separate analysis including only 7-8 year old offspring (n=520) showed that the mean height of offspring whose parents divorced/separated before they were aged 4 years was similar to that of those whose parents did not divorce, while offspring whose parents divorced between ages 4 and 7 years were shorter on average than those whose parents didn't by a height SDS of 0.27 (1.4 cm), although the difference was not significant. A difference of 0.18 (0.9 cm) remained after adjusting for other early life factors.

As the number of subjects in G3 (n=2462) was much smaller than that for G2 (n=7993 at age 7), the non-significant effects estimated for the offspring were also calculated for the sample size of the cohort members (t-tests based on the standard errors calculated from standard deviation using the G3 sample and the sample size of G2) and they remained non-significant, except for disability. Therefore the non-significance of the effects of maternal smoking, breastfeeding, maternal age, crowding, maternal education, and parental divorce on height of the offspring generation was not related to the reduction in the G3 sample compared with G2.

Summary

Apart from parental height and birthweight, birth order, number of younger siblings and housing tenure were significantly related to height of G3 in the fully adjusted model. The influence of disability on height remained strong, though became borderline significant (p=0.07) after adjusting for other factors.

As in G2, the variation in height of G3 was mainly explained by parental height SDS (18.2%), followed by birthweight (3.8%). Other early life factors together explained 2.2% of the variation in height. The total variation in height SDS of the offspring attributable to these factors was 21.6% (Table 5.5).

5.3.3 Comparison of influences on childhood height in two generations (G2 and G3)

Parental height, birthweight, birth order, number of younger siblings, housing tenure, and childhood disability were associated with childhood height in both G2 and G3.

Table 5.6 provides correlation coefficients between father-child and mother-child pairs, separately. Similar to Tables 5.3 and 5.4, the strength of the parent-child association was stronger in G3 than in G2, with the mother-child and father-child correlation coefficients of 0.41 and 0.45 in G3 compared to 0.39 and 0.35 in G2, respectively (Table 5.6).

Table 5.6 Parent-child correlation coefficients for G2 and G3

Correlation coefficient	G2	G3
	Age 7y	Age 4-18y
Father-child	0.35	0.45
Mother-child	0.39	0.41
Either parent		0.43
Mid-parent	0.45	

The correlation between mid-parental height and the height of the cohort member at the age of 7 (0.45) was similar to the correlation between parental height (father or mother) and the offspring height (0.43). But the estimation of the regression coefficient for mid-parental height SDS in G2 from the two-level model (0.56) was greater than that for parental height SDS in G3 (0.44). This was due to the fact that regression coefficients depend on variances of the two measures. The variance of mid-parental height SDS in G2 (0.74) was smaller than the variance of parental height SDS in G3 (1.03).

Table 5.7 Significance level (p) for the change of each effect on height between G2 and G3

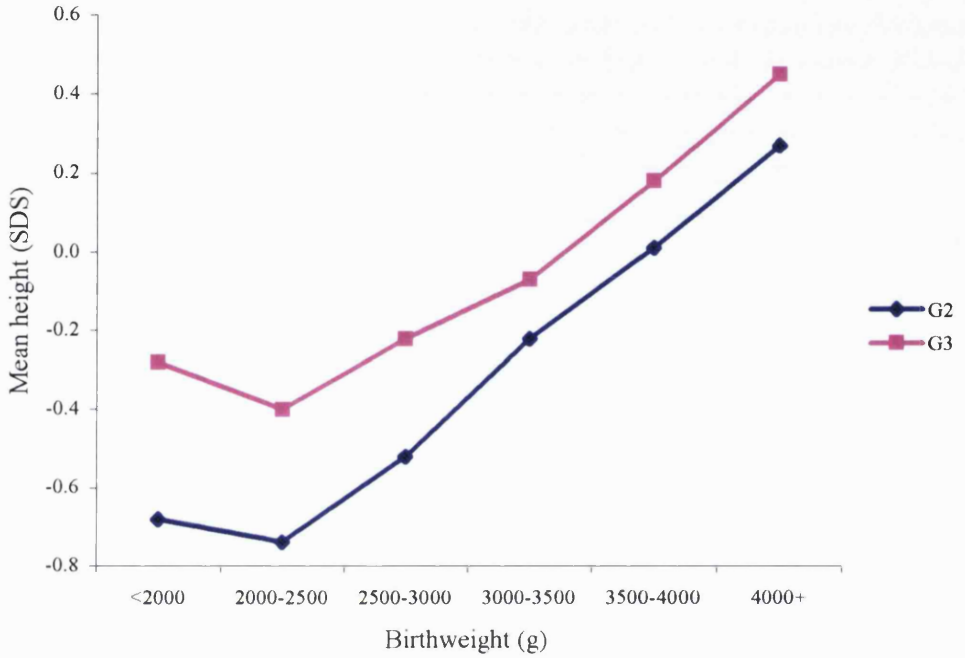
	Significance (p) for change of effects*			
	Model (1)	**Model (2)**	**Model (3)**	**Model (4)**
Maternal smoking	0.01	0.02	0.06	0.26
Birthweight	0.001	0.02	0.05	0.02
Breastfeeding	0.02	0.16	0.21	0.19
Maternal age	0.50	0.16	0.12	0.07
Birth order	0.63	0.95	0.72	0.39
Younger siblings	0.03	0.04	0.04	0.94
Social class	<0.001	0.06	0.004	0.68
Housing tenure	<0.001	0.06	0.11	0.29
Crowding	<0.001	<0.01	<0.01	0.10
Parental divorce (Yes/no)	0.07	0.04	0.07	0.07
Disability	0.78	0.77	0.75	0.84

* all effects listed were stronger in G2 than in G3 (change G3-G2<0)

The effect of birthweight on height was significant in both generations, with a stronger linear relationship in G2 (p=0.001). In both generations, the birthweight influence on height was not affected by adjusting for early life factors.

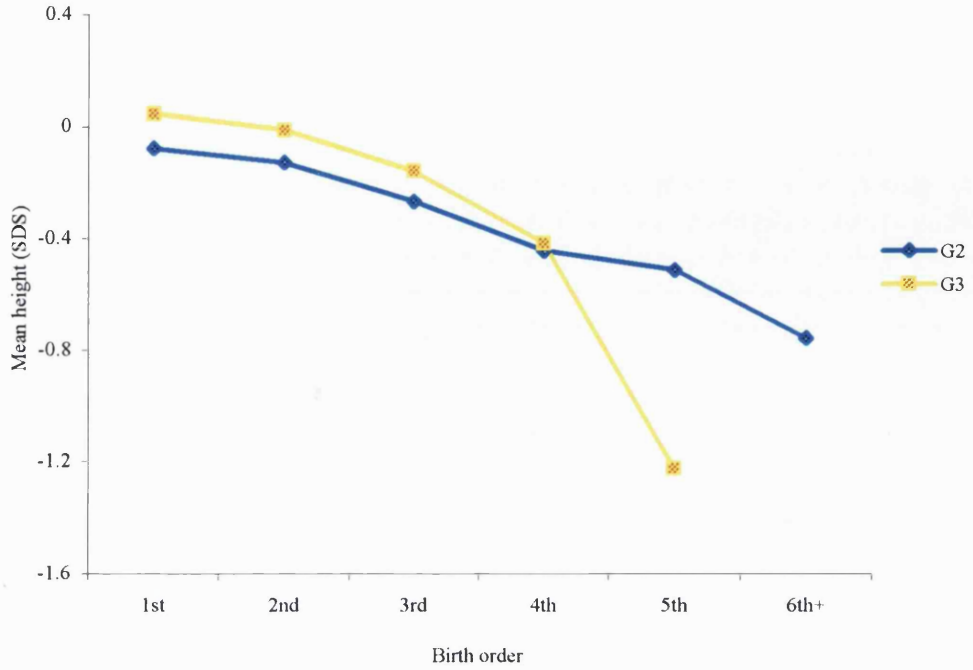
There was a quadratic relationship between birthweight and height in G3 (Figure 5.1), though it was borderline significant (p=0.07) (data not presented).

Figure 5.1 Mean height SDS for G2 and G3 by birthweight



The effect of birth order on childhood height was significant in both generations (G2 and G3), even after adjusting for other early life factors. The effect of birth order on height of G2 was due to the impact of family size, whereas in G3 it was independent of family size.

Figure 5.2 Mean height SDS for G2 and G3 by birth order



However, the strength of the association between birth order and childhood height was stronger in G2 than in G3, though the difference was non-significant (Table 5.7). Figure 5.2 illustrates the mean height SDS by birth order in G2 and G3. It shows that fifth or later born children were much shorter than the others (Figure 5.2). Thus the smaller difference between the third or later borns and first borns in G3 was possibly due to fewer high order offspring (5^{th} born children in G3, n=5) compared to G2.

The association between housing tenure and childhood height was significant in both generations, but the patterns of the relationships were different (p<0.001). In G2, cohort members from owner occupied properties were the tallest, whereas for G3, the tallest were those from private rental properties. However, in both generations children from council-rental accommodation were the shortest.

The strength of the effect of crowding was reduced significantly in the next generation (G3) as shown in Table 5.7. The difference in height SDS between children from households with less than one person per room and those with more than 1.5 persons per room was 0.65 (3.3 cm) in G2, but it was less than half (0.30) in G3.

Childhood disability was consistently associated with height and the strength of the relationship was similar in the two generations. The growth deficits due to childhood disability were independent of genetic and environmental factors.

The significant association between father's social class and height in cohort members (G2) did not persist in their offspring (G3). There was a pronounced difference in height SDS between social classes I&II and IV&V of 0.39 at the age of 7 in G2, but only a small difference of 0.05 (non-significant) was found in G3. The effect of social class on height was weakened significantly over the two generations (Table 5.7).

In G2, 26.2% of mothers stayed after minimum school-leaving age (14-15 years). In G3, 27.4% of mothers had A-level or higher education. Mother's education was significantly associated with height of cohort members at the age of 7 (G2), with a difference in height SDS of 0.22 (1.1 cm) between children whose mother stayed after the minimum school-leaving age and children whose mother did not stay. The association was explained by other early life factors. In G3, there was no difference in height between children whose mother had A-level or higher education and children whose mother did not.

Parental separation or divorce was associated with height in G2 but not in G3. However, age of the child when divorce happened was found to be associated with growth in both

generations. Children whose parents divorced between ages 4 and 7 years were shorter on average than their counterparts at age around 7 years in both generations, even after adjusting for other early life factors, although the relationship was non-significant in G3.

5.4 Discussion

It is well accepted that both genetic and environmental factors influence childhood height (Table A1.2). But whether factors that had an impact on height in the past are still important in a modern society is less clear. Several studies revealed a reduction of the strength of the effects of socio-economic status and household crowding on height [162;164;269;270], whereas the influence of family size on height was found to be persistent [162]. However, these studies used cross-sectional samples from different periods and conclusions were based on the comparison of the magnitudes of these effects between samples from different time periods. Thus changes of these effects cannot be tested statistically. There have not been any studies comparing the patterns of early life influences on height across two generations within families, possibly due to the lack of multi-generational data.

5.4.1 Methodological considerations

There are several methodological issues which should be considered in the analyses and interpretation of the results. As described in Chapter 3, the sample used in this analysis was not an independent one; the sample of G3 was a sub-sample of all children born to G2 and therefore was correlated to their parents (cohort members). Although only about 20% of

families had children in the study sample, either because some cohort members had not yet had children by the age of 33, or their children were not selected for the "Mother and Child Study", or selected but were all under 4 years of age, the correlation between cohort members (G2) and their offspring (G3) was strong (0.43). It is therefore important to take into account the covariance structure between G2 and G3.

Furthermore, our approach incorporating two generations at the same level (level 1) into a single two-level model allows us testing for the difference in an effect between G2 and G3. It should also be mentioned that the comparison of two generations should not be based only on the significance level. A difference in height SDS between groups that was highly significant in G2 might not be significant in G3 because of the smaller sample size. For example, in G2, children with disability were significantly shorter than those without disability by a height SDS of 0.14 after taking into account of other factors. However, a slightly larger difference of 0.16 seen in G3 was only borderline significant (p=0.07) due to the smaller sample size in G3. The non-significant effect of disability estimated for the offspring (G3) was however, found to be significant when calculated for the sample size of the cohort members (G2).

The comparison of height differentials between sub-groups across generations may be affected by the stage of puberty due to different age distribution in the two samples. Cohort members were all around 7 years, whereas the offspring were between ages 4 and 18 years with an average of 8.3 years.

Although there is a recent trend towards increasing maternal age [119], mothers of G3 were on average younger at child birth than G2 and general population in UK [209]. Despite the fact

that the age of the child has been adjusted throughout the analyses, our findings were still affected by the small number of children born to mothers over 30 years. Effects that were dependent on maternal age might have been under- or over-estimated in G3.

Another limitation of the data is that some important information was not collected for the partner of each cohort member, the other parent of the offspring. For example, height was only measured in the cohort member. Information on maternal education was missing for the offspring of male cohort members and consequently, the relationship between maternal education and offspring height was only assessed for a sub-group of G3.

5.4.2 Secular trends for height and birthweight

A secular trend was reported in adult height among parents and children of the 1958 cohort (G1 and G2) [87]. As most secular increase in adult height is established during childhood [102], the intergenerational trend towards increasing childhood height found between cohort members and the offspring (G2 and G3) was the continuation of that trend in a recent generation. Improved nutrition in infancy and childhood, as well as the general improvement in economic prosperity across all social classes, are reflected in the increased growth and development of children during this period.

Although it has been suggested that there are small and gradual increases in birthweight in England, Wales, and Scotland [110], birthweight has not increased over the two generations of the 1958 cohort. Possible explanations include: (1) offspring (G3) were born to young mothers who are associated with low birthweight [53], (2) birthweight of G2 was measured, whereas birthweight of G3 was reported by the cohort member after 4-18 years and was

therefore more subject to bias [61], and (3) the absence of a birthweight trend may in part relate to the improved survival rate among premature and low weight births. In our study samples, 0.9% (70/7993) of cohort members were born below 2000g, while the corresponding proportion was doubled in their offspring (1.8% (44/2462)).

5.4.3 Factors that consistently influence height

In affluent societies, heritability is likely to be higher than in societies with a low standard of living because of the stronger effect of environmental factors. The strength of the parent-child association was stronger in G3 than in G2, suggesting the improvements in the living standard in Britain since 1958 [138].

It has been recognized that the influence of maternal height on offspring height was greater than paternal height [58-60]. This was evident in cohort members (Table 5.6). But unexpectedly, a weaker effect of maternal height was seen in the offspring generation compared to paternal height. A possible explanation is that offspring born to female cohort members were on average older than those born to male cohort members, and therefore the influence of maternal height was likely to be affected by the stage of puberty.

The decline in some social environmental influences on height after adjusting for parental height suggested that some of the environmental effect on growth was mediated through parental height in both generations, reflecting the combined genetic and environmental influence of parental height. Parents and children are likely to share a similar childhood environment [57;58;61;62].

Although the linear relationship between birthweight and height was significant in both generations, the strength of the association has weakened significantly. The quadratic relationship as well as the changing distribution of birthweight with increasing number of low birthweight babies might have affected the linear relationship in G3. In addition, reported birthweight for G3 might be subject to recall bias [61] and lead to an underestimation of the birthweight-height relationship.

Apart from parental height and birthweight, factors consistently associated with height in both generations include birth order, housing tenure, and disability.

High birth order has been found to be associated with short stature in many studies [57;59;85]. In the current analysis, the association between birth order and childhood height was significant in both generations and became stronger after allowing for factors related to fetal development, indicating the negative confounding effect of birthweight [271]. The mechanism for the effect of birth order on height is not well established. It has been suggested that the postnatal nutrition may be affected by family size in developing countries [272]. Our findings showed that both in the cohort and their offspring, the impact of birth order on height was not affected by their genetic potential and a wide range of early life factors, suggesting that although it was attributed to family size in G2, postnatal growth rate might have been influenced by maternal uterine factors during fetal development. It has been shown in a recent British cohort that first-born children were smaller at birth but showed dramatic catch-up in height, over compensated for the initial size deficit and became taller in childhood [83]. A smaller difference in height between first and third or later born children seen in G3 was possibly due to the smaller number children of high birth

order in G3 who tended to be shorter than the others (2% were 4th or later borns in G3 compared to 15% in G2).

The impact of housing tenure on height remained significant in G3, although the patterns of the association differed from G2. Housing conditions have improved over the study period (1965-91), with a great increase of children living in owner occupied properties. In the meantime, the proportion of children living in council rental accommodation has fallen. In the 1958 cohort, 11% of homeowners have bought their property from a local authority or a housing association [178] and they were likely to be previously council or housing association tenants. This might have partly explained the reduced difference in height between children from owner occupied properties and those from council rental accommodation in G3.

Results in Chapter 4 showed that children with disability were shorter both in childhood and adulthood. This current analysis found that the impact of disability on height remained in the offspring generation and was also independent of genetic and early life factors.

5.4.4 Factors whose patterns or strength of the influence changed

The association between maternal smoking during pregnancy and height of the child was significant in G2, but not in G3. Results from G2 (in the current analysis or in Chapter 4) show that growth deficits due to maternal smoking observed in early childhood occurred independently of fetal retardation. But similar to findings from another recent British cohort, the reduction in childhood height was not found in the offspring generation. It seemed that children of mothers who smoked during pregnancy had complete catch-up growth in height during the first few years of life [4]. It has been suggested that impaired

growth in height due to adverse fetal conditions can be overcome by improved socio-environmental conditions in early life [244]. Thus the improved early life conditions and nutrition in the recent generation might have explained the weakened relationship in the offspring.

Breast milk provides nutritional needs during infancy. Studies of early samples in Britain demonstrated advantages of breastfeeding on postnatal growth in height. Infants who were breastfed during the 1920s-1940s in Britain were taller in childhood and adulthood after controlling for socio-economic variables [81]. But a study of the 1970 cohort showed that the effect of breastfeeding on height was explained by social factors [82], which are known to influence the choice of breastfeeding [273]. The benefit of breastfeeding on height of the 1958 cohort was attributed to the differences in other early life factors. The findings of no association between breastfeeding and childhood height in the offspring is consistent with results from the British cohort born in 1992-93. The good quality infant formula, which provides adequate energy and nutrients, may explain the reduced importance of breastfeeding in relation to growth in height.

There was a weak relationship between age of the mother at childbirth and height in G2, but not in G3. The different distributions of maternal age in the two generations, with the distribution skewed towards the lower end and 98% mothers under 30 years of age at child birth might have resulted in the lack of the maternal age effect in G3.

The unadjusted association between the number of younger siblings and height clearly seen in G2 was weakened significantly in G3 (p=0.03), while the adjusted association remained. One possible explanation is that there were fewer children in G3 who had more than 3

younger siblings and were much shorter than the others. However, the reduction was explained by other early life factors. The impact of crowding on childhood height was significant in both generations, although became attenuated in the offspring (G3). Similar to birth order, fewer children in G3 living in extremely crowded conditions (i.e. >2 persons per room) might have explained the reducing influence of household crowding on height.

In Britain, the educational level of mothers has improved over time [138]. Children whose mothers stayed after minimum school-leaving age were significantly taller than children whose mothers did not in G2, whereas in G3, only a small difference was found between children of mothers without any education and the others. There was no difference in height between children whose mother had a higher and a lower educational level.

The distress and difficulties experienced during parental separation or divorce can be a major disruption in children's lives. Our analyses revealed that children whose parents divorced between ages 4 and 7 years tended to be shorter in early childhood (7y) than children whose parents either did not divorce or divorced before the age of 4, although a similar difference seen in G3 was non-significant. The association was independent of other early life factors, indicating that the reduction in childhood height was due to the stress, over and above the change of socio-economic situation of households after the divorce as suggested by the others [94].

The total variance in height (SDS) was similar in the two generations. Among all factors, parental height and birthweight explained most of the variation in height. It has been suggested that the relative effects of genetic and environmental factors on height might have changed over time. A recent Finnish twin study showed that the heritability increased

from cohort born before 1929 to those born between 1947 and 1957, indicating that changing environmental factors affect the heritability of height [274]. Our results suggested that the relationship between parental height and height of children remained strong in G3, while effects of other early life factors were either unchanged or weakened.

A smaller proportion of variation in height explained by social environmental factors than parental height and birthweight is expected because much of individual variation in height is genetic, which is unrelated to social stratification. In addition, the division of social variables into several categories still leaves a considerable amount of socio-economic heterogeneity within levels. The proportion of total variance in height (SDS) explained by early life factors considered has diminished from 7.1% in G2 to 2.2% in G3, suggesting that there might be a decline in height inequalities in Britain.

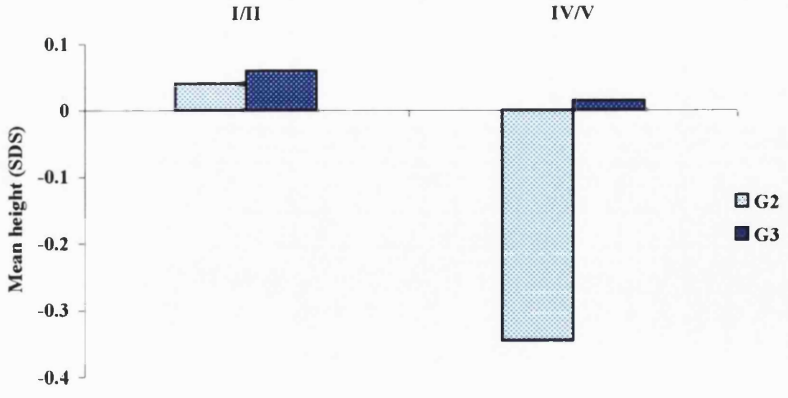
5.4.5 Reducing inequalities in height

The most noticeable change in this study was the decline in the importance of early life factors, especially those related to socio-economic conditions. Social class based on the father's occupation is associated with available family income and mother's educational status, which is important for health behaviour, feeding practices, and care of the children. Social class differences in height were pronounced in G2, but had practically disappeared in G3. The variation in height of G3 was mainly explained by biological factors such as parental height and birthweight.

There has been a tendency for children of lower social class to catch up in stature with those higher in the social scale. In Sweden, the height of the 10 year old children in the

more privileged group (defined by father's occupation and number of siblings) born in 1933, 1943, and 1953 was virtually unchanged, but the height in the less privileged group increased gradually [164]. In Croatia, the positive trends between 1973 and 1991 were more pronounced among children of manual workers [269]. In Britain, a greater height increase in lower social classes was reported in the 1958 cohort (3.7 cm in classes IV&V comparing with 2.5 cm in classes I&II among males) [154]. Similarly, our study showed that the reducing inequalities in height in the next generation of the cohort was due to a greater increase in height among children of lower social classes. While the increase in mean height SDS was hardly noticeable in classes I&II, offspring in classes IV&V increased by 0.35 (1.8 cm) with respect to cohort members (Figure 5.3). Improvements in the living standard of the low socio-economic groups might have led to a decrease in growth differences between social strata.

Figure 5.3 Mean height SDS of G2 (7y) and G3 (4-18y) for classes I&II and IV&V



Between 1965 and 1991, there has been general improvement in economic prosperity, particularly in the lower social classes. For example, housing conditions have improved in recent years, with a decrease in the number of inhabitants per room from 1.11 to 0.96. There were only 6% of G3 still living in over-crowded accommodation in 1991 compared to 17.4% of G2 in 1965. There was also a significant increase of the number of children living in owner-occupied properties. These improved social conditions of G3 may underlie the increase of growth of children in lower social groups. The social class differences in height throughout the life-course and in the two generations are further explored in detail in Chapter 6.

5.5 Conclusions

The effects of fetal, infant, and childhood factors on height were investigated in two generations of the 1958 birth cohort. Most early life factors, except birth order, number of younger siblings, housing tenure, and disability, had a greater influence on childhood height of the older generation (G2) compared to their offspring (G3), while the influences of parental height and birthweight remained strong, suggesting that the offspring (G3) were closer to their genetic potential than their parents (G2), although adult heights are needed to verify this.

The weakening relationships between early life factors and height in G3 were mainly due to the reducing number of children from extremely disadvantageous conditions as well as general improvements in the living standard of the low socio-economic groups.

Despite the greater secular increase of children in lower social strata, the growth of children with disabilities did not improve. The growth deficit due to disability was independent of their childhood environment.

Although variation in height is mainly explained by genetic factors, and early environment only explains a small proportion of variation, genetic differences in height may have no health implications, whereas failure to achieve height potential, even by only a small amount, may indicate a risk for adult health. While influences of some early life factors on height have weakened, children from extreme circumstances remained to be the shortest, even though the number of children affected has reduced. Further interventions to improve childhood health, reduce childhood disability, and monitor the growth of disabled children are necessary. In addition, providing support for children experiencing parental divorce is also important especially with the current increasing divorce rate in Britain [185].

Chapter 6

Social inequalities in height: life-course and inter-generational trends

6.1 Introduction

Secular trends in height are continuing in most west European countries [102], including Britain [87]. The secular increase in height is regarded as an indicator of improving socio-economic and health status [102] and is therefore important to a wide range of health outcomes (§1.3).

Socio-economic inequalities in height are reported in many developing and developed countries [124;275]. The tempo of growth also varies, with the slowest rate in the lowest social class and fastest in the highest class [276]. Our findings from the 1958 cohort using several alternative measures for early environment are consistent with these results.

The most notable findings in Chapter 5 are the secular increase in childhood height of 1cm between the two generations and the decline in the importance of several early life factors including father's social class. Part of the reduction in the social class effect on height might be due to changes of social structure, with the reducing number of individuals in the lower social classes and an increasing number in higher social classes, as well as height related social mobility [277]. In this chapter, we adopt a fixed social class measure (social

class of origin) for both generations to establish whether there have been any changes in inequalities in childhood height, which are due to changes in social environment.

We use information from the 1958 birth cohort and their offspring, to establish whether

i) the magnitude of social differences in height varies from childhood through to adulthood;
ii) social inequalities in height have changed across two generations;
iii) the secular trend in height has occurred at a similar rate in all social groups; and
iv) the narrowing is still evident after the effect of social class on birthweight is accounted for.

6.2 Methods and measures

Measurements on height and birthweight of the two generations and information of cohort members' socio-economic circumstances in childhood and adulthood are summarised in Table 6.1. Detailed descriptions of these measures are given in Chapter 2 (§2.3).

Table 6.1 Summary of variables used in Chapter 6

Variables	Categories
Anthropometric measures	
G2 height at 7, 11, 16, 33 years	
G3 height (at 4-18 years)	
Parental height (G1)	
Birthweight (kg) (G2 and G3)	
Measures for G2 childhood socio-economic circumstances	
Social class based on father's occupation (at 7)	I&II, IIINM, IIIM, IV&V
Housing tenure (at 7)	Owner, private rental, council rental
Measures for G2 adult socio-economic circumstances	
Social class based on cohort member's own current/most recent occupation (at 33)	I&II, IIINM, IIIM, IV&V
Cohort member's education level (at 33)	No education, <O-level, O-level, A-level or higher

Samples

Cohort members (G2): As explained in §2.5.1, the sample of respondents at age 33 years is generally representative of the original birth cohort [178]. We used data on 15826 (8129 male and 7697 female) cohort members with at least one height measure between ages 7 and 33 years (92% had more than one measure) and information on parental height and social class of origin. This sample is also similar to the original birth study with respect to social class of origin, with 24.6% of cohort members from classes IV&V, compared to 24.3% in the origin sample; and respectively 19.6% from classes I&II compared to 19.5%.

The offspring (G3): The representativeness of G3 has been discussed in detail in §2.5.2. The current analysis included a total of 2853 offspring with a height measure and social

class of their grandfather (G1). The average age of the sample was 8 years, ranging between 4 and 18 years with 94% of the sample under 14 years.

As shown in Table 6.2, the average maternal age of offspring was 24.4 years (range 15-38 years), with 98% mothers under 30 years at childbirth, and were younger on average than mothers in the general population (27y in 1986) [209]. Offspring had a mean (-0.017) and standard deviation (1.06) of height, suggesting that the study sample of the offspring (G3) is representative with respect to height [201]. The birthweight distribution for the offspring sample did not differ from all live births in England and Wales in 1991 [206]. The social class distribution for the offspring sample was similar to that of all live births to mothers under 35 years in 1991 in England and Wales [206]. Yet, children of lone mothers and no-earner families were under-represented in the G3 study sample as described earlier [210]. Therefore, offspring sample (G3) under-represented certain groups of children, but it did not differ markedly from other British children of their age with respect to birthweight, height, and social class.

Data analyses

The association between social class of origin and height of G2 at different life stages, from childhood through to adulthood was examined simultaneously using a multivariate response model. Internally derived height standard deviation scores were used here. Details of the model and the reason for using it here were explained in §3.3.1. The estimation of mean height SDS by social class of origin was estimated from the model and transformed to centimetres for males and females separately. Differences in height (SDS) among all social classes and between extreme groups were tested using contrast tests described in §3.3.1. Contrast tests were also applied to assess whether the parameter estimation for social class

differed between successive occasions. Social class differences in height were also examined with the adjustment for mid-parental height SDS.

For the comparison of height inequalities across two generations, externally derived height standard deviation scores for G3 and G2 were used (based on the 1990 British growth reference [201]). The associations of social class of origin with height of cohort members and height of the offspring were examined using a two-level model (3.9), where each family was assumed to be a level-2 unit and each individual to be a level-1 unit (§3.3.3). The estimated mean height (SDS) by social class and the difference between two extreme groups were transferred to centimetres. Adjustments for the age of the child were made throughout the analyses to reduce the confounding effect of maternal age. Similar models were repeated with covariate housing tenure as an alternative measure of childhood socio-economic position.

As the socio-economic circumstances in G2's childhood might not reflect current circumstances for G3, measures for G2's adult socio-economic position, social class and the highest education level at age 33, were also examined to assess inequalities in height in two generations.

Model (3.9) was also applied to assess the association between social class of origin (G3) and birthweight in two generations. The association between social class of origin and height of G2 and G3 was further adjusted for birthweight, to determine whether the narrowing has occurred beyond birth.

Finally, the difference in mean height (SDS) between G3 (4-18y) and G2 (7y) was estimated within each social class using a two-level model (3.8) (§3.3.2). Similar results were found for father-offspring pairs and father-son pairs; likewise for mother-offspring pairs and mother-daughter pairs. Thus data for the same sex pairs were presented in Figure 6.2.

6.3 Results

As reported in Chapter 5, the offspring were taller on average than their parents in childhood. No increase was observed in mean birthweight between the two generations. There were fewer offspring (G3) from families with four or more children (10%) compared to cohort members (30%) (Table 6.2).

Table 6.2 Selected characteristics for cohort members at 7 years (G2) and the offspring (G3)

Characteristic	Cohort members (*n*=13375)	Offspring (*n*=2853)
	7y	Mean 8y
Sex n (%)		
Boys	6894(51.5)	1406(49.3)
Girls	6481(48.5)	1447(50.7)
Age (y) mean (range)	7.3(7-8.5)	8.2(4-18)
Maternal age (y) mean (range)	27.5(14-47)	24.4(15-38)
n (%)		
<30y	8669(66.5)	2718(98.1)
≥30y	4361(33.5)	52(1.9)
Family size n (%)		
1	1161(8.7)	295(10.3)
2	4703(35.3)	1469(51.5)
3	3499(26.3)	803(28.1)
≥4	3948(29.7)	286(10.0)
Birthweight mean (sd)		
Boys	3409(524)	3361(552)
Girls	3268(511)	3252(529)
Height SDS mean (sd)†		
Boys	-0.20(1.08)	-0.01(1.06)
Girls	-0.25(1.11)	-0.02(1.07)
Total	-0.23(1.09)	-0.02(1.06)

6.3.1 Social inequalities in cohort members (G2): from childhood through to adulthood

In G2, the effect of social class on height was significant at all ages, from childhood to adulthood, with an increase in mean height from each social class to the next (Table 6.3). Differences in height between classes I&II and IV&V exceeded 2 cm at all ages, and remained significant though reduced after parental height was accounted for. Significant differences of 0.7 cm (males) and 1.1 cm (females) remained in adult height after parental height was adjusted for (Figure 6.1).

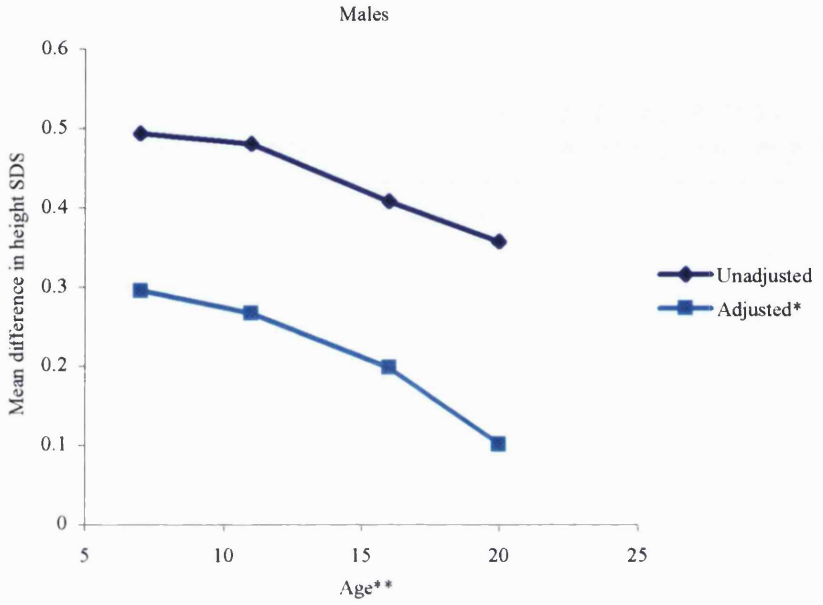
Table 6.3 Estimated mean height in cm (*n*) for cohort members (G2) at ages 7, 11, 16, and 33 years by social class in 1965

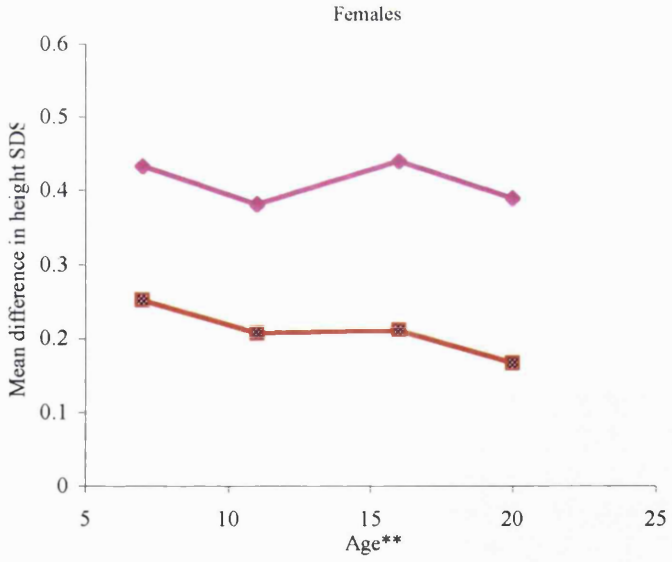
Age	Social class of G1				d†
	I&II	IIINM	IIIM	IV&V	
	Mean (*n*)	Mean (*n*)	Mean (*n*)	Mean (*n*)	
Boys					
7	124.4(1384)	123.5(675)	122.5(3145)	121.5(1690)	2.9
11	145.7(1246)	144.9(630)	143.6(2864)	142.4(1547)	3.3
16	172.0(1086)	171.2(566)	169.8(2433)	168.7(1291)	3.2
33	178.1(1363)	177.6(687)	176.5(3040)	175.7(1656)	2.4
Girls					
7	123.4(1290)	122.9(680)	121.5(2950)	120.8(1561)	2.6
11	146.4(1197)	146.0(625)	144.3(2732)	143.6(1457)	2.8
16	162.5(1034)	162.3(506)	160.6(2326)	159.7(1218)	2.7
33	164.0(1390)	163.8(710)	162.2(3273)	161.5(1728)	2.5

† differences between classes I&II and IV&V, and between all four social classes are significant for each sex at all ages ($p<0.001$)

The effect of social class on the tempo of growth differed between boys and girls. Among boys, the association with social class was at its strongest at age 7 years and remained strong until age 11, and declined thereafter (Figure 6.1). The difference in mean height (SDS) between social classes I&II and IV&V reduced significantly from 0.48 (age 11) to 0.41 (age 16), and to 0.36 in adulthood, though remaining significant ($p<0.001$). Boys from classes IV&V therefore had a faster growth rate throughout adolescence than their peers in classes I&II and continued growing after age 16. For girls, the difference in height (SDS) between classes I&II and IV&V decreased significantly from 0.43 (age 7) to 0.38 (age 11), but increased significantly to 0.44 (age 16). The divergence of growth rates between ages 11 and 16 years was explained by the effect of parental height. After age 16, the decline in the difference in growth rate resumed as girls from classes IV&V either grew more rapidly or for an extended period.

Figure 6.1 Difference in growth between children (G2) from classes I&II and IV&V





* adjusted for parental height

** adult height measured at age 33y and plotted at age 20

Table 6.4 Mean height SDS (*n*) for G2 and G3 by childhood socio-economic circumstances of the 1958 cohort (1965)

Childhood	G2 (*n*=13346)		G3 (*n*=2853)	
Circumstances	Boys	Girls	Boys	Girls
Social class				
I&II	0.10(1383)	0.01(1289)	0.15(229)	0.15(207)
IIINM	-0.04(674)	-0.07(679)	0.04(135)	0.13(108)
IIIM	-0.25(3138)	-0.32(2942)	0.07(649)	-0.01(732)
IV&V	-0.42(1686)	-0.43(1555)	0.03(393)	-0.02(400)
d*‡	0.52(2.7cm)	0.45(2.3cm)	0.12(0.6cm)	0.16(0.8cm)
Housing tenure				
Owner occupied	-0.03(2937)	-0.06(2762)	0.10(476)	0.05(448)
Private rental	-0.15(1208)	-0.26(1112)	0.25(215)	0.05(238)
Social housing	-0.41(2693)	-0.45(2559)	-0.02(592)	-0.05(604)
d†‡	0.38(2.0cm)	0.38(2.0cm)	0.13(0.7cm)	0.10(0.5cm)

* difference between classes I&II and IV&V, and differences among all four social classes are significant only among cohort members; estimates presented here may vary slightly from Table 6.3 because of the difference in sample, the reference data, and model used

† difference between owner occupied and council rental accommodation, and differences among all three tenure groups are significant only among cohort members

‡ difference in cm is based on a 7-year-old child

Table 6.5 Mean height SDS (*n*) for G2 and G3 by adult socio-economic circumstances of the 1958 cohort (1991)

Adult	G2 (*n*=11077)		G3 (*n*=2807)	
circumstances	Boys	Girls	Boys	Girls
Social class				
I&II	-0.01(1963)	-0.09(1614)	0.12(359)	0.05(337)
IIINM	-0.08(644)	-0.18(2153)	0.16(385)	0.01(420)
IIIM	-0.28(1939)	-0.35(446)	0.03(256)	0.06(260)
IV&V	-0.44(1008)	-0.47(1310)	-0.03(379)	-0.09(411)
D*‡	0.41(2.1cm)	0.38(2.0cm)	0.15(0.7cm)	0.13(0.7cm)
Education level				
None	-0.54(395)	-0.76(457)	-0.26(185)	-0.24(190)
<O-level	-0.31(576)	-0.39(778)	0.03(258)	0.10(269)
O-level	-0.22(1063)	-0.21(1691)	0.01(472)	0.06(474)
A-level	-0.17(1094)	0.01(481)	0.02(211)	0.09(209)
Higher	0.07(1316)	-0.06(1199)	0.15(251)	0.09(274)
d†‡	0.61(3.1cm)	0.71(3.6cm)	0.41(2.1cm)	0.15(0.8cm)

* difference between classes I&II and IV&V, and differences among all four social classes are significant only among cohort members

† difference between no qualification vs higher than A-level, and differences among all five education levels are significant only among cohort members and male offspring

‡ difference in cm is based on a 7-year-old child

6.3.2 Comparison of height inequalities in two generations (G2 and G3)

Estimates of mean height SDS for both generations by social class are given in Table 6.4. In contrast to the findings in G2, the effect of social class on height was no longer significant in G3, with modest differences of 0.12 (0.6cm) and 0.16 (0.8cm) between classes I&II and IV&V among boys and girls, respectively.

A similar narrowing in class gradient was found with housing tenure, an alternative measure for childhood circumstances (Table 6.4). The influence of housing tenure was significant among G2, and was not significant among G3. The difference in mean height between children from owner occupied and council rental accommodation reduced from 2.0 cm for G2 (boys and girls) to 0.7 cm and 0.5 cm for male and female G3, respectively.

Analyses for measures of adult socio-economic circumstances, social class and highest education level of cohort members at 33 years revealed similar results (Table 6.5). Influences of social class and education level at age 33 were significant among G2, but were no longer significant among G3, except for education in boys (G3), though reduced substantially. Differences in mean height between classes I&II and IV&V were 2.1 cm for boys and 2.0 cm for girls among G2, and 0.7 cm for boys and girls among G3. Differences in mean height between no qualification and higher than O-level were 3.1 cm for boys and 3.6 cm for girls among G2, and respectively 2.1 cm and 0.8 cm among G3.

Unlike height, a slightly narrowing of class gradients in birthweight was found but only in boys (data not presented). A difference in mean birthweight between classes I&II and IV&V of 88g (boys) and 80g (girls) was found in G2. A smaller difference of 45g (boys) and 66g (girls) was found in G3.

6.3.3 Height gain between two generations

Social class differences in height were lessened both in boys and girls over the two generations (Table 6.4). As shown in Table 6.4, there was no increase in mean height in classes I&II among boys and a small increase among girls (equivalent to 0.7 cm), but the

increase in classes IV&V was statistically significant (equivalent to 2.3 cm for boys and 2.1 cm for girls). Likewise, there was only a small increase in mean height among children from owner occupied properties (equivalent to 0.7 cm for boys and 0.6 cm for girls), while a greater increase (equivalent to 2.0 cm for boys and 2.1 cm for girls) was found among children from council rental accommodation.

Differences in mean height between classes I&II and IV&V reduced slightly from 2.9 cm and 2.6 cm to 2.5 cm and 2.2 cm among G2 and remained unchanged among G3 after adjusting for birthweight (Table 6.6). As a result, the declining class differences in height were still evident after birthweight differences were accounted for.

Table 6.6 Difference in mean height between classes I&II and IV&V before/after adjusting for birthweight

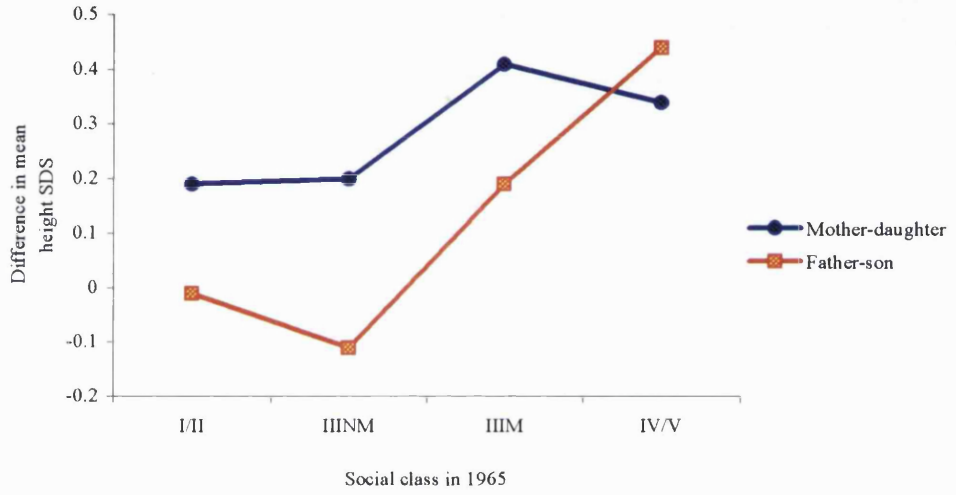
Difference in height (cm)	Unadjusted	Adjusted
G2		
Boys	2.9*	2.5*
Girls	2.6*	2.2*
G3		
Boys	0.7	0.7
Girls	0.8	0.9

* statistically significant $p<0.001$

Further analyses using members from the same family showed that height gains of offspring relative to their parents varied by social class. As shown in Figure 6.2, male offspring had a similar average height to their fathers in classes I&II, whilst in classes IV&V there was an increase of 2.1cm ($p<0.001$). For girls, height gains in offspring relative

to mothers were evident in all social classes, albeit a greater height gain in classes IV&V was not significant (p=0.12).

Figure 6.2 Difference in mean height (SDS) between offspring and their parents by social class in 1965†



† adjusted for age of the offspring

6.4 Discussion

It is well established that children from higher social classes tend to be taller than children from lower social classes [163-165]. Like the impact of early environmental factors on growth trajectory shown in Chapter 4, the association between social class and height of G2 was established in early childhood. The magnitude of the association was at its greatest at age 7 years after the genetic influence of parental height was accounted for. Parental height has

explained a greater deal of variation in height between social classes. Thus parental height is not only a marker of genetic potential, but also an indicator of the early environment of the parents, which in turn is associated with early life conditions of the offspring, as suggested in our study as well as in other studies [248].

It has been suggested that some of the socio-economic class differences seen in childhood height are due to differences in growth tempo [41]. Thus social class influences not only height at a certain age, but also the rate of growth and final adult height [278]. Our analysis from Chapter 4 showed that cohort members from classes IV&V tended to mature later than their counterparts. The current analysis showed that they continued to grow after the age of 16 years, which explains the significant decline in the social class differences in height after the age of 16 (though it is borderline significant in boys p=0.06). As a result, social class differences in height at a certain age do not fully reflect differences in attained adult height because of the phenomenon of catch-up growth during a later period.

It should be noted however, that children from higher social class did not necessarily mature early as shown in Chapter 4. This has been reflected in fact that the difference among girls did not increase at age 11, which would have explained the early growth spurt and maturation of girls from in higher social classes.

Social class differences seen in adult height were already evident in childhood. Subsequent comparison of childhood height between two generations revealed a secular increase in the offspring relative to cohort members, which was mainly due to a greater height gain in classes IV&V, though only significant among males. Thus the decline of social class differences in height between classes I&II and IV&V from more than 2 cm in childhood

among cohort members to less than 1 cm among their offspring is clearly attributed to the greater height increase in manual social class. One possible explanations for the lack of secular trend in higher classes is that environmental conditions for children from higher social classes allow the their genetic potential for growing to be expressed fully [279].

The fact that the decline of class differences in height was still present after the effect of social class on birthweight had been accounted for, suggesting that the narrowing occurred in early childhood, which is a "critical period" for growth in height.

6.4.1 Methodological considerations

A multivariate response model was adopted for the longitudinal growth data to explore the relationships between social class of origin and height at 7, 11, 16, and 33 years simultaneously as in Chapter 4 for the reason that that there were only a small number of measures over a long period of time. Similar to Chapter 5, a single two-level model was applied to compare the social class differences in childhood height in two generations. As the number of subjects in G3 (n=2853) was much smaller than that for G2 (e.g. n=13375 at age 7), the size of the social class effect estimated for cohort members was also calculated for the sample size of the offspring and the effect remained significant. Therefore the non-significance of the difference in the offspring generation was not related to the reduction in the G3 sample compared with G2.

As we have explained earlier, some important information was not collected for the partner of the cohort member. For example, in the offspring generation, only height of the cohort member was measured, while height of the other parent was not available. Therefore

analyses of height gains between mother-daughter and father-son were based on part of the sample. Another drawback created by the lack of partner data is that social class of the maternal or paternal grandfather was used for the offspring, even through their effect on growth of the third generation might be different. Similarly, alternative socio-economic measures, housing tenure and education level were collected only on the cohort member. All analyses therefore had to assume that the maternal and paternal effects of these characters on height of G3 were similar.

Social class of origin for cohort members was used in both generations for several reasons. *Firstly*, the classification of occupations has changed over years, with some jobs previously classified in an unskilled class being reclassified upwards. But social environment of individuals in these occupations might not have been improved more than the others. *Secondly*, social mobility is height related [280;281]. Individuals upwardly mobile are on average taller than those remaining in lower classes, yet shorter than those who are already in higher classes. The reverse is true for individuals who are downwardly mobile [277]. Therefore changes in the structure of society, with relatively large numbers of individuals moving into classes I&II, has resulted in a decrease in size of unskilled social classes. Consequently, the lowest social class has become a more extreme group while the highest social class constitutes a larger part of the population [282]. It has been previously reported that the proportion of men in social classes IV&V declined from 23% in 1965 to 16% in 1991. In contrast, the proportion of individuals in classes I&II increased from 21% to 36% [277].

It has been suggested that changes in structure of society, i.e. with a general trend of upward mobility, have contributed to the diminished inequalities in adult height in the

cohort members. Therefore selective social mobility might have counteracted an equalisation of the height between the two extreme groups. Hence, using a fixed social class measure for both generations ensured that changes in height inequalities were mainly due to changes in social environment. The same measures, housing tenure at age 7, social class and highest educational level at age 33, were used in both generations.

6.4.2 Narrowing inequalities in height

While social class differences in growth still exist in a wide variety of populations [41;86], a trend towards improved standards of living in different socio-economic classes resulting in diminishing of differences in growth has been found in many western countries, though fluctuations and inconsistent trends have been observed [87-89;152;162;164;166;175;268;269;283-285].

A previous study of the 1958 cohort and their parents showed that a secular trend of increase in adult height between two generations was mainly due to a greater height gain in the lowest social classes among males (3.7 cm in classes IV&V comparing with 2.5 cm in classes I&II) [154]. Another study of parents and children of the 1946 and the 1958 cohorts revealed that social class differences in height have diminished gradually for boys in recent years [87]. This current study extended these cross-generational comparisons to a more recent sample. Our finding of a greater height gain for classes IV&V among a younger generation (G3) appears to be a continuation of this trend. More importantly the trend has strengthened in recent years and is now evident for females. Our findings provided further evidence of a greater increase in height in manual class in a recent generation. It has been suggested that social class may not fully reflect early environment, and social inequalities should be assessed by a wider range of socio-economic measures [286]. Our analysis using the

additional measure of childhood socio-economic conditions, housing tenure in 1965, and adult measures, cohort members' social class and highest education level at age 33 also revealed a substantial narrowing. Our results are in agreement with the findings of a narrowing from the 1946 cohort to the 1970 cohort in girls (10 years) and to a recent generation born in the 1980s (Nine Town Study) in boys (7 years) [87].

Although there is little evidence for a reduction in income inequality, the average income has increased over recent decades [210]. Health and welfare have improved in Britain. The diminishing height inequality has occurred during a period of socio-demographic change, such as the reduction in family size, increase in income and home ownership, and improved healthcare and access to higher education, which could partly account for the narrowing [138]. The National Study of Health and Growth (NSHG), measuring height in 5-11 year old children in 1972, 1979, and 1986, also provided supporting evidence on diminishing social class differences in height, as a result of improvements in the mean height of children from unskilled manual classes [287]. In our study, the reduction in the number of children living in extreme disadvantageous conditions in manual classes might have resulted in reducing inequalities in height

We would expect a weaker relationship between social class of origin and height in G3, as the social class of origin for G2 would not necessarily capture the current socio-economic circumstances of the offspring. The intergenerational relationship of social class and height would also be expected to get weaker in successive generations. However, analyses of current socio-economic measures (social class and education level of G2 at age 33) revealed a similar weakening relationship over time.

6.5 Conclusions

The impact of social class on height of cohort members was established in early childhood and was stronger in childhood than in adulthood due to the catch-up growth. The effect of social class of origin on height observed among the 1958 birth cohort has weakened substantially in the offspring generation and was further confirmed by alternative socio-economic measures and adult social position. The significant narrowing of class inequalities was associated with a greater height gain (relative to their parents) among offspring from manual social backgrounds, showing positive progress in the reduction of inequalities in a contemporary sample. As early childhood is a "critical period" for adult disease, the narrowing inequalities are likely to have an impact on health inequalities in the future population, although the causes of this reduced inequality require further clarification.

Chapter 7

Discussion

It has been recognised that factors related to growth in early life may have a long-term impact on adult health. Birthweight and childhood growth have been commonly used as surrogate markers for prenatal and childhood environment. One important purpose of a life-course study is to understand when and how a particular exposure in early life acts on later health. As childhood growth reflects not only early exposures, but also the risk for future health, it is important to understand when an early exposure starts to act and when it is at its strongest, so that critical periods for the early exposure may be identified.

Associations between early life conditions and height at one age are well established. However, rate of growth also mirrors childhood environment. Growth rate from age 3 years to age 20 years was found to be inversely related to blood pressure and serum cholesterol in young adults, independent of birthweight [29]. To date, the evidence on early life influences on the full growth trajectory is sparse, possibly due to the limitation of data available. The the 1958 cohort with longitudinal data from birth to early adulthood and also information on the offspring is a unique sample to examine how early life conditions influence the whole picture of growth from early childhood through to final adult height, and whether these influences extend to the next generation. There have been few published data on the full growth trajectory in a large cohort and height measures of offspring. According to our knowledge, this is the first study to investigate contributions of a wide range of early

environmental factors, including prenatal and early childhood factors, on growth trajectories in detail. Findings from this analysis will provide the evidence of "critical period" during early growth period, which is sensitive to early exposures.

In addition, this is also the first study to explore how early life influences on height have changed across two generations. The findings from a younger generation will enable us to identify factors that remain to be important to growth in height and possibly, to later health.

Before reviewing the main findings of the study, we first discuss the major methodological considerations for our study, in particular, those relating to the strengths and weaknesses of the data, measures, and the statistical approach.

7.1 Methodological considerations

Life-course studies are both theoretically and conceptually complex. Even if the data are ideally suited to the purpose of the study, a life-course approach presents challenges in terms of hypothesis development and methodology. Inevitably, both data structure and limitations require statistical methods that are suited to the research questions posed and are also practical in view of data available. For example, in a study of growth trajectories in the 1958 cohort, height measures would ideally have been taken at more frequent and regular intervals. Additionally, the comparison between two generations would also have included all children of the cohort, rather than only those born to cohort members up to a certain age (33y). However, in practice, complete data coverage is difficult to achieve due to the cost

and time involved. Thus the statistical approaches chosen to test life-course hypotheses should be able to accommodate the data structure and limitations.

Loss in follow-ups is another issue which may lead to problems regarding validity of the inferences drawn from the analysis. Testing for the missing patterns and choosing a statistical approach that can be used even with incomplete data are essential.

7.1.1 Statistical methods

Life-course studies are often interested in longitudinal relationships of early exposures and later health outcomes and have repeated measures from each individual. They sometimes also involve multi-generation studies. One of our study objectives was to explore statistical models that can be applied to make inferences from longitudinal and multi-generational data of the 1958 cohort. In particular, to explore how influences of early conditions on growth vary from childhood to adulthood in one generation and whether these influences persist to their offspring.

The most common approaches for analysing repeated growth measures include growth models and multivariate response models where the correlations of the repeated height measures within each individual are incorporated in the analyses. As discussed in Chapter 3 (§3.3.1), growth models which can provide estimates for growth curves in different groups are suitable when there are a sufficient number of observations for each individual, or when the intervals between successive measures are reasonably small. However, fitting a growth curve becomes impractical when observations are sparse, i.e. at ages 7, 11, 16, and 33 years. As a result, the growth trajectory or the effect of an early life factor on the trajectory

cannot be modelled smoothly, or with a complex function. Therefore, multivariate response models were adopted here to explore the impact of early life circumstances on height growth at different stages and final adult height simultaneously. Even though a multivariate response model assumes the time of each measurement to be a fixed occasion and the length of time between any two measurements is not accounted for, it has unique advantages to compare the strength of an effect on height at different ages directly as well as to test for the time trend of the effect.

Similar to growth models, a multivariate response model also has the flexibility for studying changes and comparing trajectories in the presence of incomplete data on response variables. It is therefore possible to include subjects with one height measure (or more) in the analysis. The estimates from the multivariate response model should be efficient as the assumptions that the response variable is missing at random (MAR) and the missing patterns do not affect the relationships under investigation are valid in the data.

For the comparison of early life influences on childhood height in two generations of the cohort, the analysis was complicated by the fact that the two generations were not independent. We adopted a single two-level model, which incorporates the data structure, that is, the correlation between cohort members and the offspring from the same family and the offspring (G3) from the same family. The model assumes that cohort members and the offspring are at the same level (level-1) and clustered in the higher-level units (families) so that the difference in an effect between two generations can be tested.

7.1.2 Strengths and limitations of the data

This study is based on a large population sample over three decades, with relevant data across three generations. Such data have major strengths for exploring life-course relationships in each generation and how these relationships change across two generations.

Generalising our findings from the cohort to current adults in Britain requires that the sample is representative of the population. While members of the original 1958 cohort were predominantly white, the present British population of 45-year-olds includes a diversity of ethnic groups. Although immigrants born in the study week were added to the sample in childhood, there has been a great increase in immigration in recent decades. Ethnic minorities are likely to be under-represented in the 1958 cohort. However, the sample surveyed in 1991 is similar to the national population with respect to key socio-economic characteristics [178]. Thus, inferences drawn from the cohort should still be relevant to the current adult population in Britain.

We would expect that life-course relationships will vary between individuals born at different times or in different places because of the variation in early nutrition and environment. Height of the 1958 cohort was a measure of early life conditions over three decades ago. Thus cohort members would have experienced more socio-economic adversity in childhood compared to current British children. It is therefore not clear whether life-course relationships found in the cohort generation would still apply to the next generation. However, the recognition of changes in the impact of early life conditions on height over time is important within life-course epidemiology. Factors that are associated with childhood growth in a younger generation are likely to be still associated with risks for adult disease in future population. Even though the impact of some early life factors on

height found in the cohort was weakened in their offspring, the offspring findings are useful for determining (1) whether height is still a mirror of conditions in society in the younger generation, and (2) the extent of current height inequalities in children in Britain.

Therefore, results from the offspring generation are relevant to current height inequalities and also possibly to future inequalities in adult health, whereas the findings reported for the older generation are still important for understanding how early life influences have affected growth, because these early growth patterns found in the cohort as well as their determinants are expected to be relevant to disease risks in this contemporary adult population.

Early life environment includes times during both fetal life and childhood. One important advantage of studying the 1958 cohort and their offspring is to identify the "critical periods" during fetal development as well early childhood, when the associations between early conditions and height are established. For example, the period during fetal development is "critical"; adverse fetal conditions are not only associated with being small at birth, but also have an impact on postnatal growth. Although children with growth deficits during fetal development normally catch up during infancy, early catch-up is sensitive to early nutrition and environment. Thus infancy is also crucial in relation to growth in height and adult health. Final adult height is set early in childhood and early life conditions seem to affect adult height to a greater extent than conditions in later life. Thus exposure in childhood may have a life-long impact on later health.

It is important to note that cross-generational comparisons should take into account the changing structure of society [138] and height related social mobility [277]. Compared to their

parent's generation or children of their age in general, the offspring were born to parents with a smaller age variation, whereas offspring themselves had a much larger age range, which may affect some relationships due to their stage of puberty. However, despite the under-representation of lone- and young-parent families and over-representation of first-born children, the offspring sample was comparable with children of their age in the general population with respect major characteristics such as birthweight, height, and social class. Thus, influences on height of the offspring should still be relevant to children of their age in Britain.

One disadvantage of the data for the cohort is that height measures on individuals are widely spaced and it is therefore impossible to identify any changes of the early life influences on growth occurring between two measurements. For example, if the influence of a specific factor on height reduced between two successive ages, it may not have reduced monotonically and may have increased at any stage during that period. Events may be missing for vital points of a trajectory, for example, at the start of a growth spurt or the maximum growth velocity. In life-course analysis, it may be hard to identify critical periods for specific exposures, which are associated with events such as the growth spurt.

7.2 Main findings and comparison with other studies

7.2.1 Main findings

Six main findings are identified from this study. *First*, within the cohort, early life factors including maternal smoking, family size, household crowding, social class, and parental

divorce were associated with height at all ages, with the associations being stronger in childhood than in adulthood. *Second*, among these factors, family size, household crowding and social class were also associated with age of maturation. *Third*, in both generations parental height was most strongly associated with offspring height among all factors. Its impact persisted throughout childhood, and was stronger by adulthood. *Fourth*, while the impact of parental height and birthweight on offspring height remained strong, many early life factors, such as breastfeeding, maternal smoking during pregnancy, maternal age at childbirth, number of younger siblings, social class, household crowding, and maternal education were no longer significant in the next generation. The only factors that were consistently associated with height in both generations were birth order and housing tenure. *Fifth*, there was an increase of 1 cm in childhood height between the two generations, while no increase was found in birthweight. This increase in postnatal growth was due to a greater height gain in manual social groups compared to non-manual classes. *Finally*, the social class difference in height observed in cohort members was reduced and no longer significant among their offspring, showing a narrowing in inequalities in height.

Whist the influence of all the factors investigated on height have already been established in early childhood, their impact on subsequent growth trajectory differs by age depending on how they affect the tempo of growth. Thus some factors were associated with delayed growth, whereas the impact of other factors remained constant throughout the life-course.

With the improvement of socio-economic conditions in recent decades [138], we would expect that the impact of many early environmental influences on height to have reduced, while the effect of biological influences would remain. For example, factors influencing or indicating fetal development, such as maternal smoking, parity, and birthweight are thought

to be biological and therefore their influence on postnatal growth should persist to the recent generation.

In this study, we were able to show how biological and environmental influences during fetal and childhood development change through the life-course from a generation born in the 1950s to a recent generation of children in Britain.

7.2.2 Fetal environment

A large literature has shown a strong positive association between birthweight and height in childhood [161;244;288] and adulthood [244;289]. Even though we have found a correlation of 0.18 between birthweight and parental height in the cohort, birthweight is still an important predictor of final height with respect to target height. This is supported by a twins study, which shows that the twin who was heavier at birth was taller as an adult [290]. Our results from the 1958 cohort suggest that reduced intrauterine growth, indicated as small for gestational age, has a long-term effect on growth, as shown in other studies [64;288;291]. Although infants with low birthweight may experience catch-up growth during the first two years, they are more likely to remain shorter throughout childhood. We would expect that the influence of birthweight on height was weakened with increasing age due to catch-up growth, but surprisingly, the effect of birthweight was stronger on adult height than on childhood height, which was due to a genetic influence rather than the socio-environmental components of birthweight.

An impact of maternal smoking on postnatal growth was found in the 1958 cohort, independent of birthweight, suggesting the possibility of postnatal growth inhibition caused

by tobacco exposure in utero [71]. It has been suggested in other studies that deficits in height due to maternal smoking persist even to adulthood [68-70]. But in our study there was no evidence of a direct causal effect of maternal smoking on final adult height. Our results also showed a faster growth rate and a longer growth period among children of smoker mothers (though non-significant) as suggested by others [70]. The mechanisms that regulate postnatal catch-up growth are not clear. It is likely that postnatal growth rates are influenced by maternal uterine factors. Results from the cohort suggest that tobacco exposure in utero is not only due to the social environment. Thus we might expect that an impact of maternal smoking on childhood growth is biological and as such, it should still apply to the younger generation. But we found that the reduction in childhood height did not persist to the offspring generation. This suggests that offspring had complete catch-up in the first few years of life due to the improved nutrition and social environment. Similar findings have been reported in a recent British birth cohort (ALSPAC cohort), in which children of smoker mothers had complete catch-up growth in height over the first two years [4].

Birth order is known to be associated with both birthweight and height [83;85] . The direction of the association between birth order and growth has reversed after birth; first-born children were lighter and shorter at birth, but they show dramatic catch-up growth in height that over-compensate their impaired fetal growth and over take their counterparts to become tall in stature as suggested by others [83]. Our results show that the impact of birth order on postnatal growth remained strong, even when genetic potential and socio-economic background were considered. Thus, same as birthweight, birth order may be reflecting a biological rather than an environmental influence on height.

Children with fetal growth retardation would experience catch-up growth during early childhood. Postnatal growth rates seem to be strongly influenced by a drive to compensate for the adverse fetal environment. Evidence has shown that catch-up growth is predicted by low leptin levels at birth, which is associated with maternal smoking and low birthweight [252;253]. Lower levels of leptin may lead to the increased appetite which results in the greater postnatal growth rate among children with restrained fetal growth [252;253;292]. Thus restriction in *utero* can be compensated by early nutrition. We have shown that the influence of birth order on height is explained by family size. Thus first-born children who over took their counterparts in height were likely to have the better conditions in early life, as they are more likely to come from small families. Similarly, the improved nutrition during infancy might have explained the weakened relationship in the offspring.

Adverse fetal environment does not necessarily lead to short adult stature due to catch-up growth at a later stage, insults during fetal development or delay in growth due to the insults may have life-long health consequences. For example, perinatal growth failure has been associated with increased risk for obesity, insulin resistance, and cardiovascular disease in adulthood [293]. Maternal smoking during pregnancy is also linked to increased susceptibility to respiratory diseases, behavioural disorder, deficits in bone mineral density, and obesity [294-297]. Therefore, intrauterine environment is crucial not only for growth in height, but also for adult health.

7.2.3 Early childhood environment

We would expect that the influence of early environment (1) to be greater on childhood height than adult height due to catch-up growth, and (2) to be weaker in the next generation due to the improvement of socio-economic conditions in Britain.

It has been reported that breastfeeding in the early 1920s-1940s in Britain had a significant positive impact on growth in height, which persisted to adulthood [81]. This implicates early nutrition as an important influence on growth. However, good quality alternatives to breastfeeding are now widely available in UK and in many other countries. As we would have expected, we found no association between breastfeeding and childhood height in the 1958 cohort and in the offspring after taking into account of other early life factors, suggesting that it is early nutrition, rather than breast milk that is important to early growth in height. In a British cohort born in 1991-1992 (ALSPAC cohort), breastfed children even had a slower length gain than bottle-fed children during infancy, suggesting that bottle-fed babies might have higher total energy and protein intake than breastfed babies [83].

In contrast to parental height and birthweight, factors representing early life environment including family size, crowding, and social class, had a stronger impact on childhood than adult height in our study as suggested by others [151], with children from large families, overcrowded conditions, and manual social class showing catch-up throughout the growth period. Our findings highlighted the importance of the early growth period, as childhood height is more sensitive to early environment than final adult height. This catch-up growth is due to the fact that early life conditions influence height partly through their influence on the tempo of growth [84]. Although children with growth deficits due to unfavourable early conditions may catch up, if not fully, at least partially, it remains uncertain whether delay in

growth will have an impact on later health. It has been suggested that poor growth in childhood resulting from adversity in early life may underlie the relationship between adverse early exposure and cardiovascular diseases and respiratory diseases [5;14;15;23;36;37]. Impaired postnatal growth has been found to be associated with increased blood pressure, cardiovascular disease, and poor cognitive function [26-31]. There is a large literature showing a strong link between adult stature and mortality and morbidity (Table A1.1), it may be that delay in growth as well as failure to catch up are associated with increased risk for later diseases. However, it remains to be seen whether delayed growth with catch-up at a later stage has a life-long health impact.

Child health and nutrition, and material circumstances of childhood have improved dramatically over recent decades. This is reflected in the continuing secular increase in height found between the cohort and the offspring (1 cm). A decline in social class variation in height has been seen in Britain. The social class differences in childhood height were greatly reduced between successive cohorts (1946, 1958, and 1970 cohorts) due to a greater increase by children in the lowest social classes [138]. Our finding of the decline in the importance of early life factors in offspring provided further evidence of the diminishing social inequalities in height. Given that height reflects childhood circumstances and risks for later health, the inequalities in height found in cohort members provide evidence for health inequalities in current British adult population. More importantly, the findings on the relationship between socio-environment and height among the offspring are valuable for the reason that they reflect not only the state of inequalities in the current society, but also inequalities in health in the future adult population in Britain.

It is important to note that the weaker environmental effects in the younger generation may be partly due to reduced variation in environmental conditions in the offspring; the proportions of offspring living in overcrowded conditions, from large families or lower social classes were smaller than for cohort members. In a comparison of three British cohorts, average income, number of homeowners, and access to higher education have all been found to have improved over recent generations [138]. The improvement of the socio-economic conditions among the offspring of the 1958 cohort was likely to be the continuation of this trend.

Parental divorce was associated with short stature in childhood, independent of socio-economic conditions in boys, suggesting the possibility of an effect of stress, rather than the hardship due to the divorce. No association was found between parental divorce and height in the offspring, possibly due to the different stages of growth, as the duration was found to be important. In both generations, children whose parents separated between 4-7 years were significantly shorter at age 7 years than the others even after adjusting for early life factors. Whether the delay of growth due to stress will have a life-long impact on health is not clear. However, it has been suggested that stress in childhood is associated with depression, anxiety, and personality disorder, which are all thought to increase the risk of cardiovascular disease, stroke, and chronic lung diseases [298].

In summary, childhood height is sensitive to environment, while adult height is more genetically influenced. The relationship between parental height and height of children has strengthened and in the meantime the proportion of total variation in height contributable to early circumstances has diminished in the next generation. Hereditability is likely to be higher in a generation with a higher standard of living because of the weaker effect of

environmental factors. Even so, height of offspring is still a "mirror" of the society, which shows the improvement of social and material conditions in Britain.

7.3 Potential area for future development

Results from the current study suggest that childhood height is a better indicator for early circumstances than final adult height, while adult height fails to capture the full impact of early life circumstances. Thus studies of the effect of postnatal growth on adult health should use height in childhood, preferably, the full growth trajectory. With the collection of new information on cohort member at age 41, and most recently health outcomes at age 43 years, the causal pathways effects of fetal development, childhood to adult growth trajectory, components of height (i.e. leg or trunk length), and exposures at all life stages (including previous generation, fetal, childhood and later life conditions), in relation to adult disease can be explored in detail, in particular to investigate whether delay in growth has a life-long health impact which may be modified by catch-up growth.

Another potential area for future development is to investigate height and BMI trajectories, and tempo of growth (age of menarche) simultaneously to explore their inter-relationships as well as their associations with early life exposures to enhance our knowledge of the causal pathways and underlying mechanism of adult disease.

References

1. Hertzman C, Power C, Matthews S, Manor O. Using an interactive framework of society and lifecourse to explain self-rated health in early adulthood. *Soc.Sci.Med.* 2001;**53**:1575-85.

2. Leon DA, Koupilova I, Lithell HO, Berglund L, Mohsen R, Vagero D, Lithell UB, McKeigue PM. Failure to realise growth potential in utero and adult obesity in relation to blood pressure in 50 year old Swedish men [see comments]. *BMJ* 1996;**312**:401-6.

3. Forsen T, Eriksson JG, Tuomilehto J, Osmond C, Barker DJ. Growth in utero and during childhood among women who develop coronary heart disease: longitudinal study. *BMJ* 1999;**319**:1403-7.

4. Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunger DB. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. *BMJ* 2000;**320**:967-71.

5. Davey-Smith G, Hart C, Blane D, Hole D. Adverse socioeconomic conditions in childhood and cause specific adult mortality: prospective observational study. *BMJ* 1998;**316**:1631-5.

6. Eriksson JG, Forsen T, Tuomilehto J, Winter PD, Osmond C, Barker DJ. Catch-up growth in childhood and death from coronary heart disease: longitudinal study. *BMJ* 1999;**318**:427-31.

7. Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJ. Early growth and coronary heart disease in later life: longitudinal study. *BMJ* 2001;**322**:949-53.

8. Brunner E, Shipley MJ, Blane D, Smith GD, Marmot MG. When does cardiovascular risk start? Past and present socioeconomic circumstances and risk factors in adulthood. *J.Epidemiol.Community Health* 1999;**53**:757-64.

9. Kuh, D. and Ben-Shlomo, Y. A Life Course Approach to Chronic Disease Epidemiology. Oxford: Oxford University Press, 1997.

10. Waaler HTH. Height, weight and mortality. The Norwegian experience. *Acta Medica Scandinavica* 1984;**S679**:1-56.

11. Marmot MG, Shipley MJ, Rose G. Inequalities in death--specific explanations of a general pattern? *Lancet* 1984;**1**:1003-6.

12. Nystrom Peck AM, Vagero DH. Adult body height, self perceived health and mortality in the Swedish population. *J.Epidemiol.Community Health* 1989;**43**:380-4.

13. Yarnell JW, Limb ES, Layzell JM, Baker IA. Height: a risk marker for ischaemic heart disease: prospective results from the Caerphilly and Speedwell Heart Disease Studies. *Eur.Heart J* 1992;**13**:1602-5.

14. Leon DA, Davey-Smith G, Shipley M, Strachan D. Adult height and mortality in London: early life, socio economic confounding or shrinkage? *J.Epidemiol.Community.Health.* 1995;**49**:5-9.

15. Davey-Smith G, Hart C, Upton M, Hole D, Gillis C, Watt G, Hawthorne V. Height and risk of death among men and women: aetiological implications of associations with cardiorespiratory disease and cancer mortality. *J.Epidemiol Community Health* 2000;**54**:97-103.

16. McCarron P, Okasha M, McEwen J, Smith GD. Height in young adulthood and risk of death from cardiorespiratory disease: a prospective study of male former students of Glasgow University, Scotland. *Am.J.Epidemiol.* 2002;**155**:683-7.

17. Hebert PR, Rich-Edwards JW, Manson JE, Ridker PM, Cook NR, O'Connor GT, Buring JE, Hennekens CH. Height and incidence of cardiovascular disease in male physicians. *Circulation* 1993;**88**:1437-43.

18. Goldbourt U, Tanne D. Body height is associated with decreased long-term stroke but not coronary heart disease mortality? *Stroke* 2002;**33**:743-8.

19. Wannamethee SG, Shaper AG, Whincup PH, Walker M. Adult height, stroke, and coronary heart disease. *Am.J.Epidemiol.* 1998;**148**:1069-76.

20. Hart CL, Hole DJ, Smith GD. Risk factors and 20-year stroke mortality in men and women in the Renfrew/Paisley study in Scotland. *Stroke* 1999;**30**:1999-2007.

21. McCarron P, Greenwood R, Ebrahim S, Elwood P, Smith GD. Adult height is inversely associated with ischaemic stroke. The Caerphilly and Speedwell collaborative studies. *J.Epidemiol.Community Health* 2000;**54**:239-40.

22. Albanes D, Jones YD, Schatzkin A, Micozzi MS, Taylor PR. Adult stature and risk of cancer. *Cancer.Res.* 1988;**48**:1658-62.

23. Gunnell DJ, Smith GD, Holly JM, Frankel S. Leg length and risk of cancer in the Boyd Orr cohort. *BMJ* 1998;**317**:1350-1.

24. Davey-Smith G, Shipley M, Leon DA. Height and mortality from cancer among men: prospective observational study. *BMJ* 1998;**317**:1351-2.

25. Meyer HE, Tverdal A, Falch JA. Risk factors for hip fracture in middle-aged Norwegian women and men. *Am.J.Epidemiol* 1993;**137**:1203-11.

26. Whincup PH, Cook DG, Adshead F, Taylor S, Papacosta O, Walker M, Wilson V. Cardiovascular risk factors in British children from towns with widely differing adult cardiovascular mortality. *BMJ* 1996;**313**:79-84.

27. Montgomery SM, Berney LR, Blane D. Prepubertal stature and blood pressure in early old age. *Arch.Dis.Child* 2000;**82**:358-63.

28. Gaskin PS, Walker SP, Forrester TE, Grantham-McGregor SM. Early linear growth retardation and later blood pressure. *Eur.J.Clin.Nutr.* 2000;**54**:563-7.

29. Miura K, Nakagawa H, Tabata M, Morikawa Y, Nishijo M, Kagamimori S. Birth weight, childhood growth, and cardiovascular disease risk factors in Japanese aged 20 years. *Am.J.Epidemiol* 2001;**153**:783-9.

30. Gunnell DJ, Davey Smith G, Frankel S, Nanchahal K, Braddon FEM, Pemberton J, Peters TJ. Childhood leg length and adult mortality: follow up of the Carnegie (Boyd Orr) Survey of Diet and Health in Pre-war Britain. *J Epidem Comm Health* 1998;**52**:142-52.

31. Richards M, Hardy R, Kuh D, Wadsworth ME. Birthweight, postnatal growth and cognitive function in a national UK birth cohort. *Int.J.Epidemiol.* 2002;**31**:342-8.

32. Cooper C, Eriksson JG, Forsen T, Osmond C, Tuomilehto J, Barker DJ. Maternal height, childhood growth and risk of hip fracture in later life: a longitudinal study. *Osteoporos.Int.* 2001;**12**:623-9.

33. Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJ. Early growth, adult income, and risk of stroke. *Stroke* 2000;**31**:869-74.

34. Wadsworth M, Hardy R, Paul A, Marshall S, Cole T. Leg and trunk length at 43 years in relation to childhood health, diet and family circumstances; evidence from the 1946 national birth cohort. *Int.J.Epidemiol.* 2002;**31**:383-90.

35. Davey-Smith D, Greenwood R, Gunnell D, Sweetnam P, Yarnell J, Elwood P. Leg length, insulin resistance, and coronary heart disease risk: the Caerphilly Study. *J.Epidemiol.Community Health* 2001;**55**:867-72.

36. Andersson SO, Wolk A, Bergstrom R, Adami HO, Engholm G, Englund A, Nyren O. Body size and prostate cancer: a 20-year follow-up study among 135006 Swedish construction workers. *J.Natl.Cancer Inst.* 1997;**89**:385-9.

37. Frankel S, Gunnell DJ, Peters TJ, Maynard M, Davey SG. Childhood energy intake and adult mortality from cancer: the Boyd Orr Cohort Study. *BMJ* 1998;**316**:499-504.

38. Barker DJP. Mothers, Babies and Disease in Later Life. Tavistock, London: BMJ, 1994.

39. Luo ZC, Karlberg J. Critical growth phases for adult shortness. *Am.J.Epidemiol.* 2000;**152**:125-31.

40. Bielicki T. Physical Growth as a Measure of the Economic Well-being of Populations: The Twentieth Century. In Falkner F, Tanner JM, eds. *Human Growth*, New York: Plenum Press, 1986.

41. Eveleth PB, Tanner JM. Environmental influences on growth. In *Worldwide Variation in Human Growth.* Cambridge: CUP, 1990.

42. World Health Organisation. New trends and approaches in the Devivery of Maternal and Child Care in Health Services. *Sixth report of the WHO Expert Committee on Maternal and Child Care, WHO techenique reports Series no 600*, Geneva: WHO, 1976.

43. Butler, N. R. and Alberman, E. Perinatal Problems. Edinburgh and London: E. & S. Livingstone Ltd, 1969.

44. Kantero RL, Tiisala R. Studies on growth of Finnish children from birth to 10 years. IV. Height, weight and sitting height increments for children from birth to 10 years. A mixed longitudinal study. *Acta Paediatr.Scand.Suppl* 1971;**220**:18-26.

45. Sinclair DDP. Human Growth After Birth. Oxford Medical Publications, 1998.

46. Douglas JWB, Simpson HR. Height in relation to puberty, family size and social class. A longitudinal study. *Milbank Memorial Fund Quarterly* 1964;**42**:20-35.

47. Qamra SR, Mehta S, Deodhar SD. A mixed-longitudinal study on the pattern of pubertal growth: relationship to socioeconomic status and caloric-intake--IV. *Indian Pediatr.* 1991;**28**:147-56.

48. Sanchez-Andres A. Genetic and environmental factors affecting menarcheal age in Spanish women. *Anthropol.Anz.* 1997;**55**:69-78.

49. Preece MA, Heinrich I. Mathematical modelling of individual growth curves. *Br.Med.Bull.* 1981;**37**:247-52.

50. Karlberg J, Engstrom I, Karlberg P, Fryer JG. Analysis of linear growth using a mathematical model. I. From birth to three years. *Acta Paediatr.Scand.* 1987;**76**:478-88.

51. Karlberg J, Fryer JG, Engstrom I, Karlberg P. Analysis of linear growth using a mathematical model. II. From 3 to 21 years of age. *Acta Paediatr.Scand.Suppl* 1987;**337**:12-29.

52. Karlberg J. On the modelling of human growth. *Stat.Med.* 1987;**6**:185-92.

53. Karlberg J. A biologically-oriented mathematical model (ICP) for human growth. *Acta Paediatr.Scand.Suppl* 1989;**350**:70-94.

54. Bock RD, Thissen DM. Fitting multicomponent models for growth in stature. *Proceedings of the Ninth International Biometric Conference, Boston, August 22-27, The Biometric Society, Releigh, North Carolina* 1976;431-42.

55. Jolicoeur P, Pontier J, Pernin MO, Sempe M. A lifetime asymptotic growth curve for human height. *Biometrics* 1988;**44**:995-1003.

56. Jolicoeur P, Pontier J, Abidi H. Asypototic Models for the Longitudinal Growth of Human Stature. *Am.J.Human Biol.* 1992;**4**:461-8.

57. Goldstein H. Factors influencing the height of seven-year-old children. Results from the National Child Development Study (1958 cohort). *Hum.Biol.* 1971;**43**:92-111.

58. Gulliford MC, Chinn S, Rona RJ. Social environment and height: England and Scotland 1987 and 1988. *Arch.Dis.Child* 1991;**66**:235-40.

59. Herngreen WP, van Buuren S, van Wieringen JC, Reerink JD, Verloove-Vanhorick SP, Ruys JH. Growth in length and weight from birth to 2 years of a representative sample of Netherlands children (born in 1988-89) related to socioeconomic status and other background characteristics. *Ann.Hum.Biol.* 1994;**21**:449-63.

60. Bobak M, Kriz B, Leon DA, Danova J, Marmot M. Socioeconomic factors and height of preschool children in the Czech Republic. *Am.J.Public Health* 1994;**84**:1167-70.

61. Rona RJ, Swan AV, Altman DG. Social factors and height of primary schoolchildren in England and Scotland. *J.Epidemiol Community Health* 1978;**32**:147-54.

62. Tanner JM, Goldstein H, Whitehouse RH. Standards for children's height at ages 2-9 years allowing for heights of parents. *Arch.Dis.Child* 1970;**45**:755-62.

63. Wright CM, Cheetham TD. The strengths and limitations of parental heights as a predictor of attained height. *Arch.Dis.Child* 1999;**81**:257-60.

64. Schmidt IM, Jorgensen MH, Michaelsen KF. Height of conscripts in Europe: is postneonatal mortality a predictor? *Ann.Hum.Biol.* 1995;**22**:57-67.

65. Pietilainen KH, Kaprio J, Rasanen M, Winter T, Rissanen A, Rose RJ. Tracking of body size from birth to late adolescence: contributions of birth length, birth weight, duration of gestation, parents' body size, and twinship. *Am.J.Epidemiol.* 2001;**154**:21-9.

66. Butler NR, Goldstein H, Ross EM. Cigarette smoking in pregnancy: its influence on birth weight and perinatal mortality. *Br.Med.J.* 1972;**2**:127-30.

67. Sexton M, Hebel JR. A clinical trial of change in maternal smoking and its effect on birth weight. *JAMA* 1984;**251**:911-5.

68. Butler NR, Goldstein H. Smoking in pregnancy and subsequent child development. *Br.Med.J.* 1973;**iv**:573-5.

69. Rantakallio P. A follow-up study up to the age of 14 of children whose mothers smoked during pregnancy. *Acta Paediatr.Scand.* 1983;**72**:747-53.

70. Fogelman K, Manor O. Smoking in pregnancy and development into early adulthood. *BMJ* 1988;**297**:1233-6.

71. Fox NL, Sexton M, Hebel JR. Prenatal exposure to tobacco: I. Effects on physical growth at age three. *Int.J.Epidemiol.* 1990;**19**:66-71.

72. Garza C, Frongillo E, Dewey KG. Implications of growth patterns of breast-fed infants for growth references. *Acta Paediatr.Suppl* 1994;**402**:4-10.

73. Adair L, Popkin BM, VanDerslice J, Akin J, Guilkey D, Black R, Briscoe J, Flieger W. Growth dynamics during the first two years of life: a prospective study in the Philippines. *Eur.J.Clin.Nutr.* 1993;**47**:42-51.

74. Dewey KG, Peerson JM, Brown KH, Krebs NF, Michaelsen KF, Persson LA, Salmenpera L, Whitehead RG, Yeung DL. Growth of breast-fed infants deviates from current reference data: a pooled analysis of US, Canadian, and European data sets. World Health Organization Working Group on Infant Growth. *Pediatrics* 1995;**96**:495-503.

75. Dewey KG. Cross-cultural patterns of growth and nutritional status of breast-fed infants. *Am.J.Clin.Nutr.* 1998;**67**:10-7.

76. Eckhardt CL, Rivera J, Adair LS, Martorell R. Full breast-feeding for at least four months has differential effects on growth before and after six months of age among children in a Mexican community. *J.Nutr.* 2001;**131**:2304-9.

77. Mosley WH, Chen LC. Child survival strategies for research. *Population and Development Review* 1984;**10**:94-105.

78. Stephensen CB. Burden of infection on growth failure. *J.Nutr.* 1999;**129**:534S-8S.

79. Donma MM, Donma O. Infant feeding and growth: a study on Turkish infants from birth to 6 months. *Pediatr.Int.* 1999;**41**:542-8.

80. Ng'andu NH, Watts TE. Child growth and duration of breastfeeding in urban Zambia. *J.Epidemiol Community Health* 1990;**44**:281-5.

81. Martin RM, Smith GD, Mangtani P, Frankel S, Gunnell D. Association between breast feeding and growth: the Boyd-Orr cohort study. *Arch.Dis.Child Fetal Neonatal Ed* 2002;**87**:F193-F201.

82. Taylor B, Wadsworth J. Breast feeding and child development at five years. *Dev.Med.Child Neurol.* 1984;**26**:73-80.

83. Ong KK, Preece MA, Emmett PM, Ahmed ML, Dunger DB. Size at birth and early childhood growth in relation to maternal smoking, parity and infant breast-feeding: longitudinal birth cohort study and analysis. *Pediatr.Res.* 2002;**52**:863-7.

84. Fogelman, K. Ed.Fogelman, K. Ed. Growing up in Great Britain. London: Macmillan, 1983.

85. Kuh DL, Wadsworth M. Parental height: childhood environment and subsequent adult height in a national birth cohort. *Int.J.Epidemiol* 1989;**18**:663-8.

86. Lasker GW, Mascie-Taylor CGN. Effects of social class differences and social mobility on growth in height, weight and body mass index in a British cohort. *Ann.Hum.Biol.* 1989;**16**:1-8.

87. Kuh DL, Power C, Rodgers B. Secular trends in social class and sex differences in adult height. *Int.J.Epidemiol.* 1991;**20**:1001-9.

88. Lindgren GW, Cernerud L. Physical growth and socioeconomic background of Stockholm schoolchildren born in 1933-63. *Ann.Hum.Biol.* 1992;**19**:1-16.

89. Brundtland GH, Liestol K, Walloe L. Height, weight and menarcheal age of Oslo schoolchildren during the last 60 years. *Ann.Hum.Biol.* 1980;**7**:307-22.

90. Cernerud L. Are there still social inequalities in height and body mass index of Stockholm children? *Scand.J.Soc.Med.* 1994;**22**:161-5.

91. Elliott BJ, Richards MP. Effects of parental divorce on children. *Arch.Dis.Child* 1991;**66**:915-6.

92. Power C, Manor O. Asthma, enuresis and chronic illness: long-term impact on height. *Arch.Dis.Child.* 1995;**73**:298-304.

93. Hulanicka B, Gronkiewicz L, Koniarek J. Effect of familial distress on growth and maturation of girls: a longitudinal study. *American Journal of Human Biology* 2001;**13**:771-6.

94. Montgomery SM, Bartley MJ, Wilkinson RG. Family conflict and slow growth. *Arch.Dis.Child* 1997;**77**:326-30.

95. Wales JK, Herber SM, Taitz LS. Height and body proportions in child abuse. *Arch.Dis.Child* 1992;**67**:632-5.

96. Rona RJ, Florey CdV. National study of health and growth: respiratory symptoms and height in primary schoolchildren. *Int.J.Epidemiol.* 1980;**9**:35-43.

97. Hauspie R, Susanne C, Alexander F. Maturational delay and temporal growth retardation in asthmatic boys. *J.Allergy Clin.Immunol.* 1977;**59**:200-6.

98. Peckham C, Butler N. A national study of asthma in childhood. *J Epidem Comm Health* 1978;**32**:79-85.

99. Hughes JM, Li L, Chinn S, Rona RJ. Trends in growth in England and Scotland, 1972 to 1994. *Arch.Dis.Child* 1997;**76**:182-9.

100. Xu X, Wang WP, Guo ZP, Cheung YB, Karlberg J. Seasonality of growth in Shanghai infants (n=4128) born in 11 consecutive years. *Eur.J.Clin.Nutr.* 2001;**55**:714-25.

101. Tanner JM, Hayashi T, Preece MA, Cameron N. Increase in length of leg relative to trunk in Japanese children and adults from 1957 to 1977: comparison with British and with Japanese Americans. *Ann.Hum.Biol.* 1982;**9**:411-23.

102. Cole TJ. Secular trends in growth. *Proc.Nutr.Soc.* 2000;**59**:317-24.

103. Hauspie RC, Vercauteren M, Susanne C. Secular changes in growth and maturation: an update. *Acta Paediatr.Suppl* 1997;**423**:20-7.

104. Takaishi M. Growth standards for Japanese children-an overview with special reference to secular trend in growth. In Hauspie R, Lindgren G, Falkner F, eds. *Essays on auxology presented to James Mourilyannnn Tanner by former collegues and fellows*, 1995.

105. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, Roede MJ, Verloove-Vanhorick SP, Wit JM. Continuing positive secular growth change in The Netherlands 1955-1997. *Pediatr.Res.* 2000;**47**:316-23.

106. Liestol K, Rosenberg M. Height, weight and menarcheal age of schoolgirls in Oslo--an update. *Ann.Hum.Biol.* 1995;**22**:199-205.

107. Lindgren GW, Hauspie RC. Heights and weights of Swedish school children born in 1955 and 1967. *Ann Human Biol* 1989;**16**:397-406.

108. Rosenberg M. Birth weights in three Norwegian cities, 1860-1984. Secular trends and influencing factors. *Ann.Hum.Biol.* 1988;**15**:275-88.

109. Alberman E. Are our babies becoming bigger? *J Roy Soc Med* 1991;**84**:257-60.

110. Power C. National trends in birth weight: implications for future adult disease. *BMJ* 1994;**308**:1270-1.

111. Moser K, Li L, Power C. Social inequalities in low birthweight in England and Wales: trends and implications for future population health. *J.Epidemiol Community Health* 2003; **To appear**.

112. Eveleth PB, Tanner B. Worldwide Variation in Human Growth. Cambridge: CUP, 1990.

113. Cameron N. The growth of London schoolchildren 1904-1966: an analysis of secular trend and intra-county variation. *Ann.Hum.Biol.* 1979;**6**:505-25.

114. Olesen AW, Jeune B, Boldsen JL. A continuous decline in menarcheal age in Denmark. *Ann.Hum.Biol.* 2000;**27**:377-86.

115. Gerver WJ, De Bruin R, Drayer NM. A persisting secular trend for body measurements in Dutch children. The Oosterwolde II Study. *Acta Paediatr.* 1994;**83**:812-4.

116. Danker-Hopfe H, Roczen K. Secular trends in height, weight and body mass index of 6-year-old children in Bremerhaven. *Ann.Hum.Biol.* 2000;**27**:263-70.

117. Takaishi M. Secular changes in growth of Japanese children. *J.Pediatr.Endocrinol.* 1994;**7**:163-73.

118. Chinn S, Rona RJ, Price CE. The secular trend in height of primary school children in England and Scotland 1972-79 and 1979-86. *Ann.Hum.Biol.* 1989;**16**:387-95.

119. Werner B. Fertility trends in the UK and in thirteen other development countries, 1966-86. *Population Trends* 1988;**51**:18-24.

120. van Wieringen. Secular growth changes. In Falkner F, Tanner J, eds. *Human Growth*, New York: Plenum Press, 1986.

121. Rockhill B, Moorman PG, Newman B. Age at menarche, time to regular cycling, and breast cancer (North Carolina, United States). *Cancer Causes Control* 1998;**9**:447-53.

122. Power C, Lake JK, Cole TJ. Body mass index and height childhood to adulthood in the 1958 British born cohort. *Am.J.Clin.Nutr.* 1997;**66**:1094-101.

123. Adair LS, Gordon-Larsen P. Maturational timing and overweight prevalence in US adolescent girls. *Am.J.Public Health* 2001;**91**:642-4.

124. Bielicki T, Waliszko A, Hulanicka B, Kotlarz K. Social-class gradients in menarcheal age in Poland. *Ann.Hum.Biol.* 1986;**13**:1-11.

125. Veronesi FM, Gueresi P. Trend in menarcheal age and socioeconomic influence in Bologna (northern Italy). *Ann Hum.Biol* 1994;**21**:187-96.

126. Karpati AM, Rubin CH, Kieszak SM, Marcus M, Troiano RP. Stature and pubertal stage assessment in American boys: the 1988-1994 Third National Health and Nutrition Examination Survey. *J.Adolesc.Health* 2002;**30**:205-12.

127. Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. Relation of age at menarche to race, time period, and anthropometric dimensions: the Bogalusa Heart Study. *Pediatrics* 2002;**110**:e43.

128. Huen KF, Leung SS, Lau JT, Cheung AY, Leung NK, Chiu MC. Secular trend in the sexual maturation of southern Chinese girls. *Acta Paediatr.* 1997;**86**:1121-4.

129. Liestol K. Social conditions and menarcheal age: the importance of early years of life. *Ann.Hum.Biol.* 1982;**9**:521-37.

130. Adair LS. Size at birth predicts age at menarche. *Pediatrics* 2001;**107**:E59.

131. Wu T, Mendola P, Buck GM. Ethnic differences in the presence of secondary sex characteristics and menarche among US girls: the Third National Health and Nutrition Examination Survey, 1988-1994. *Pediatrics* 2002;**110**:752-7.

132. Brundtland GH, Liestol K. Seasonal variations in menarche in Oslo. *Ann.Hum.Biol.* 1982;**9**:35-43.

133. Cooper C, Kuh D, Egger P, Wadsworth M, Barker D. Childhood growth and age at menarche. *Br.J.Obstet.Gynaecol.* 1996;**103**:814-7.

134. Persson I, Ahlsson F, Ewald U, Tuvemo T, Qingyuan M, von Rosen D, Proos L. Influence of perinatal factors on the onset of puberty in boys and girls: implications for interpretation of link with risk of long term diseases. *Am.J.Epidemiol.* 1999;**150**:747-55.

135. dos Santos Silva, I, De Stavola BL, Mann V, Kuh D, Hardy R, Wadsworth ME. Prenatal factors, childhood growth trajectories and age at menarche. *Int.J.Epidemiol.* 2002;**31**:405-12.

136. Power C. A review of child health in the 1958 birth cohort: National Child Development Study. *Paed Perinat Epidem* 1992;**6**:81-110.

137. Wadsworth ME, Kuh DJ. Childhood influences on adult health: a review of recent work from the British 1946 national birth cohort study, the MRC National Survey of Health and Development. *Paediatr.Perinat.Epidemiol.* 1997;**11**:2-20.

138. Ferri, E, Bynner, J., and Wadsworth, M.Ferri, E, Bynner, J., and Wadsworth, M. Changing Britain Changing Lives. Institute of Education, University of London, 2003.

139. Goldstein H. Multilevel Statistical Models. NewYork: John Wiley&sons Inc., 1995.

140. Zeger SL, Liang K-Y, Albert PS. Models for longitudinal data: a generalised estimating equation approach. *Biometrics* 1988;1049-60.

141. Robins JM, Blevins D, Ritter G, Wulfsohn M. G-estimation of the effect of prophylaxis therapy for Pneumocystis carinii pneumonia on the survival of AIDS patients [published erratum appears in Epidemiology 1993 Mar;4(2):189] [see comments]. *Epidemiology* 1992;**3**:319-36.

142. Everitt BS. An introduction to Latent Variable Models. London: Chapman and Hall, 1984.

143. Bartholomew DJ. Latent Variable Models and Factor Analysis. London: Charles and Griffin & Company Limited, 1987.

144. Dunn G, Everitt B, Pickles A. Modelling Covariances and Latent Variables Using EQS. London: Chapman & Hall, 1993.

145. Bentler PM. EQS Structure Equations. Encino, CA: Multivariate Software, Inc, 1995, 1995.

146. Jones P, Rodgers B, Murray R, Marmot M. Child development risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet* 1994;**344**:1398-402.

147. Kramer MS, Joseph KS. Enigma of fetal/infant-origins hypothesis. *Lancet* 1996;**348**:1254-5.

148. Goldstein H, Woodhouse G. Efficient estimation with missing data for multilevel models. *Eleventh International Workshop on Statistical Modelling, Orvieto, Italy* 1996.

149. Day N, Cornelius M, Goldschmidt L, Richardson G, Robles N, Taylor P. The effects of prenatal tobacco and marijuana use on offspring growth from birth through 3 years of age. *Neurotoxicol.Teratol.* 1992;**14**:407-14.

150. Geva D, Goldschmidt L, Stoffer D, Day NL. A longitudinal analysis of the effect of prenatal alcohol exposure on growth. *Alcohol Clin.Exp.Res.* 1993;**17**:1124-9.

151. Cavelaars AE, Kunst AE, Geurts JJ, Crialesi R, Grotvedt L, Helmert U, Lahelma E, Lundberg O, Mielck A, Rasmussen NK, Regidor E, Spuhler T, Mackenbach JP. Persistent variations in average height between countries and between socio-economic groups: an overview of 10 European countries. *Ann.Hum.Biol.* 2000;**27**:407-21.

152. Rona RJ. The impact of the environment on height in Europe: conceptual and theoretical considerations. *Ann.Hum.Biol.* 2000;**27**:111-26.

153. Fogelman K. Smoking in pregnancy and subsequent development of the child. *Child: care, health, and development* 1980;**6**:233-51.

154. Alberman E, Filakti H, Williams S, Evans SJ, Emanuel I. Early influences on the secular change in adult height between the parents and children of the 1958 birth cohort. *Ann.Hum.Biol.* 1991;**18**:127-36.

155. Tibbenham A, Gorbach P, Peckham C, Richardson K. The influence of family size on height. In Fogelman K, ed. *Growing Up in Great Britain*, pp 45-55. London: Macmillan for the National Children's Bureau, 1986.

156. Power C, Fogelman K, Fox AJ. Health and social mobility during the early years of life. *Quarterly Journal of Social Affairs* 1986;**2**:397-413.

157. Mascie-Taylor CG, Boldsen JL. Regional analysis of height variation in a contemporary British sample. *Ann.Hum.Biol.* 1985;**12**:315-24.

158. Essen J, Fogelman K, Head J. Children's housing and their health and physical development. *Child Care Health Dev* 1978;**4**:357-69.

159. Fried PA, Watkinson B, Gray R. Growth from birth to early adolescence in offspring prenatally exposed to cigarettes and marijuana. *Neurotoxicol.Teratol.* 1999;**21**:513-25.

160. Vik T, Jacobsen G, Vatten L, Bakketeig LS. Pre- and post-natal growth in children of women who smoked in pregnancy. *Early Hum.Dev.* 1996;**45**:245-55.

161. Binkin NJ, Yip R, Fleshood L, Trowbridge FL. Birth weight and childhood growth. *Pediatrics* 1988;**82**:828-34.

162. Cernerud L. The association between height and some structural social variables: a study of 10-year-old children in Stockholm during 40 years. *Ann.Hum.Biol.* 1993;**20**:469-76.

163. Gunnell DJ, Smith GD, Frankel SJ, Kemp M, Peters TJ. Socio-economic and dietary influences on leg length and trunk length in childhood: a reanalysis of the Carnegie (Boyd Orr) survey of diet and health in prewar Britain (1937-39). *Paediatr.Perinat.Epidemiol.* 1998;**12 Suppl 1**:96-113.

164. Cernerud L. Differences in height between socially more and less privileged 10 year old Stockholm children born in 1933-1963. *Scand.J.Soc.Med.* 1992;**20**:5-10.

165. Cernerud L, Elfving J. Social inequality in height. A comparison between 10-year-old Helsinki and Stockholm children. *Scand.J.Soc.Med.* 1995;**23**:23-7.

166. Lindgren G, Aurelius G, Tanner J, Healy M. Socio-economic circumstances and the growth of Stockholm preschool children: the 1980 birth cohort. *Acta Paediatr.* 1994;**83**:1209-11.

167. Meyer HE, Selmer R. Income, educational level and body height. *Ann.Hum.Biol.* 1999;**26**:219-27.

168. Weber G, Seidler H, Wilfing H, Hauser G. Secular change in height in Austria: an effect of population stratification? *Ann.Hum.Biol.* 1995;**22**:277-88.

169. De Stefano GH, Froment D. Height-weight standards in Italy: a critical report. *Anthrop Kozl* 1986;**30**:139-46.

170. Prebeg Z, Juresa V, Kujundzic M. Secular growth changes in Zagreb schoolchildren over four decades, 1951-91. *Ann Hum.Biol* 1995;**22**:99-110.

171. Padez C, Johnston F. Secular trends in male adult height 1904-1996 in relation to place of residence and parent's educational level in Portugal. *Ann.Hum.Biol.* 1999;**26**:287-98.

172. Bielicki T, Szklarska A. Secular trends in stature in Poland: national and social class-specific. *Ann.Hum.Biol.* 1999;**26**:251-8.

173. Prado C. Secular changes in height, weight, and menarche in Spain during the last three decades (1955-1985). *J.Hum.Ecol.* 1990;**1**:21-9.

174. Gyenis G. Continuing positive growth changes in height and weight of Hungarian university students. *Ann Hum.Biol* 1997;**24**:475-9.

175. Cernerud L, Lindgren GW. Secular changes in height and weight of Stockholm schoolchildren born in 1933, 1943, 1953 and 1963. *Ann.Hum.Biol.* 1991;**18**:497-505.

176. Tsuzaki S, Matsuo N, Ogata T, Osano M. Lack of linkage between height and weight and age at menarche during the secular shift in growth of Japanese children. *Ann Hum.Biol* 1989;**16**:429-36.

177. Butler, N. R. and Bonham, D. G.Butler, N. R. and Bonham, D. G. Perinatal Mortality. Edinburgh and London: E.&S. Livingstone Ltd, 1963.

178. Ferri E. Life at 33:the fifth follow-up of the National Child Development Study. London: National Children's Bureau, 1993.

179. NLS Handbook 2001: The National Longitudinal Surveys. U.S. Bureau of Labour Statistics, 2001.

180. Joshi H, Cooksey EC, Wiggins RD, McCullogh A, Verropoulou G, Clarke L. Diverse family living situatutions and child development: a multilevel analysis comparing longitudinal evidence from Britain and the United States. *International Journal of Law, Policy and the Family* 1999;**13**:292-314.

181. Power C, Li L. Cohort study of birthweight, mortality, and disability. *BMJ* 2000;**320**:840-1.

182. Lake JK. Body Size in Child and Adulthood: Implications for Adult Health. PHD Dissertation, University College London, 1998.

183. Moran SE, Strachan DP, Johnston ID, Anderson HR. Effects of exposure to gas cooking in childhood and adulthood on respiratory symptoms, allergic sensitization and lung function in young British adults. *Clin.Exp.Allergy* 1999;**29**:1033-41.

184. Tanner JM. Growth at Adolescence. Oxford: Blackwell Scientific Publications, 1962.

185. Haskey J. Trends in the numbers of one-parent families in Great Britain. *Population Trends* 1993;**71**:26-33.

186. Stewart AL. The reliability and validity of self-reported weight and height. *J.Chronic.Dis.* 1982;**35**:295-309.

187. O'Sullivan JJ, Pearce MS, Parker L. Parental recall of birth weight: how accurate is it? *Arch.Dis.Child* 2000;**82**:202-3.

188. Seidman DS, Slater PE, Ever-Hadani P, Gale R. Accuracy of mothers' recall of birthweight and gestational age. *Br.J.Obstet.Gynaecol.* 1987;**94**:731-5.

189. Lumey LH, Stein AD, Ravelli AC. Maternal recall of birthweights of adult children: validation by hospital and well baby clinic records. *Int.J.Epidemiol.* 1994;**23**:1006-12.

190. McCormick MC, Brooks-Gunn J. Concurrent child health status and maternal recall of events in infancy. *Pediatrics* 1999;**104**:1176-81.

191. Pless CE, Pless IB. How well they remember. The accuracy of parent reports. *Arch.Pediatr.Adolesc.Med.* 1995;**149**:553-8.

192. Hoekelman RA, Kelly J, Zimmer AW. The reliability of maternal recall. Mother's remembrance of their infant's health and illness. *Clin.Pediatr.(Phila)* 1976;**15**:261-5.

193. Sanderson M, Williams MA, White E, Daling JR, Holt VL, Malone KE, Self SG, Moore DE. Validity and reliability of subject and mother reporting of perinatal factors. *Am.J.Epidemiol.* 1998;**147**:136-40.

194. Kark JD, Troya G, Friedlander Y, Slater PE, Stein Y. Validity of maternal reporting of breast feeding history and the association with blood lipids in 17 year olds in Jerusalem. *J.Epidemiol Community Health* 1984;**38**:218-25.

195. Huttly SR, Barros FC, Victora CG, Beria JU, Vaughan JP. Do mothers overestimate breast feeding duration? An example of recall bias from a study in southern Brazil. *Am.J.Epidemiol* 1990;**132**:572-5.

196. Raisler J, Alexander C, O'Campo P. Breast-feeding and infant illness: a dose-response relationship? *Am.J.Public Health* 1999;**89**:25-30.

197. Feldman Y, Koren G, Mattice K, Shear H, Pellegrini E, MacLeod SM. Determinants of recall and recall bias in studying drug and chemical exposure in pregnancy. *Teratology* 1989;**40**:37-45.

198. Tomeo CA, Rich-Edwards JW, Michels KB, Berkey CS, Hunter DJ, Frazier AL, Willett WC, Buka SL. Reproducibility and validity of maternal recall of pregnancy-related events. *Epidemiology* 1999;**10**:774-7.

199. Joshi H, Cooksey EC, Clarke L, Wiggins RD, McCulloch A. Family disruption and the cognitive and behavioural development of children in longitudinal data from Britain and USA. *NCDS User Support Group Working Paper* 1998;**No 50**.

200. Clarke L, Joshi H, Di Salvo P. Children's family change: reports and records of mothers, fathers and children compared. *Popul.Trends* 2000;24-33.

201. Freeman JV, Cole TJ, Chinn S, Jones PR, White EM, Preece MA. Cross sectional stature and weight reference curves for the UK, 1990. *Arch.Dis.Child* 1995;**73**:17-24.

202. Goldstein H. A study of response rates of 16-year-olds in the NCDS. In Fogelman K, ed. *Growing up in Great Britain*, pp 9-18. London: Macmillan Press, 1983.

203. Power C, Manor O, Fox AJ. Health and Class: the Early Years. London: Chapman&Hall, 1991.

204. Hemminki E, Gissler M. Births by younger and older mothers in a population with late and regulated childbearing: Finland 1991. *Acta Obstet.Gynecol.Scand.* 1996;**75**:19-27.

205. Singh S, Darroch JE, Frost JJ. Socioeconomic disadvantage and adolescent women's sexual and reproductive behavior: the case of five developed countries. *Fam.Plann.Perspect.* 2001;**33**:251-8, 289.

206. OPCS. Mortality Statistics. Perinatal and infant: social and biological factors 1991. Series DH3 no. 25. London: HMSO, 1991.

207. Cole TJ, Freeman JV, Preece MA. Body mass index reference curves for the UK, 1990. *Arch.Dis.Child* 1995;**73**:25-9.

208. Prescott-Clarke P, Primatesta P. Health Survey for England '96: Findings. London: The Stationary Office, 1998.

209. Central Statistical Office: Social Trends (Vol. 21). 1991.

210. Gregg P, Harkness S, Machin S. Poor Kids: Trends in the Child Poverty in Britain, 1968-96. *Fiscal Studies* 1999;**20**:163-87.

211. Haskey J. Birth cohort analyses of dependent children and lone mothers living in one-parent families in Great Britain. *Popul.Trends* 1998;15-22.

212. Vestbo J, Rasmussen FV. Baseline characteristics are not sufficient indicators of non-response bias follow up studies. *J.Epidemiol.Community Health* 1992;**46**:617-9.

213. Laird NM. Missing data in longitudinal studies. *Stat.Med.* 1988;**7**:305-15.

214. Little RJA, Rubin DB. Statistical Analysis with Missing Data. New York: John Wiley, 1987.

215. Little RJA. Regression with missing X's: a review. *J.American Statistical Association* 1992;**87**:1227-37.

216. Kleinbaum DG. Applied Regression Analysis and Other Multivariate Methods. Pacific Grove: Duxbury Press, 1998.

217. McCullagh B, Nelder JA. Generalized Linear Models. London: Chapman&Hall, 1989.

218. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics* 1982;**38**:963-74.

219. Ware JH. Linear models for the analysis of longitudinal studies. *American Statistician* 1985;**39**:95-101.

220. Zeger SL, Liang K-Y. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986;121-30.

221. Liang K-Y, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika* 1986;**73**:13-22.

222. Goldstein H. Efficient statistical modeling of longitudinal data. *Ann.Hum.Biol.* 1986;**13**:129-41.

223. Raudenbush SW. Comparing personal trajectories and drawing causal inferences from longitudinal data. *Annu.Rev.Psychol.* 2001;**52**:501-25.

224. Dwyer J, Feinleib M. Introduction to statistical models for longitudinal observation. In Dwyer J, Feinleib M, Lippert P, Hoffmeister H, eds. *Statistical Models for Longitudinal Studies of Health*, pp 3-48. Oxford: Oxford University Press, 1992.

225. Ecob R, Jones K. Mortality variations in England and Wales between types of place: an analysis of the ONS longitudinal study. Office of National Statistics. *Soc.Sci.Med.* 1998;**47**:2055-66.

226. Breeze E, Sloggett A, Fletcher A. Socioeconomic and demographic predictors of mortality and institutional residence among middle aged and older people: results from the Longitudinal Study. *J.Epidemiol Community Health* 1999;**53**:765-74.

227. Rothman KJ, Greenland S. Moden Epidemiology. Philadelphia: Lippincott-Raven, 1998.

228. Power C, Li L, Manor O, Davey-Smith G. Combination of Low Birthweight and High Adult BMI: at what age is it established and what are its determinants? *J.Epidemiol Community Health* 2003;**To appear**.

229. Keiding N. Event history analysis and inference from observational epidemiology. *Stat.Med.* 1999;**18**:2353-63.

230. Cox DR, Oakes D. Analysis of Survival Data. London: Chapman and Hall, 1985.

231. Oldham PD. A note on the analysis of repeated measurements of the same subjects. *Journal of Chronic Diseases* 1962;**15**:969-77.

232. Hayes RJ. Methods for assessing whether change depends on initial value. *Stat.Med.* 1988;**7**:915-27.

233. Dixon WJ. BMDP Statistical Software. Berkeley: University of California Press, 1983.

234. Little RJA. A test of missing completely at random for multivariate data with missing values. *Journal of the American Statistical Association* 1988;**83**:1198-202.

235. Park T, Lee SY. A test of missing completely at random for longitudinal data with missing observations. *Stat.Med.* 1997;**16**:1859-71.

236. Montgomery DC. Design and Analysis of Experiments. New York: John Wiley&Sons, 1991.

237. Lamont D, Parker L, White M, Unwin N, Bennett SM, Cohen M, Richardson D, Dickinson HO, Adamson A, Alberti KG, Craft AW. Risk of cardiovascular disease measured by carotid intima-media thickness at age 49-51: lifecourse study. *BMJ* 2000;**320**:273-8.

238. Victora CG, Huttly SR, Fuchs SC, Olinto MT. The role of conceptual frameworks in epidemiological analysis: a hierarchical approach. *Int.J.Epidemiol.* 1997;**26**:224-7.

239. Williams S, Poulton R. Twins and maternal smoking: ordeals for the fetal origins hypothesis? A cohort study. *BMJ* 1999;**318**:897-900.

240. Davis JA. The Logic of Causal Order. London: SAGS Publications, 1985.

241. Joreskog K, Sorbom D. Advance in Factor Analysis and Structure Equation Models. Cambridge: MA: ABT Assoc., 1979.

242. Duncan TE, Duncan SC, Strycker LA, Li F, Alpert A. An Introduction to Latent Variable Growth Curve Modeling: Concepts, Issues, and Applications. Mahwah (NJ): Lawrence Earlbaum Associates, 1999.

243. Pearce N. Time-related confounders and intermediate variables [editorial; comment]. *Epidemiology* 1992;**3**:279-81.

244. Teranishi H, Nakagawa H, Marmot M. Social class difference in catch up growth in a national British cohort. *Arch.Dis.Child* 2001;**84**:218-21.

245. Stark O, Peckham C, Moynihan C. Weight and age of menarche. *Arch.Dis.Child.* 1989;**64**:383-7.

246. Mascie-Taylor CG, Boldsen JL. Recalled age of menarche in Britain. *Ann.Hum.Biol.* 1986;**13**:253-7.

247. Goldblatt PE. Longitudinal Study: Mortality and Social Organisation 1971-1981. London: HMSO, 1990.

248. Spencer NJ, Logan S. The treatment of parental height as a biological factor in studies of birth weight and childhood growth. *Arch.Dis.Child* 2002;**87**:184-7.

249. Saigal S, Stoskopf BL, Streiner DL, Burrows E. Physical growth and current health status of infants who were of extremely low birth weight and controls at adolescence. *Pediatrics* 2001;**108**:407-15.

250. Fried PA, O'Connell CM. A comparison of the effects of prenatal exposure to tobacco, alcohol, cannabis and caffeine on birth size and subsequent growth. *Neurotoxicol.Teratol.* 1987;**9**:79-85.

251. Conter V, Cortinovis I, Rogari P, Riva L. Weight growth in infants born to mothers who smoked during pregnancy. *BMJ* 1995;**310**:768-71.

252. Ong KK, Ahmed ML, Sherriff A, Woods KA, Watts A, Golding J, Dunger DB. Cord blood leptin is associated with size at birth and predicts infancy weight gain in humans. ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. *J.Clin.Endocrinol.Metab* 1999;**84**:1145-8.

253. Ong KK, Ahmed ML, Dunger DB. The role of leptin in human growth and puberty. *Acta Paediatr.Suppl* 1999;**88**:95-8.

254. Fried PA, James DS, Watkinson B. Growth and pubertal milestones during adolescence in offspring prenatally exposed to cigarettes and marihuana. *Neurotoxicol.Teratol.* 2001;**23**:431-6.

255. Barr HM, Streissguth AP, Martin DC, Herman CS. Infant size at 8 months of age: relationship to maternal use of alcohol, nicotine, and caffeine during pregnancy. *Pediatrics* 1984;**74**:336-41.

256. Jacobson SW, Jacobson JL, Sokol RJ. Effects of fetal alcohol exposure on infant reaction time. *Alcohol Clin.Exp.Res.* 1994;**18**:1125-32.

257. Little RE. Moderate alcohol use during pregnancy and decreased infant birth weight. *Am.J.Public Health* 1977;**67**:1154-6.

258. Wright JT, Waterson EJ, Barrison IG, Toplis PJ, Lewis IG, Gordon MG, Macrae KD, Morris NF, Murray-lyon IM. Alcohol consumption, pregnancy, and low birthweight. *Lancet* 1983;**1**:663-5.

259. Rona RJ. Genetic and environmental factors in the control of growth in childhood. *Br.Med.Bull.* 1981;**37**:265-72.

260. Cook J, Altman DG, Moore MC, Topp SG, Holland WW, Elliott A. A survey of the nutritional status of schoolchildren. Relation between nutrient intake and socio-economic factors. *Br.J.Prev.Soc.Med.* 1973;**27**:91-9.

261. Preece MA. Prepubertal and pubertal endocrinology. In Falkner J, Tanner JM, eds. *Human Growth*, London: Plenum Press, 1985.

262. Dedman DJ, Gunnell D, Davey SG, Frankel S. Childhood housing conditions and later mortality in the Boyd Orr cohort. *J.Epidemiol.Community Health* 2001;**55**:10-5.

263. Maclean M. Households after divorce: the availability of resources and their impact on children. In Brannen J, Wilson G, eds. Allen and Unwin, 1987.

264. Skuse D, Albanese A, Stanhope R, Gilmour J, Voss L. A new stress-related syndrome of growth failure and hyperphagia in children, associated with reversibility of growth-hormone insufficiency. *Lancet* 1996;**348**:353-8.

265. Voss LD, Mulligan J, Betts PR, Wilkin TJ. Poor growth in school entrants as an index of organic disease: the Wessex growth study. *BMJ* 1992;**305**:1400-2.

266. Sharma K, Talwar I, Sharma N. Age at menarche in relation to adult body size and physique. *Ann Hum.Biol* 1988;**15**:431-4.

267. Shangold MM, Kelly M, Berkeley AS, Freedman KS, Groshen S. Relationship between menarcheal age and adult height. *South.Med.J.* 1989;**82**:443-5.

268. Kromeyer K, Hauspie RC, Susanne C. Socioeconomic factors and growth during childhood and early adolescence in Jena children. *Ann.Hum.Biol.* 1997;**24**:343-53.

269. Prebeg Z. Changes in growth patterns in Zagreb school children related to socio- economic background over the period 1973-1991. *Ann.Hum.Biol.* 1998;**25**:425-39.

270. Bielicki T, Malina RM, Waliszko H. Monitoring the dynamic of social stratification: statural variation among Polish conscripts in 1976 and 1986. *American Journal of Human Biology* 1992;**4**:345-52.

271. Seidman DS, Ever-Hadani P, Stevenson DK, Slater PE, Harlap S, Gale R. Birth order and birth weight reexamined. *Obstet.Gynecol.* 1988;**72**:158-62.

272. Prentice A, Cole TJ, Whitehead RG. Impaired growth in infants born to mothers of very high parity. *Hum.Nutr.Clin.Nutr.* 1987;**41**:319-25.

273. Riva E, Banderali G, Agostoni C, Silano M, Radaelli G, Giovannini M. Factors associated with initiation and duration of breastfeeding in Italy. *Acta Paediatr.* 1999;**88**:411-5.

274. Silventoinen K, Kaprio J, Lahelma E, Koskenvuo M. Relative effect of genetic and environmental factors on body height: differences across birth cohorts among Finnish men and women. *Am.J.Public Health* 2000;**90**:627-30.

275. Lindgren G. Height, weight and menarche in Swedish urban school children in relation to socio-economic and regional factors. *Ann.Hum.Biol.* 1976;**3**:501-28.

276. Tanner JM. Foetal into man:physical growth from conception to maturity. London: Open Books, 1978.

277. Power C, Manor O, Li L. Are inequalities in height underestimated by adult social position? Effects of changing social structure and height selection in a cohort study. *BMJ* 2002;**325**:131-4.

278. Tanner JM. A History of the Study of Human Growth. Cambridge University Press, 1981.

279. Hauspie RC, Vercauteren M, Susanne C. Secular changes in growth. *Horm.Res.* 1996;**45 Suppl 2**:8-17.

280. Nystrom Peck AM. Childhood environment, intergenerational mobility, and adult health--evidence from Swedish data. *J.Epidemiol Community Health* 1992;**46**:71-4.

281. Marmot MG. Social inequalities in Mortality: the social environment. In Wilkison R, ed. *Class and health research and longitudinal data*, London: Travistock, 1986.

282. Marmot MG, Rose G. Employment grade and coronary heart disease in British civil servants. *J.Epidemiol.Community.Health.* 1978;**32**:244-9.

283. Meredith HV. Body size of infants and children around the world in relation to socioeconomic status. *Adv.Child Dev.Behav.* 1984;**18**:81-145.

284. Nystrom Peck AM, Vagero DH. Adult body height and childhood socioeconomic group in the Swedish population. *J.Epidemiol.Community Health* 1987;**41**:333-7.

285. Mackenbach JP. Narrowing inequalities in children's height. *Lancet* 1991;**338**:764.

286. Rona RJ. Social class and height in Britain. In Ulijaszek SJ, Johnston FE, Preece MA, eds. *The Cambridge Encyclopedia of Human Growth and Development*, Cambridge Press, 1998.

287. Rona RJ. A surveillance system of growth in Britain. *Auxology '88. Perspectives in the Science of Growth and Development.* Selected Papers from the Fifth International Auxology Congress. Exter UK, July 1988. In Tanner J, ed. London, Smith-Gordon (Nishiura), 1989.

288. Hediger ML, Overpeck MD, Maurer KR, Kuczmarski RJ, McGlynn A, Davis WW. Growth of infants and young children born small or large for gestational age: findings from the Third National Health and Nutrition Examination Survey. *Arch.Pediatr.Adolesc.Med.* 1998;**152**:1225-31.

289. Sorensen HT, Sabroe S, Rothman KJ, Gillman M, Steffensen FH, Fischer P, Sorensen TI. Birth weight and length as predictors for adult height. *Am.J.Epidemiol* 1999;**149**:726-9.

290. Loos RJ, Beunen G, Fagard R, Derom C, Vlietinck R. Birth weight and body composition in young women: a prospective twin study. *Am.J.Clin.Nutr.* 2002;**75**:676-82.

291. Karlberg J, Albertsson-Wikland K. Growth in full-term small-for-gestational-age infants: from birth to final height. *Pediatr.Res.* 1995;**38**:733-9.

292. Farooqi IS, Jebb SA, Langmack G, Lawrence E, Cheetham CH, Prentice AM, Hughes IA, McCamish MA, O'Rahilly S. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. *N.Engl.J.Med.* 1999;**341**:879-84.

293. Ong KK, Dunger DB. Perinatal growth failure: the road to obesity, insulin resistance and cardiovascular disease in adults. *Best.Pract.Res.Clin.Endocrinol.Metab* 2002;**16**:191-207.

294. Billaud N, Lemarie P. Negative effects of maternal smoking during the course of pregnancy. *Arch.Pediatr.* 2001;**8**:875-81.

295. Boezen HM, Vonk JM, van Aalderen WM, Brand PL, Gerritsen J, Schouten JP, Boersma ER. Perinatal predictors of respiratory symptoms and lung function at a young adult age. *Eur.Respir.J.* 2002;**20**:383-90.

296. Jones G, Riley M, Dwyer T. Maternal smoking during pregnancy, growth, and bone mass in prepubertal children. *J.Bone Miner.Res.* 1999;**14**:146-51.

297. Power C, Jefferis BJ. Fetal environment and subsequent obesity: a study of maternal smoking. *Int.J.Epidemiol* 2002;**31**:413-9.

298. Egle UT, Hardt J, Nickel R, Kappis B, Hoffmann SO. [Long-term effects of adverse childhood experiences - Actual evidence and needs for research1/2]. *Z.Psychosom.Med.Psychother.* 2002;**48**:411-34.