Fetal growth and cardiovascular risk factors in an Australian Cohort

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Abstract

There is an extensive history to the idea that experiences during early life have long lasting effects on health. The fetal origins theory, which is more specific than its predecessors, was proposed and developed from the late 1980s by Barker and his colleagues.

According to the fetal origins theory, growth before birth is a potent influence on the risk of cardiovascular disease, as well as other chronic diseases, in later life. Poor fetal growth, manifest in the weight and shape of the baby at birth, is thought to be related to adult cardiovascular disease events through enduring physiological changes which accompany impaired growth.

A number of cohort studies, primarily from Britain and the United States, have demonstrated an inverse association between birth weight and risk of incipient or fatal cardiovascular disease. Internationally, more than 20 studies have now found an inverse relationship between birth weight and later blood pressure, which is hypothesised to amplify with age. Far fewer studies have considered blood lipids; relationships between birth weight and this outcome are inconsistent.

More recently Barker has identified certain patterns of disproportionate fetal growth, thought to result from undernutrition in different periods of gestation, as additional markers for elevated risk of cardiovascular disease. The disproportions are: thinness, possibly accompanied by a small head; and shortness with a large head circumference compared to chest size. Discrepancies between the weight of the baby and its placenta are also considered to indicate increased risk of cardiovascular disease. These specific propositions are based on work undertaken mainly in Britain by Barker and his colleagues. Relevent international evidence lacks coherence and is limited, due in part to detailed information about birth dimensions being rarely available.

Barker's interpretation of associations with birth weight has been contested. Critics have argued most strongly that the results may be explained by adverse socio-economic circumstances which contribute to low birth weight initially and thereafter, through established behavioural risk factors, to increased likelihood of clinical risk factors and cardiovascular disease. Studies which take into account the socio-economic environment at birth and during childhood as well as contemporary circumstances have been called for.

In the present study relationships between fetal growth, as manifest in size and shape at birth, and later blood pressure and blood lipids were investigated in an Australian cohort. Data on these outcomes for cohort members at age 8 years were available from a previous study. Birth details (body weight, placental weight, head circumference, chest circumference and length) were abstracted from hospital records. In addition, a follow up of cohort members was undertaken to collect new data pertaining to the two cardiovascular risk factors at 20 years of age. Socio-economic circumstances were characterised at birth, age 8 and age 20.

The cohort comprised 856 individuals born in the Queen Victoria Hospital in Adelaide, South Australia, during 1975-76. Members were enrolled in the cohort through participation in a study of cardiovascular risk factors at age 8 years. By the time of the follow up conducted 12 years later, around one per cent of cohort members had withdrawn or died and only 2 per cent of the remaining members could not be traced. Thus, almost all cohort members were invited to take part in the follow up and over 70 per cent eventually did so.

At age 8, for boys and girls together, relationships between birth weight and blood pressure were weak and not statistically significant. There was some evidence of simultaneous effects of birth weight and placental weight, the latter variable being positively associated with blood pressure in childhood.

At age 20, among males, there was little evidence of relationships between birth dimensions and current blood pressure. In contrast, among females at age 20, a one kilogram increase in full-term birth weight was associated with a decrease in systolic pressure of 4.4 mm Hg (95% CI 2.1 to 6.7), after adjustment for current weight and height. In females, amplification of the relationship between birth weight and blood pressure had occurred between age 8 and age 20. Furthermore, there was evidence that each of the birth disproportions specified by Barker were linked to elevated blood pressure in early adulthood.

Concerning blood lipids, both thinness and shortness at birth were associated with poor lipid profiles at age 8, for all children born at term, after adjustment for sex, current weight and age. At age 20, among males born at term, shortness and thinness at birth were again associated with elevated concentrations of total cholesterol and low density lipoprotein cholesterol, after adjustment for current weight and age. However, these patterns were largely unseen in women at age 20. Birth weight was not related to lipid profiles at either age.

Associations between birth dimensions and later cardiovascular risk factors that emerged in the present study did not appear to the product of behaviours that affect these risk factors, nor did they appear to be a consequence of socio-economic variation. This study offers some insight with regard to the lack of coherence in results from other studies.

Overall the findings were mixed and the present study does not give unequivocal support to the fetal origins theory. Nevertheless, there was evidence that poor fetal growth was associated with later cardiovascular risk factors.

Declaration

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis being made available for loan and photocopying.

Vivienne Moore

May 1997

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grateful to him for his foresight and encouragement.

Author's contribution

I was responsible for the design and co-ordination of the follow-up study undertaken when members of the Adelaide Children's Hospital Family Heart Study cohort were 20 years of age. This included developing the questionnaire and data forms, arranging appointments for those who responded, pursuing missed appointments, telephone recruitment of non-responders, assisting with clinics on heavily booked days, and forwarding results to study subjects. I identified and implemented strategies for tracing subjects lost to follow up. I carried out the telephone tracing of lost subjects, shared the electoral roll tracing with two clerical assistants, and contacted all potential matches from the electoral roll. I supervised the data entry and undertook all data management and cleaning.

With regard to the other sources of data, I completed the abstraction of birth details from hospital records (the major part of this work having been undertaken previously by Dr Andrew Miller) and supervised a research assistant who abstracted comparison details for families that did not become involved in the Adelaide Children's Hospital Family Heart Study although they were eligible to do so. I was also responsible for the retrieval, translation and cleaning of the original data sets pertaining to the study of cohort members at age 8.

I designed and organised the test of the repeatability of measurements, but analysis of those data was carried out by a student on a vacation scholarship, under the direction of myself and Dr Philip Ryan. I undertook all other statistical analyses with guidance from Dr Philip Ryan.

Chapter 1
Introduction

1.1 The notion that adult diseases have origins in early life

The idea that experiences during early life have long lasting effects which contribute to diseases in adulthood was revitalised by Barker in the late 1980s. A specific theory concerning the origins of cardiovascular disease, among other chronic diseases, has been developed, largely through work conducted by Barker and his colleagues. This thesis concerns an investigation of some aspects of that theory.

Essentially, Barker has proposed that the growth of a baby before birth and during infancy has a profound influence on the diseases it will develop in later life. Cardiovascular disease, non-insulin dependent diabetes, and chronic obstructive airways disease are the main adverse health outcomes thought to be influenced by fetal and infant growth. Increased susceptibility to these chronic diseases is held to be due to the resetting, or altered programming, of physiological systems as a consequence of poor growth. In more recent expositions of the theory, Barker has identified specific patterns of poor fetal growth as the start of a train of processes that culminate in adult disease. The health and nutrition of the mother before and during pregnancy are thought to be important underlying influences on the baby's growth and lifelong disease experience (Barker 1992; 1994; 1995).

The proposition that early life experiences have enduring consequences is not new. Kuh and Davey Smith (1993) have written a fascinating account of the popularity and evolution of this idea, at least through the 20th century. Briefly, the belief that health in adulthood could be improved by addressing the health of mothers and their children was central to the public health perspective in Britain (and elsewhere) from the turn of the century until World War II. Support for this view was widespread. It was

reflected in activities as diverse as the deliberations of a committee investigating the poor health of potential army recruits and the work of actuaries and statisticians exploring changes in life expectancy. Adverse early life experiences were thought to have a general impact on vitality, which eventually gave rise to greater morbidity and mortality. Childhood nutrition and hygiene were commonly cited as responsible factors, although there were also vocal supporters of a genetic basis for the association. The early life focus in the context of health was concordant with theories being developed within psychoanalysis, behavioural psychology and biological science at that time.

After World War II, however, adult lifestyles or behaviours became the subject of massive efforts to identify the causes of chronic diseases. For some time there was little discussion of early life influences. However, this theme re-emerged in the 1970s, particularly with Forsdahl's (1978) suggestion that nutritional deprivation in early childhood, followed by relative affluence, contributed to the occurrence of coronary heart disease. From the late 1980s, Barker and his colleagues have been pursuing a specific theory concerning the influence of early life on adult diseases. Kuh and Davey Smith (1993) fairly suggest that the work of Barker and his colleagues represents the re-creation of a strong constituency for an existing model, rather than development of a new model.

Details of the model advanced by Barker and his colleagues are certainly new, and the theory and evidence tendered in its support have generated heated debate. Locating the causes of adult diseases in adult lifestyles is so firmly woven into late 20th century public health and community zeitgeist that an early life theory may well appear radical and suspect. Against this backdrop, it requires some effort to be open-minded towards a novel theory.

After 40 years of research and more than 20 years of intense health promotion efforts, it is clear that adult behaviours have a role in cardiovascular disease and other chronic diseases (Hetzel & McMichael 1987). But it is also clear that there must be other influences, since differences in adult behaviours do not account for all, or even most, of the variation in cardiovascular deaths between countries or across socio-economic groups (Rose & Marmot 1981; Nerbrand, Kullman, Schwan, et al. 1992; Nilsson, Moller & Ostergren 1995). Reviews of large-scale intervention studies have found that changing adult lifestyles does not necessarily lead to large reductions in risk (McCormick & Skrabanek 1988), and pathological work shows that processes central to the development of cardiovascular disease begin well before adulthood (Labarthe, Eissa & Varas 1991).

Cardiovascular disease is still the leading cause of death among adults in Australia and most other western societies. The fetal origins theory potentially offers a more complete understanding of the aetiology of this disease, and new approaches to prevention; it therefore deserves close scrutiny.

1.2 Ecological studies linking early life to adult disease

Barker's ideas arose from results of ecological epidemiological studies within Britain. In these studies, death rates for cardiovascular disease from 212 regions in England and Wales were compared with maternal and infant death rates from 60 years before. Contemporary mortality rates for ischaemic heart disease were found to be strongly correlated with the regional rate of infant deaths from a much earlier time (Barker & Osmond 1986). Mortality rates for ischaemic heart disease and stroke were also correlated with the much earlier maternal death rates (Barker & Osmond 1987). When infant deaths were separated into neonatal deaths (before one month of age) and post-neonatal deaths, the mortality rate for ischaemic heart disease 60 years on was related to both infant death rates, but the mortality rate for stroke was associated only with the

neonatal death rate (Barker, Osmond & Law 1989). Neonatal deaths appear to be linked to intra-uterine factors, while post-neonatal deaths seem to be influenced more by the early post-natal environment. Other sources indicated that poor maternal health and physique and low birth weight babies were connected with high rates of maternal and neonatal deaths in the past, so Barker reasoned that these factors or underlying ones might be predisposing survivors to chronic disease in adult life.

Several other studies in Britain (Williams, Roberts & Davies 1979; Ben-Shlomo & Davey Smith 1991), one in Norway (Forsdahl 1977), and one in the United States (Buck & Simpson 1982), had also examined relationships between early life experience and geographical variation in adult cardiovascular deaths. Together with the studies of Barker and colleagues, these studies were reviewed by Elford, Shaper and Whincup (1992). The reviewers agreed that all of the studies supported a strong association, but they disputed the interpretation that the link was causal. They maintained that the relationship was more likely to be due to persisting social and economic disadvantage experienced by individuals born in communities where there was a relatively high occurrence of events such as maternal and infant deaths. A lack of specificity was also noted as, in many of the studies, indices of early life experience were correlated with other causes of adult death besides cardiovascular disease. Several inconsistencies within and between studies were documented, the main one being a lack of agreement on the aetiological mechanisms whereby early life experiences contributed to adult cardiovascular disease. In their conclusion, however, Elford and colleagues allowed that the value of ecological studies lay in generating rather than in testing hypotheses, with rigorous testing requiring studies based on individuals.

Studies of individuals had already commenced, and in the few years since the review of Elford, Shaper and Whincup (1992) more results have been reported; it is to these

that attention will now turn. Such studies present an interesting epidemiological problem as they require knowledge of events a lifespan apart.

1.3 Birth weight related to cardiovascular deaths, and interpretations

In the first of the studies of individuals, begun in the late 1980s, Barker, Winter, Osmond et al. (1989) looked at what had become of a group of babies listed in a series of ledgers kept by midwives in the early part of the century. The babies had been born in Hertfordshire, a county north of London, during 1911-30. The birth records for more than 5,000 males were first matched with data concerning deaths from National Health Service files, revealing a strong association between weight at birth and death from ischaemic heart disease during 1951-87. The death rate was highest for men with the lowest birth weights, and fell progressively as birth weight increased. The association was specific to cardiovascular disease; there was, for example, no relationship between birth weight and death from lung cancer.

The trouble with this result, as the critics quickly recognised, was not in the association but in its interpretation (Elford 1989). Clearly it is quite possible that other factors known to influence the risk of cardiovascular disease could have been concentrated among the men who had been small as babies. They might have smoked more, had poor diets and lacked exercise. In broader terms, they might well have had the poorest social and economic environments, a circumstance that could explain both their low birth weights and their elevated risk of cardiovascular disease.

At that stage, Barker and his colleagues had information on social class only for men who had died, and no data concerning relevant behavioural practices of any of the men. They went on to collect this information in follow-up studies of members of the Hertfordshire cohort who were still alive, work which is described in subsequent

sections (2.5 and 3.5). For the time being, however, the critics' case was a strong one.

There is substantial evidence of associations between socio-economic status and both pregnancy outcomes and cardiovascular disease: the most disadvantaged individuals fare worst on both accounts (Rose & Marmot 1981; Ericson, Eriksson, Kallen, et al. 1989; Kaplan & Keil 1993; Wilcox, Smith, Johnson, et al. 1995). In fact, with few exceptions, at almost all ages individuals from impoverished social and economic circumstances experience the greatest morbidity and mortality, whatever the cause (Black, Morris, Smith, et al. 1980; Wilkinson 1986).

Socio-economic status is a concept or construct concerning access to and control of resources. It is commonly indicated by occupation, education, or income, although none of these measures capture the full complexity of the construct. The occupation of the head of the household has the longest history of use as a simple means of characterising the social position of family members, with well-established international validity. For cohorts of elderly people, such as those followed up by Barker and colleagues, it is a reasonably good indicator of socio-economic status, but as a consequence of changes within society it is increasingly inappropriate to younger groups; ensembles of social characteristics need to be used for these groups (McQueen & Seigrist 1982; Marmot, Kogevinas & Elston 1987; Najman 1988; Davies 1994).

Disputes about the interpretation of the findings of Barker and his colleagues prompted the publication of several studies showing that living conditions in childhood were associated with adult cardiovascular disease risk (Hasle 1990; Kaplan & Salonen 1990; Gliksman, Kawachi, Hunter, et al. 1995) and one even presented a strong association between father's social class and the offspring's adult cardiovascular disease risk (Wannamethee, Whincup, Shaper, et al. 1996). This evidence does not prove the fetal origins theory incorrect, nor does it establish that other factors are responsible for the

association, although this is clearly a possibility; it highlights the continuity in risk from childhood, without providing insight as to the specific causes.

The issue is not easily resolved. As a minimum it requires that socio-economic circumstance be taken into account in epidemiological studies, as well as specific behaviours affecting cardiovascular disease risk. Critics have vehemently pointed this out (Baker 1994). Even then, it may be argued that the definition and measurement of socio-economic status is not sufficiently precise for residual confounding to be ruled out. Moreover, Kramer and Joseph (1996) contend that socio-economic status at birth and during early childhood need to considered, not just adult circumstances. Ultimately, tests of mechanisms whereby poor fetal growth conveys an increased risk of cardiovascular disease, independently of social class or any other factor, are required.

Another explanation of the association between birth weight and cardiovascular deaths was in terms of a genetic factor (Bradley 1991). This interpretation is much easier to refute than the socio-economic argument because genetic factors appear to make only a minor contribution to birth weight. Ounsted (1965) compared mothers of low birth weight and normal weight infants and concluded that although maternal factors influenced fetal size, this did not appear to be genetically determined. There have been many other studies of the factors contributing to birth weight and, in particular, of genetic influences, as summarised by Kline, Stein and Susser (1989). The similarity of birth weight in twins, other siblings or relatives, has been examined by many, but this approach is not truly able to disentangle genetic factors from shared environmental factors, and such studies had often mistakenly inflated the role of genes. Data sets containing birth weights of parents and their children have only recently been assembled, and analyses of these point to a very modest role for genes. For example, Carr-Hill, Campbell, Hall, et al. (1987) carefully examined birth weights of 505 pairs of grandmothers and mothers, as well as birth weights of the grandchildren. There

was a small correlation for inter-generational birth weights, which was diminished when maternal size, pregnancy factors and length of gestation were taken into account. On the basis of such inter-generational studies, Klein and colleagues concluded that the mother's adult size, which was partly determined by her environment and partly genetic, had a strong influence on the birth weights of her children, but direct influences of both maternal and paternal genotype were only small.

A number of studies have now demonstrated an association between birth weight and either death from cardiovascular disease or manifestations of cardiovascular disease in living individuals. Some of these studies do contain information on the subjects' social and economic circumstances and on adult behaviours.

Following the study of Hertfordshire men, Barker and his colleagues confirmed that birth weight was inversely associated with the likelihood of death from coronary heart disease among women from Hertsfordshire (Osmond, Barker, Winter, et al. 1993) and men from Sheffield (Barker, Osmond, Simmonds, et al. 1993). In the Sheffield study, where other birth measurements were available, deaths from coronary heart disease were also elevated in men who had been thin or had a small head circumference at birth.

Koupilova and Leon (1996) found an inverse relationship between birth weight and mortality from ischaemic heart disease and stroke among more than 1,000 Swedish men who participated in a cohort study in the the 1970s, when they were about 50 years old. The relationships with birth weight persisted after socio-economic status, smoking habit, adult blood pressure and body mass index were taken into account.

The same pattern has been observed in data from the Nurses' Health Study, which is a United States cohort study of 121,000 women aged 30-35 in 1976 (Rich-Edwards, Stampfer, Manson et al. 1995), and in data from two other cohorts of health

professionals in the United States (Rich-Edwards 1996). Likewise, birth weight was inversely related to both fatal and non-fatal coronary heart disease in more than 1,000 men from Caerphilly and surrounding towns in Wales. Neither social nor behavioural variables accounted for this relationship (Frankel, Elwood, Sweetnam, et al. 1996). Incipient coronary heart disease was associated with low birth weight, short birth length, and small head circumference at birth in a group of men and women aged 38 to 60 years living in the south of India (Stein, Fall, Kumaran, et al. 1996). On the other hand, no link between birth weight and ischaemic heart disease was found for another group of Swedish men (Eriksson, Tibblin & Cnattingius 1994) nor for a large group of Swedish twins (Vagero & Leon 1994).

Elford, Whincup and Shaper (1991) reviewed the individual level data concerning early life experience and adult cardiovascular disease before most of the studies summarised above had been published. Many of the 19 studies they reviewed did not examine relationships with birth weight, but instead considered relationships with general indices of early life environment, such as social position, region of birth, or adult height. Elford and colleagues concluded that the studies failed to meet established criteria for causality, by a large margin. Interestingly, three of the four studies in which birth weight was available did provide supportive evidence; the weaker or contradictory evidence came from studies with a more general focus.

A much stronger picture emerges from the studies reported in the 1990s. The data from the United States are especially impressive in terms of quantity and length of follow up. Recent discussions suggest that critics find this evidence more persuasive, but are troubled by other inconsistencies in results and remain uncertain about the underlying causes (Crouse 1993; Dobbing 1993; Paneth 1994; Baker 1994; Scrimshaw 1995; Paneth & Susser 1995). Kramer and Joseph (1996) express considerable interest in the fetal orgins theory but clearly set out the problems that beset the evidence: results from different studies sometimes disagree (especially in relation to

the importance of particular birth dimensions) and some studies have yielded negative or opposing results; the theory does not explain trends in cardiovascular disease over time or differences between countries; in addition, there may be residual confounding within studies and also selection bias through large losses to follow up. These problems will be examined further in due course.

1.4   The theory of the fetal origins of cardiovascular disease

Barker's recent descriptions of the fetal origins theory are detailed and specific, especially in relation to cardiovascular disease. He has moved on from the general proposition that poor fetal growth is a cause of cardiovascular disease to specifying that "coronary heart disease is associated with specific patterns of disproportionate fetal growth that result from fetal undernutrition in middle to late gestation" (Barker 1995).

Disproportionate growth is thought to be related to later cardiovascular disease through accompanying physiological changes. During fetal life, growth may be disrupted by a lack of oxygen or nutrients. A disruption may result in disproportionate growth because tissues are affected differently, depending on whether or not they are undergoing a critical period of growth at that time. A critical period is one in which rapid cell division occurs; this happens at different stages of gestation for different body tissues. The nature of the accompanying physiological changes is not known, but could include reduced cell numbers in particular organs, changes in the distribution of cell types, altered patterns of hormonal secretion or metabolic activity, and changes to organ structure. It is proposed that in the longer term such physiological changes are manifest in raised blood pressure and cholesterol, other clinical risk factors, and ultimately increased occurrence of cardiovascular disease (Barker 1995).

Two particular forms of disproportionate growth are held to be related to later cardiovascular disease, one resulting in a baby that is thin, possibly with a small head

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at birth, the other seen in a baby that is short with a large head relative to its chest at birth. These disproportions are believed to be the consequences of undernutrition at different stages of gestation, second trimester undernutrition possibly leading to the thin birth phenotype, and third trimester undernutrition to the short phenotype. Another important discrepancy in birth characteristics, more generally indicative of poor growth, is that between the weight of the baby and its placenta. In his current working hypothesis, Barker suggests that the thin baby is predisposed to later high blood pressure and non-insulin dependent diabetes, and thereby to cardiovascular disease, whereas the short baby is at increased risk of high blood pressure, high cholesterol, and elevated fibrinogen, and thence cardiovascular disease (Barker 1995).

In explaining why birth disproportions are risk factors for later cardiovascular disease, Barker invokes two main ideas. One is that birth dimensions are indicative of fetal growth, and the other is that there is a direct connection with cardiovascular disease through physiological pathways. There are good biological bases for both of these ideas.

The setting or re-setting of physiological systems during critical periods in early life is a phenomenon referred to as programming. It is well accepted that programming occurs naturally in animals and humans. One example proffered by Barker (1994) is the determination of sex and other characteristics of reptiles by the environmental temperature. It is also well established that manipulations of the early life environment can influence or elicit programming. For example, Dubos, Savage and Schaedler (1966) described a number of experiments in which the manipulation of early feeding regimes of mice, or inducement of sub-clinical infection antenatally, had permanent effects on subsequent growth or resistance to disease. Chapter 2 of Barker's (1994) book comprises a comprehensive review of existing knowledge about programming. What is original in Barker's use of the programming concept is that it also applies to

blood pressure and cholesterol, and possibly other elements of physiological systems relevant to cardiovascular disease.

There is also a long history to the study of fetal growth and its imputation through measurements made at birth. Tanner (1981) recounts the beginnings of systematic measurement of newborn babies during the 19th century, motivated by a desire to assess chances of survival and also the need to determine whether the death of a baby really had occurred pre-birth or whether it was more likely to have been infanticide. Some measurements of fetuses at different stages of gestation had been made the previous century, the first probably those of Buffon and his collaborators in the 1740s. Subsequently, Roederer conducted a study of the size of newborn babies and, in 1753, published details of birth weight, length and placental weight for 34 babies. Roederer sought reliable information concerning average birth weight, so he could refute exaggerated claims from other sources.

According to Tanner (1981), reliable curves depicting the progression of body weight and length over the course of gestation were not published until the early 20th century. Stratz, the gynaecologist responsible for that work, was also interested in proportions of the fetus during development and by 1930 many others had investigated and published on this subject. Scammon and Calkins (1929) drew this work together in a tome so thorough that Tanner marvelled. The review showed that throughout gestation nearly every dimension of the normal fetus was linearly related to its length. Thus disproportions at birth would seem to be indicative of perturbations in fetal growth. This idea was extended in more modern work.

Discrepancies between birth weight and placental weight as well as thinness at birth and reduced head size have all been discussed as markers of poor fetal growth (Sinclair 1948; Rosso & Winick 1974; Molteni, Stys & Battaglia 1978; Crane & Kopta 1980). Specific causes of these different disproportions and the importance of timing during

gestation are uncertain, however. Shortness at birth appears not to have received attention (Godfrey & Barker 1995). It seems fair to say that Barker's (1994; 1995) accounts of the significance of different phenotypes are over-simplified, although he does emphasise that the ideas put forward serve as a framework for further research and that much is unknown.

Briefly, it appears to be widely understood that symmetrically small babies have experienced reduced growth throughout gestation, whereas babies exhibiting disproportions at birth have experienced reduced growth in the latter half of gestation (Klein, Stein & Susser 1989). This understanding derived from various sources, including studies of women who had been pregnant during the Dutch famine in World War II (Smith 1947; Bergner & Susser 1970) and the work of Gruenwald (1966a; 1966b) which suggested that restricted growth was manifest first in depletion of soft tissue, then in the skeleton, and lastly in the head and brain, with only the most severe (long-term) restriction affecting all three domains. Strong support was provided by the experiments of McCance and Widdowson (1974). These authors found that pigs which were nutritionally deprived throughout gestation were symmetrically small and stunted for life, whereas pigs that suffered deprivation at a later stage in gestation developed asymmetrically and their stunting could be reversed.

However, as discussed by Owens, Owens and Robinson (1995), other evidence indicates that disproportions at birth may result from arrested growth at any stage of pregnancy. For example, Kramer, McLean, Olivier, et al. (1989) carefully studied almost 9,000 infants born in Canada and did not find evidence of distinctly proportional and disproportional growth retardation; reduced growth at all gestational ages was manifest in disproportionality, and increasing severity of retardation was reflected in increasing disproportionality rather than symmetry.

From at least the 1960s there have been suggestions that different asymmetries have particular antenatal precursors (Klein, Stein & Susser 1989). Malnutrition has long been suspected (Naeye 1965). Owens, Owens and Robinson (1995) remark that it is because these infants appear malnourished that the primary cause is presumed to be a lack of essential substrates, particularly nutrients. Data supporting the various hypotheses is patchy, however. There is some evidence that placental enlargement may be a consequence of lack of oxygen or iron deficiency (Kruger & Arias-Stella 1970; Beischer, Sivasamboo, Vohra, et al. 1970; Godfrey, Redman, Barker, et al. 1991). Thinness at birth has been linked to maternal smoking (Haste, Anderson, Brooke et al. 1991).

Clearly, a much stronger understanding of the determinants of disproportionate fetal growth in humans is required if the theory is to yield further opportunities for prevention of cardiovascular disease. At present, however, the appropriate emphasis for research is in establishing whether associations between fetal growth patterns and later disease exist, and in elucidating possible mechanisms in pursuit of evidence that associations are causal.

1.5 Purpose and scope of this thesis

This thesis is concerned with an investigation of whether fetal growth, particularly disproportionate growth, is associated with cardiovascular disease risk in an Australian population. In this context, birth measurements are used as indicators of fetal growth. Two clinical risk factors for cardiovascular disease, blood pressure and blood lipids, are the outcomes of interest.

Elaboration of mechanisms that might explain such an association, and the determinants of disproportionate fetal growth, are beyond the scope of this thesis. The

work undertaken in this thesis is part of the foundation required for these other areas of research.

In the next Chapter the literature concerning blood pressure is reviewed, starting with its role in cardiovascular disease, then turning to factors known to influence blood pressure, as these factors need to be taken into account in an epidemiological study concerning another possible influence. The existing evidence linking fetal growth to later blood pressure is described and the specific research questions to be addressed within this thesis are set out. In Chapter 3 an analgous review is undertaken for blood lipids, and the research questions concerning blood lipids are detailed.

Both sets of research questions are addressed through a cohort study, in two parts. In the first part, new analyses were undertaken using existing data collected when cohort members were aged 8, to which data from hospital birth records were added. In the second part a follow up of cohort members was undertaken to collect new data pertaining to cardiovascular risk factors at 20 years of age. Methods for each part of the study are described in Chapter 4.

Results are presented in Chapters 5 and 6, the former concerning analyses of the age 8 data and the latter concerning the follow up at age 20. In Chapter 7 the results are discussed and their concordance with the fetal origins theory appraised.

Chapter 2
Literature review: blood pressure

2.1 Raised blood pressure as a risk factor for cardiovascular disease

Raised blood pressure is a well-established risk factor for cardiovascular disease. A wealth of evidence for this relationship has been provided by large-scale prospective observational studies; two famous examples are the Framingham Study and the Seven Countries Study.

The Framingham Study was the second of the large cohort studies with a focus on cardiovascular disease to be undertaken in the United States (Keys 1980). Initiated by the National Heart Institute in 1949, the study was based on a random sample of almost 4,500 residents of Framingham, Massachusetts, supplemented by other volunteers (Dawber, Kannel, Revotskie, et al. 1959). According to Susser (1985), the original aim was to establish the incidence of cardiovascular disease in a general population, but departures from rigorous sampling that occurred from the outset meant that the study could not yield reliable estimates of incidence. Instead, the aim was changed to the more appropriate one of ascertaining factors relevant to the development of cardiovascular disease.

Characteristics of Framingham cohort members assessed at baseline included systolic blood pressure, serum total cholesterol, body size and cigarette smoking. A standard cardiovascular examination was performed every two years, at least to begin with. After the first six years of follow up, elevated blood pressure and serum total cholesterol levels were clearly identified as the most important risk factors for coronary heart disease (Dawber, Kannel, Revotskie, et al. 1959).

The Framingham cohort was enlarged over ensuing years, with the data being used to address many intricate questions concerning cardiovascular disease risk. However, after an impressive 30 years of follow up of the original cohort members, the picture was essentially unchanged: raised blood pressure was found to contribute to the risk of all manifestations of cardiovascular disease considered (coronary heart disease, intermittent claudication, congestive heart failure, stroke and transient ischaemic attack) while serum total cholesterol was associated with manifestations other than stroke and transient ischaemic attack (Stokes, Kannel, Wolf, et al. 1987).

The Seven Countries Study (Keys 1980) began almost a decade after the Framingham Study, in 1957. It comprised 16 cohorts of men aged 40 to 59 years at entry, from Italy, Yugoslavia, Finland, Greece, the Netherlands, the United States and Japan. By that time several other prospective studies undertaken in the United States had produced results concordant with those of the Framingham Study. Therefore, the main aims of the Seven Countries Study were to document the incidence of cardiovascular disease and to investigate cardiovascular risk factors in diverse countries, using a common protocol. Of particular interest were possible cultural or nutritional influences on risk.

Within all of the Seven Countries cohorts, the entry characteristics of age and resting blood pressure were the best predictors of coronary heart disease occurrence over the next 10 years. Among middle-aged men, each 10 mm Hg increase in systolic blood pressure was associated with a 15 to 22 per cent increase in the risk of death from all causes and with a similar increase in the risk of death from coronary heart disease in particular (Keys 1980).

McMahon, Peto, Cutler, et al. (1990) reviewed evidence concerning the association between blood pressure and cardiovascular disease from nine major prospective observational studies (including the Framingham Study), involving 420,000

individuals. The review is especially interesting because the authors investigated and corrected for regression dilution bias. As explained by MacMahon and colleagues, this bias arises from the substantial random fluctuations surrounding baseline blood pressure measurements, which can lead to real associations between baseline blood pressure and subsequent disease being systematically under-estimated. In the review, information on repeated blood pressure measurements available from a few studies was used to correct results for the total pooled data. Corrected estimates of the association between diastolic blood pressure and cardiovascular disease risks were about 60 per cent greater than those obtained in uncorrected analyses. After correction, a 7.5 mm Hg reduction in usual diastolic blood pressure was associated, overall, with a 46 per cent reduction in the risk of stroke and a 29 per cent reduction in the risk of coronary heart disease. (From Fraser (1986), the same change in systolic pressure would be expected to carry similar reductions in risk.)

In addition, the review of McMahon, Peto, Cutler, et al. (1990) explicitly examined the nature of cardiovascular disease risks at the lower end of the spectrum of diastolic blood pressure, in order to assess propositions currently circulating in the literature of a threshold or even an increase in risk in this region. The data synthesis clearly showed strong, continuous, positive associations between diastolic blood pressure and cardiovascular diseases, over the entire range of blood pressure measurements.

The case for an important role of blood pressure in cardiovascular disease risk, built on results of observational studies, supported by clear biological plausibility, was well-accepted by the 1960s (McMichael 1989). It should nevertheless be noted that randomised controlled trials of drugs to reduce blood pressure have continued to provide compelling evidence of this relationship (see for example the review of Collins, Peto, McMahon, et al. 1990).

2.2 Influences on adult blood pressure

The cohort studies that established the link between raised blood pressure and increased likelihood of cardiovascular disease also identified characteristics and behaviours that influence blood pressure levels. Subsequently, other shorter-term and cross-sectional studies focused directly on determinants of blood pressure.

In the context of this thesis, established influences on blood pressure are of interest insofar as they potentially confound or account for associations between newly postulated predictors (indices of fetal growth) and blood pressure. From this perspective, a set of reasonably independent, established influences on adult blood pressure are identified as sex, age, body size or fatness, and alcohol consumption. In addition, smoking habit and salt intake may be contributors, although effects are likely to be weak at the individual level. While amount of physical activity may also affect blood pressure, this relationship is likely to be mediated by body weight. Evidence for these associations is summarised below.

As described by Fraser (1986), blood pressure rises with age in most populations, generally those that are urbanised and industrialised. Exceptions to this are found among some primitive tribal communities such as Eskimos and Cook Islanders. Blood pressure values of women tend to be slightly lower than those of men until late middle-age, after which time women have increasingly higher values than men, so that hypertension is markedly more prevalent in women than in men over the age of 65 years (Wenger 1995).

Again from Fraser (1986), virtually all studies of blood pressure in western countries have found that it is strongly related to indices of body size, including weight, height, obesity, and body surface area. Body fat appears to be the key element, although mechanisms for this effect are not well understood. Detailed research suggests that

centrally located body fat is of greatest importance, although central and peripheral fat often occur together. The influence of age on blood pressure is not completely explained by concurrent changes in body fatness. In adults, body fatness is commonly indicated by body mass index (weight divided by the square of height).

Numerous epidemiological studies of alcohol consumption and blood pressure have been undertaken, with the results of more than 60 studies reviewed by Beilin, Puddey and Burke (1996) generally indicating a positive linear relationship. In some studies there appeared to be a threshold around 2-3 drinks per day. Beilin and colleagues noted the inconsistency of this form of relationship with the more general protective effect of moderate alcohol consumption on cardiovascular disease risk. A few reports of a J-shaped relationship between alcohol consumption and blood pressure have appeared recently (Moore, Levine, Southard, et al. 1990; Gillman, Cook, Evans, et al. 1995), which suggests it would be prudent to distinguish between abstainers and moderate drinkers and not to assume a linear function in any analysis.

Smoking is a strong risk factor for cardiovascular disease. However, research data, including results of the Framingham Study, do not support the popular belief that smoking leads to elevated blood pressure. In fact, a relationship is found inconsistently and, when manifest, is usually inverse (Fraser 1986; Salvaggio, Periti, Quaglia, et al. 1992; Hughes, Leong, Sothy, et al. 1993). Curiously, a recent study from Britain examining blood pressure prior to the uptake of smoking showed that children with lower blood pressure were more likely to become smokers than other children (Charlton & While 1995). Further indication that any effects of smoking on blood pressure are quite weak is provided by reports of at most small changes in blood pressure following cessation of smoking (Green & Harari 1995).

Diet has been examined in a number of large epidemiological studies, with the general finding that few elements of diet are clearly related to blood pressure independently of

body size. Exceptions are alcohol consumption (mentioned above), and possibly phosphorous, calcium and salt intakes (Harlan, Hull, Schmouder, et al. 1984; Kotchen, Kotchen & Boegehold 1991; Pryer, Cappuccio & Elliott 1995; McCarron & Hatton 1996). Of the minerals, salt has received the greatest attention but its role in hypertension is still contentious. Athough an association was apparent in early ecological studies, effect estimates based on individual data within populations tended to be low and quite variable. Recent results from the Intersalt Study (Elliott, Stamler, Nichols, et al. 1996) add greatly to this debate, supporting a positive association, but many experts are yet to be convinced (Thelle 1996).

Associations between physical activity and blood pressure have been widely documented, but the extent to which this relationship is merely a reflection of differences in body size is unclear (Puddey & Beilin 1995). Kelley and McClellan (1994) reviewed nine randomised controlled trials of aerobic exercise to reduce blood pressure, and found a very small overall effect. They felt there was a need for more meticulously controlled investigations. Blumenthal, Thyrum, Gullette, et al. (1995) agreed that most available studies were methodologically unsound, with concomitant changes in body weight not usually taken into account.

Stress, in the form of Type A behaviour patterns or more general lifestyle, employment and inter-personal stresses, has been associated with increased risk of death from coronary heart disease in many studies (Boman 1988). A path of action through physiological risk factors for coronary heart disease, particularly raised blood pressure, has not been convincingly established, however. The available evidence on this matter is subject to dramatically different interpretations. Among the many examples of polarised views are those of Rosenman (1991 p 296) who asserts that "although acute anxiety or stress elicits acute pressor responses, there is little support for their significant role in sustained hypertension" and Boone (1991 p 623) who finds mental stress to be "clearly and inextricably linked to the development and maintenance

of high blood pressure". Recent advances in ambulatory blood pressure monitoring may facilitate progress in this area of research (Pickering, Schwartz & James 1995).

2.3 The connection between childhood and adult blood pressure

Raised blood pressure in adulthood is not without premonition. Within a group followed over time, individuals tend to maintain their rank order by blood pressure, so that initial blood pressure values are predictive of future levels. This phenomenon is known as tracking.

Szklo (1979) reviewed the literature on blood pressure tracking and unearthed reports dating back to 1933. In all, Szklo found a dozen studies concerning adults and concluded that blood pressure did indeed track through adult life. Less coherent was the evidence for tracking of blood pressure through childhood, despite some 11 studies with confirmatory results, including one documenting tracking from six months of age. Concerns arose from two studies of children that offered only weak evidence of tracking, and from suggestions that the pattern observed for the majority of children was one of variable rather than stable blood pressure. In concluding, Szklo reported that early results of the Bogalusa Heart Study - a landmark in terms of its rigour and clinical procedures - were supportive, and he looked forward to further results which, if consistent, would do much to resolve this matter.

Evidence for blood pressure tracking has continued to accumulate. Most importantly in view of Szklo's (1979) comments, recently published data from the Bogalusa Heart Study showed tracking of blood pressure in children, aged 5 to 14 years initially, over 15 years of follow up (Bao, Threefoot, Srinivasan, et al. 1995). Likewise, Nelson, Ragland and Syme (1992) demonstrated tracking of blood pressure from childhood through to adulthood in a Californian cohort, finding that blood pressure at age 50 years was best predicted by blood pressure measurements from school age and early

puberty. Also noteworthy is the work of Tate, Manfreda, Krahn, et al. (1995) concerning adult males living in Canada and followed up over a 40 year period: blood pressure was found to track at all ages, most strongly during middle age. Tracking of blood pressure appears to be weakest during the adolescent years, possibly as a result of developmental changes occuring in this period (Lever & Harrap 1992).

That blood pressure tracks over time, and in particular from early childhood, suggests several things. One is that it is possible to identify children who are likely to have raised blood pressure in adult life, and from this flows the possibility of early intervention, if the determinants of raised blood pressure in childhood are known and modifiable; this has motivated detailed studies of blood pressure in children and environmental determinants. The broader implication is that adult behaviours are clearly not the only influences on blood pressure: raised blood pressure has its origins considerably earlier in life (Lever & Harrap 1992).

2.4 Influences on childhood blood pressure

In addition to reviewing studies of blood pressure tracking, Szklo (1979) contemplated the factors that influence blood pressure during childhood. He found that blood pressure was positively related to age, it was related to sex from adolescence and possibly earlier (mean values being slightly higher in boys than in girls), and it was positively associated with weight. With regard to effects of race, sexual or biological maturation, salt intake and sundry other variables, results were divided.

In a more recent review of 129 studies, Brotons, Singh, Nishio, et al. (1989) documented the rise of blood pressure with age and confirmed that distributions for boys and girls were identical up to about age 9 years for systolic blood pressure (remaining quite similar until 14 years) and up to age 16 years for diastolic blood pressure.

Likewise, the more detailed picture emerging from a later review of obesity and blood pressure in children, by Labarthe, Mueller and Eissa (1991), is still closely in line with Szklo's (1979) summary. In the later review, where weight and body mass index were used to assess obesity, it was clear that a positive relationship held in general although it varied considerably with subjects' age and sex. The investigations of Ballew, Liu, Levinson, et al. (1990) showed that the relationship between obesity and blood pressure was stable, regardless of what form of weight-for-height index was used. Waist to hip ratio appears not to be an informative index in children (Moussa, Skaik, Selwanes, et al. 1994). Skinfold thicknesses measured at different sites have been used to indicate fatness, and also to distinguish between central and peripheral body fat, the former being related to blood pressure more strongly than the latter (Shear, Freedman, Burker, et al. 1987). Sangi, Mueller, Harrist, et al. (1992) demonstrated that, in children, size or weight-for-height was more important than the distribution of body fat in relation to blood pressure.

The National Heart and Lung Institute in the United States was involved in establishing two large longitudinal studies of cardiovascular risk factors in children during the early 1980s. They were the Bogalusa Heart Study and the Muscatine Study, and from them has emerged a great deal of information concerning blood pressure in children. The studies confirm that the predominant influences are age and body size. There is little evidence of any other direct influences, although roles for diet and exercise are often discussed, mainly as moderators of body weight (Lauer, Burns & Clarke 1985; Burke, Voors, Shear, et al. 1987; Berenson, Wattigney, Bao, et al. 1994).

In the context of this thesis, established influences on childhood blood pressure are of interest insofar as they potentially confound or account for associations between newly postulated predictors (indices of fetal growth) and blood pressure. Thus the emphasis here is on identifying reasonably independent, established predictors of childhood blood pressure: these appear to be limited to age and body size.

2.5 Birth weight and later blood pressure

As described in the Chapter 1, the revival by Barker of the idea that adult disease had its origins in early life was based on results of ecological studies and a study in which individual birth weights of Hertfordshire men were observed to be inversely associated with cardiovascular deaths (Barker, Winter, Osmond, et al. 1989). Barker's interpretation of these findings was rightly debated, as the available evidence was compatible with at least two other explanations: a poor socio-economic environment throughout life underlying both low birth weight and detrimental adult lifestyle practices that eventually culminated in early death; and, alternatively, genetic susceptibility to both low birth weight and cardiovascular disease.

Barker and his colleagues recognised that more detailed research was needed to discriminate among the competing explanations. In particular, processes that might link fetal growth to cardiovascular disease needed investigation, and potential confounding factors had to be taken into account. Accordingly, Barker and his colleagues undertook three major epidemiological studies in Britain, locating archival records about birth and infancy, and following up men and women now middle-aged, elderly, or deceased. The broad aim of these studies was to examine relationships between birth measurements and clinical risk factors for cardiovascular disease assessed in adult life. The cohorts are referred to by their birth locations: Hertfordshire, Preston and Sheffield.

While work with the three retrospectively established cohorts was in progress, Barker and his colleagues re-analysed data from two existing national birth cohorts in Britain, one pertaining to persons born during a certain week in 1970 and the other to persons born during a certain week in 1946. Blood pressure for the former had been measured at age 10 years and for the latter, most recently, at age 36 years. Birth weight was among the many variables contained in data bases relating to the cohorts. For both

cohorts, systolic pressure was inversely related to birth weight, independently of current weight. For the 36-year-olds, the relationship was also independent of cigarette smoking and birth order (Barker, Osmond, Golding, et al. 1989).

This relationship had in fact been reported previously, but in other contexts, so it had received little attention. Several prior instances (Cater & Gill 1984; Simpson, Mortimer, Silva, et al. 1981; Gennser, Rymark & Isberg 1988) were listed in the first paper on the subject by Barker and colleagues (Barker, Osmond, Golding, et al. 1989) and Szklo's (1979) review also cited papers in which this relationship appeared.

Barker and his colleagues went on to examine the relationship between birth weight and blood pressure in the Hertsfordshire and Preston cohorts. An inverse relationship was observed in each case. The relationship was independent of social class (at birth or current) in Hertfordshire (Hales, Barker, Clark, et al. 1991). For the Preston cohort, it was reported that the relationship was independent of current body mass index and alcohol intake, it was present within each level of social class (at birth or current), and it was not affected by smoking habit, room temperature, length of gestation, or birth order (Barker, Bull, Osmond, et al. 1990). The Preston study yielded more surprising results concerning other birth measurements and blood pressure, discussed in a subsequent section.

A systematic review of the literature concerning the relationship between birth weight and blood pressure has just been undertaken by Law and Shiell (1996). Published literature dating back to 1956 was scoured for reports of this relationship, and all studies of subjects from normal populations that presented quantitative details of the relationship were included in the review. In all, 34 studies (described in 32 papers) that met these criteria were identified, albeit with results in disparate forms. Some 15 studies had been carried out in Britain but there was also one each from Israel, New

Zealand, Japan, India and Jamaica, with the remainder from continental Europe and the United States.

The most informative studies retrieved by Law and Shiell (1996) were 17 cohort studies (some involving several age groups) that contained results of a linear regression of blood pressure on birth weight, with adjustment for current body size. Nearly all found an inverse relationship. In the nine sets of results for children, a one kilogram increase in birth weight was typically associated with a 2 to 3 mm Hg decrease in systolic pressure. The six sets of results for adolescents were less consistent. However, the 12 studies of adults all showed an inverse relationship, the magnitude of the effect tending to increase with age.

Another 12 studies scrutinised by Law and Shiell (1996) did not present regression analyses but compared mean blood pressures of different birth weight groups or performed some other quantitative analysis. Results from these 12 studies were mixed. For neonates, the relationship was consistently positive and for adults the relationship was consistently negative.

Law and Shiell (1996) concluded that the literature supported a negative association between birth weight and blood pressure in children and in adults. The inconsistent findings in adolescents were thought to be related to disturbances of blood pressure that accompany the adolescent growth spurt. The overall findings were not reliant on results from a single academic group, country or method of analysis.

2.6   The amplification hypothesis

Law, de Swiet, Osmond, et al. (1993) pieced together results of four separate studies of the relationship between birth weight and blood pressure, and noticed that the magnitude of the relationship was steadily greater in the older samples than in those

younger. Law and colleagues therefore proposed that the relationship between birth weight and blood pressure was amplified throughout life.

In response, critics pointed out that the distribution of blood pressure was known to exhibit greater spread in older samples compared with younger groups, and a larger effect size could simply follow from this. Longitudinal studies of the same individuals were arguably the only sound way to assess amplification (Whincup, Papacosta & Cook 1993).

In the systematic review carried out by Law and Shiell (1996), five studies that made repeated blood pressure measurements in the same individuals, thus offering a superior test of the amplification hypothesis, were identified. In four studies (three from Britain and one from the Netherlands) both the first and the repeated blood pressure readings had been made during childhood (Law, de Swiet, Osmond et al. 1993; Launer, Hofman & Grobbee 1993; Fall, Pandit, Law, et al. 1995; Whincup, Cook, Papacosta, et al. 1995). A positive relationship between birth weight and systolic pressure during infancy was reported in two of these studies. Blood pressure measurements in older children were almost always negatively associated with birth weight, and there was some indication of amplification, although this was not formally assessed.

In the original publication of Whincup, Cook, Papacosta, et al. (1995) a very detailed examination of amplification of effects in children assessed at age 5 to 7 years and again at age 9 to 11 years was presented. At the earlier age a one kilogram increase in birth weight was associated with a 2.3 mm Hg decrease in systolic pressure, while at the later age the same change in birth weight was associated with a 4.0 mm Hg decrease in systolic pressure. Using a within subject analysis, this difference was shown to be statistically significant. The extent to which individuals of different birth weight changed their ranking by blood pressure between assessments was also investigated, the idea being that individuals of low birth weight might progressively be

located higher up in the blood pressure distribution. In practice, this appeared not to be the case.

In the fifth study identified by Law and Shiell (1996), from New Zealand, the initial blood pressure readings had been made at age 7 years and the association with birth weight was negative, while the repeat measurements were made at age 18 years and the association was positive (Williams, St George & Silva 1992). In the light of other spurious findings among adolescents this last study contributes little to an assessment of amplification.

The proposition of Law, de Swiet, Osmond, et al. (1993) concerning amplification was based on observations from groups spanning much of the spectrum of age: children aged 0 to 10 years, men and women aged 36 years, men and women aged 46 to 54 years, and men and women aged 59 to 71 years. The increase in effect size was particularly marked between childhood and adulthood, and from early to late adulthood. The assessments of amplification reported above are confined to childhood or, in one instance, late adolescence. Longitudinal studies in which initial or repeated measurements were made in adulthood have not been reported, but would be illuminating.

2.7 Other birth measurements and blood pressure

Relationships between birth measurements other than birth weight and blood pressure have been reported in a few studies. While birth weights are commonly recorded, more detailed birth measurements are not usually made routinely, so are generally not available for analysis. However, as discussed in Chapter 1, other birth characteristics provide additional insight into fetal growth.

One of the three hoards of old birth records that Barker and his colleagues discovered in Britain related to births in the Sharoe Green Hospital in Preston, Lancashire, during 1935-43. The birth records were unusually detailed in that they contained measurements of placental weight, crown-heel length, head and chest circumference, as well as birth weight. Almost 90 per cent of the 1,298 members of this birth cohort were traced through the National Health Service central register. Some 500 members were still living in Lancashire, and 449 of these participated in assessments of cardiovascular risk at around 50 years of age (Barker, Bull, Osmond, et al. 1990).

Among the Preston men and women, blood pressure was inversely related to birth weight and, simultaneously, positively associated with placental weight. Raised blood pressure was related to the combination of high placental weight and relatively low birth weight more strongly than it was to birth weight alone. Systolic pressure rose by 15 mm Hg as placental weight increased from less than or equal to 1 lb to more than 1.5 lb, and simultaneously fell by 11 mm Hg as birth weight increased from less than or equal to 5.5 lb to greater than 7.5 lb. These relationships were independent of current body size, alcohol consumption, length of gestation, and social class (at birth or current). The relationships were very strong, with routine birth measurements predicting adult blood pressure better than current body measurements or any adult lifestyle factor (Barker, Bull, Osmond, et al. 1990).

Furthermore, in the Preston cohort, adult blood pressure was related to body proportions at birth, with individuals who were characterised by relative shortness or thinness at birth having a greater likelihood of high blood pressure than those who were normally proportioned at birth (Barker, Godfrey, Osmond, et al. 1992). These relationships were complex, in that they were most apparent in subgroups formed on the basis of placental weight. Among individuals whose placental weight had been below average, both ponderal index (a measure of thinness, defined as birth weight divided by the cube of birth length) and head circumference at birth were inversely

related to adult blood pressure, although not independently. (Systolic pressure fell by 13 mm Hg as ponderal index increased from the lowest to the highest quartile.) Among individuals whose placental weight had been above average, length at birth was inversely related to adult blood pressure. (Systolic pressure fell by 12 mm Hg as birth length increased from less than 20 inches to more than 21 inches.)

For the Sheffield cohort, blood pressure was also ascertained at about 50 years of age, for 80 per cent of the individuals who still lived in Sheffield (approximately 30 per cent of the original cohort). Birth weight, birth length, head circumference and abdominal circumference were all inversely related to blood pressure at age 50. (Systolic pressure fell by 9 mm Hg over tertiles of birth length; it fell by 11 mm Hg over quartiles of abdominal circumference at birth; and it fell by 4 mm Hg over tertiles of head circumference.) These relationships were independent of gestional age at birth, alcohol consumption, smoking habit and social class. However, placental weight and ponderal index at birth were not related to the adult blood pressure values (Martyn, Barker, Jespersen, et al. 1995).

To date, it appears that relationships between detailed birth measurements and blood pressure have been investigated thoroughly in only a few other studies. Most concerned children, and results are not entirely consistent.

One of only two other cohort of adults with relevant data is that studied by Leon, Koupilova, Lithell, et al. (1996). All men living in Uppsala, Sweden, who were born in 1920-24, were invited to participate in a health survey during 1970-73; more than 80 per cent of men chose to take part. Leon and colleagues recently sought birth details for this cohort and re-analysed the data from the examinations at age 50 in conjunction with the birth data. Of the 2,200 men who had actually been born in Sweden, birth weight was retrieved for 1,333 and birth length for 1,187. Birth weight was inversely related to blood pressure at age 50: a one kilogram increase in birth weight was

associated with a decrease in systolic pressure of approximately 2 mm Hg and with a slightly smaller decrease in diastolic pressure. These effects were strengthened when analysis was restricted to men born at term. Neither ponderal index at birth nor discrepancies between birth weight and placental weight were associated with blood pressure at age 50. However, adult blood pressure was highest among men who had been light at birth but were tall as adults. Leon and colleagues suggested that this discordance was an indicator of failure to fulfil growth potential *in utero*. As pointed out by Law, Martyn, Fall, et al. (1996), and tacitly recognised by Leon and colleagues, this marker of poor fetal growth would be pertinent in Sweden, an affluent society where it may be assumed that most adults experienced optimal growth during childhood and fulfilled their adult height potential, but would be less informative in countries or social classes where this assumption cannot be made. Interestingly, Leon and colleagues also reported an interaction between birth weight and adult body mass index in relation to adult blood pressure, such that men with the lowest birth weights and the highest adult body mass indices had markedly elevated blood pressure at age 50. Leon and colleagues suggested that the propensity to develop high blood pressure was only fully expressed in those who became obese in adult life.

The other study of adults involved men and women who were born in Aberdeen, Scotland (Campbell, Hall, Barker, et al. 1996). For this group, blood pressure at age 40 was inversely related to birth weight. A separate inverse relationship with placental weight, that was not statistically significant, was also mentioned.

Law, Barker, Bull, et al. (1991) assessed blood pressure at age 4 years for approximately 400 children born and living in Salisbury, England. Systolic pressure was inversely associated with birth weight and, simultaneously, positively associated with placental weight, although neither of these trends was statistically significant. Stronger relationships were observed with other birth dimensions: ponderal index was inversely related to blood pressure at age 4, as was head circumference at birth; length

at birth was positively related to later blood pressure. Most of these relationships were concordant with those reported for the Preston cohort.

By contrast, Whincup, Cook, Papacosta, et al. (1995) examined blood pressure in 473 children attending primary school in Carlisle, Wales, for whom birth weight and placental weight were available from hospital birth records. These authors reported inverse relationships with blood pressure for both birth weight and placental weight, and little independent effect of placental weight after birth weight was taken into account. These results were not dependent on duration of gestation.

Likewise, among 610 Jamaican children aged 10 years or less, Forrester, Wilks, Bennett, et al. (1996) found that blood pressure was inversely related to both birth weight and placental weight, with the latter association not independent of the former. Although other birth dimensions were recorded, no relationships with later blood pressure were reported.

For some 450 children who had been born pre-term with birth weights less than 1,850 grams, birth weight, birth length, and ponderal index were not related to blood pressure at about 8 years of age. There was some evidence that blood pressure decreased with decreasing birth weight for gestational age (Morley, Lister, Leeson-Payne, et al. 1994). The fetal origins theory is, however, chiefly concerned with the consequences of moderate growth restriction in term babies; outcomes for very small pre-term babies might be more complicated and effects are perhaps best seen in comparisons with normal babies.

Both birth weight and placental weight were measured in a study of blood pressure among Gambian children, but relationships between placental weight and later blood pressure were not described (Margetts, Rowland, Foord, et al. 1991). In a study of children from Dunedin, New Zealand (Williams, St George & Silva 1992),

relationships between blood pressure and a broad set of birth measurements were examined, but the series of comparison groups created and the comparisons reported hamper assessment of overall relationships in this sample.

Most recently, Taylor, Whincup, Cook, et al. (1997) examined relationships between birth dimensions and later blood pressure among 1,573 British school children aged 8 to 11 years. Each of the birth phenotypes identified by Barker (1994) as having a role in later blood pressure were investigated. Among girls, birth weight was inversely related to systolic blood pressure, after adjustment for current body size (using height and ponderal index). In addition, both head circumference and length at birth were inversely related to blood pressure, but ponderal index at birth and the ratio of length to head circumference at birth (used to indicate shortness) were not. Placental weight was inversely related to blood pressure, but not independently of birth weight, among girls. Among boys, birth weight was only weakly related to later blood pressure. Apart from a positive association between placental weight and blood pressure, there were no other relationships with birth dimensions among boys.

2.8   Interpretation

Barker and his colleagues have interpreted the findings concerning birth weight and later blood pressure as evidence of an underlying link between poor fetal growth and persistently altered metabolic processes, culminating in elevated blood pressure and increased risk of cardiovascular disease. Associations between other birth dimensions and blood pressure are thought to indicate that hypertension may arise from different forms of fetal growth retardation (Barker 1994; 1995).

The majority of studies concerning birth weight and later blood pressure, as reviewed by Law and Shiell (1996), support an inverse association. The findings concerning other birth dimensions and later blood pressure are not completely coherent, however.

In Preston, discrepancies between birth weight and placental weight, thinness at birth, and shortness at birth were markers of elevated blood pressure in later life. In Sheffield, shortness at birth featured again, as did thinness, but only when indicated by abdominal circumference rather than ponderal index; and placental weight was not informative. The study of Swedish men found that birth weight, but not birth disproportions, was predictive of later blood pressure. Among the cohorts of children, only the Salisbury study provided support for the importance of different birth characteristics.

To some degree, invoking different phenotypes to explain the different patterns of association has the appearance of a *post hoc* convenience, and there are insufficient replications with which to appraise this aspect of the theory. Effects of birth weight on blood pressure have generally been weaker in children than in adults, so null results in this age group are not especially worrying; the problem is more a lack of hypothesis-driven testing in adults. From this perspective, if Barker is correct, one might expect to find some evidence of relationships between each phenotype and later blood pressure within the same sample. This was the case in Preston, but not in the other cohorts.

One difficulty with such analyses is that the short and thin phenotypes are mathematically opposing, since thin babies either do not have compromised length or are relatively long. This means that elevations in blood pressure associated with shortness at birth could be disguised by the presence of elevations in blood pressure due to thinness, and vice versa. Subgroup analyses are one way to overcome this problem, but they entail a loss of statistical power. Modelling with interaction terms may be another solution, but this also has grave implications for power.

Another problem with the studies of Barker and colleagues, to which critics drew attention (Paneth & Susser 1995), was the fact that the people eventually examined in

the studies constituted only a minority of the original birth cohorts. Additionally, the Preston and Sheffield cohorts were based on births in certain hospitals at a time when women commonly delivered at home. Barker and his colleagues maintain that such selection biases would only operate if the associations were different among those lost to follow up or not included in a birth cohort, and they believe there is no obvious reason why this would be the case. Although this position is reasonable, the absence of data leaves the point open to argument.

Other interpretations of the straightforward association between birth weight and later blood pressure were offered vigorously to begin with, but less often over the past few years as supportive evidence from other countries has accrued. In line with the alternative explanations for the association between birth weight and cardiovascular deaths, critics suggested the findings could reflect persisting deprivation or genetic factors (Bradley 1990; Baker 1994). As before, the socio-economic argument is quite plausible, the genetic one less so.

There is a long history of research documenting similar patterns of blood pressure within families. Szklo (1979) described many studies in which blood pressure values for children were consistently found to be correlated with those of their parents and those of other siblings. Szklo recognised that these results did not enable a distinction between possible genetic and environmental origins of familial aggregation. However, studies of twins and adoptees had led other authors to claim a very significant role for heredity. Szklo was not entirely convinced, being at pains to point out that the presence of familial aggregation in these studies was still not synonymous with genetic causation, even suggesting intrauterine and gestational factors as an alternative explanation. There has been similar confusion in studies of the determinants of birth weight but, as noted previously, recent work summarised in the review of Kline, Stein and Susser (1987) indicates only a minor role for genes. This would seem to largely

rule out an underlying genetic cause of the birth weight and blood pressure relationship.

An inverse relationship between socio-economic status and blood pressure has frequently been documented (Fraser 1986). In this regard, educational attainment has been used most extensively as an indicator of socio-economic circumstances, including in a study of the offspring of Framingham cohort members (Stamler, Shipley, Elliott, et al. 1992; Teconi, Romanelli, Gigli, et al. 1992; Garrison, Gold, Wilson, et al. 1993; Luepker, Rosamond, Murphy, et al. 1993). Data from another famous United States study, the Stanford Five City Project, have been used to compare the contributions of education, occupation and income, with educational attainment observed to be most strongly and most consistently related to cardiovascular risk factors, including blood pressure (Winkleby, Jatulis, Frank, et al. 1992). The association between socio-economic status and blood pressure appears to be partly due to differences in behaviours that have a bearing on blood pressure, as well as body size, although the extent to which there is an effect of socio-economic status that is independent of these factors has not been a research issue. (As noted earlier, however, in relation to the outcome of cardiovascular deaths, questions concerning the contribution of behavioural differences to socio-economic variation have been pursued.) As seen in Chapter 1, birth weight is also related to socio-economic status, so the association between birth weight and blood pressure could primarily be a reflection of this circumstance.

The classical epidemiological approach to resolving such an issue would be to ascertain socio-economic status and to examine relationships between birth weight and blood pressure taking it into account. This Barker and his colleagues did, but were met with charges of not having measured socio-economic status sensitively enough (Paneth & Susser 1995). Again, this is a fair rejoinder, as socio-economic status is difficult to characterise and an index with few categories cannot allow fine discrimination.

However, Barker and his colleagues did use a standard index in relatively old groups of individuals who were not geographically mobile, and probably not socially mobile either, and relevant adult behaviours were also assessed. This is where replication of results in different settings and countries becomes crucial in epidemiological research, and where the need for experimental work is heightened.

A number of animal experiments, designed specifically to test the fetal origins theory in relation to later blood pressure, have been undertaken. In the first of these experiments, Persson and Jansson (1992) restricted the growth of guinea pigs *in utero* by ligation of a uterine artery. This procedure reduces placental blood flow to one of the uterine horns and results in a litter in which pups in the affected side of the uterus experience reduced growth, but pups in the opposite horn do not. Pups experiencing the severest growth retardation *in utero* weighed approximately half as much as normal at birth, and were still under-weight at around 3 to 4 months of age, when guinea pigs are sexually mature and have achieved adult size. At that time, blood pressure values for the pups were found to be inversely correlated with their size at birth. The pups that had undergone the most severe fetal growth retardation had mean blood pressure 8 mm Hg higher than their normal birth weight controls.

Another animal model was developed by Langley and Jackson (1994) who altered fetal growth in rats through different maternal feeding regimes. The dams were fed diets of either 6, 9, 12 or 18 per cent protein, the latter being the normal laboratory diet, for 14 days prior to mating. The diets were continued at the different levels throughout pregnancy but were restored to normal after the rats had given birth. At 9 weeks of age the offspring of rats given the low protein diets had higher blood pressures than pups in the control group. The relationship was graded, with mean blood pressure being highest for offspring from the lowest protein group. The difference in mean blood pressure between the 12 per cent protein group and the control group was 15 mm Hg, although this restriction in maternal protein was only mild and did not change

the reproductive ability of the dams or appear to compromise the growth of the pups *in utero*. The more severe restrictions of maternal protein did retard the growth of the pups. Differences in the pups' blood pressures were observed through to the conclusion of the experiment at 21 weeks of age. Subsequently, Langley-Evans, Phillips and Jackson (1994) demonstrated that blood pressure effects in the offspring were independent of changes in maternal blood pressure, and Langley-Evans (1996) showed that similar effects could be produced by feeding pregnant rats a diet rich in saturated fats.

Langley-Evans, Gardner and Jackson (1996) also showed that subjecting pregnant rats to a low protein diet led to disproportionate growth of the fetus as well as to elevated blood pressure in later life. In mid-gestation the pups carried by mothers fed a low protein diet were relatively heavy but had smaller brains and were longer in proportion to their weight compared with controls. In late gestation, pups from mothers on the restricted diet were relatively short in relation to their weight. At birth they had lower body mass for length compared with control animals; their placentae were relatively heavy just before term. Once again, after they were weaned the pups of mothers fed a low protein diet had higher blood pressures than controls.

Maternal undernutrition has also been associated with raised blood pressure in fetal sheep. In an experiment by Harding and Johnson (1995), this change in blood pressure was observed following only a 10 day period of maternal undernutrition in late pregnancy; it is not known whether the rise in blood pressure persisted into the post-natal period.

Another deprivation, in the form of maternal anaemia, has been found to alter birth phenotype and blood pressure of the offspring. In rats, pups of anaemic mothers had increased ratios of placental weight to birth weight. In the immediate post-natal period,

the pups of anaemic mothers had lower blood pressure than pups in the control group, but after three months this pattern was reversed (Crowe, Dandekar, Fox et al. 1996).

Both pre-natal and post-natal nutrition of rats were manipulated by Lucas, Baker, Desai, et al. (1996). In the control group, dams were normally fed throughout pregnancy and lactation. In one experimental group the dams had a low protein diet during pregnancy and lactation. In a second experimental group the dams were malnourished during pregnancy but their pups were crossed to normally fed mothers following birth, while in the last experimental group, conditions were normal for pregnancy but the pups were fostered by protein-restricted mothers following birth. Lipid concentrations were the main outcome of interest, but the authors also mentioned that they found mean blood pressure values for the offspring in all experimental groups to be lower than values for controls. This finding is the opposite of that of Langley and Jackson (1996), although the model used was very similar; Lucas and colleagues did not offer any explanation but pointed out that they had at least managed to show that maternal nutrition was capable of influencing physiological factors in the offspring.

Exploration of possible mechanisms using animal studies has commenced, although this area of research will not be reviewed here. One argument being pursued is that maternal nutrition may have an impact on fetal growth through altered hormonal activity (Langley-Evans & Jackson 1996). Influential roles for maternal corticosteroids and angiotensin II have received most attention thus far (Tangalakis, Lumbers, Moritz, et al. 1992; Edwards, Benediktsson, Lindsay et al. 1993; Langley-Evans & Jackson 1995).

By and large, the animal experiments support the epidemiological findings with regard to birth weight and blood pressure. They provide some additional evidence that certain

birth phenotypes are pertinent to later blood pressure. Also supported is the notion that maternal nutrition can be an important underlying factor.

A few of the epidemiological studies concerning birth weight and later blood pressure also contained information about the nutritional status of the mother during pregnancy. Margetts, Rowland, Foord, et al. (1991) found that blood pressures of children living in Gambian villages were related to weight and weight gain of their mothers in the last trimester of pregnancy (but not to birth weight). The relationships were complex, in that for children aged less than 8 years, blood pressure was positively related to mother's weight 6 months into pregnancy. For older children, however, blood pressure was inversely related to mother's weight gain in the last trimester of pregnancy. These findings were independent of the mother's blood pressure during pregnancy and the child's current weight. The authors thought this pattern of results could indicate that adverse effects of poor fetal growth only became apparent in late childhood, and planned to revisit the younger children to test this hypothesis.

Another study was based on a group of Jamaican women who took part in a study of nutrition during pregnancy. Their haemoglobin concentrations, skinfold thicknesses and weights were recorded. Later, Godfrey, Forrester, Barker, et al. (1994) followed up 77 children born to these women for assessment of blood pressure at 10 to 12 years of age. The child's systolic pressure was found to be inversely related to indices of maternal nutrition during pregnancy, in particular, to mother's weight gain and triceps skinfold thickness, although no relationship with birth weight was evident.

Most interestingly, Campbell, Hall, Barker, et al. (1996), studied 253 people currently living in or near Aberdeen, Scotland, who were born there around 40 years ago. While pregnant, their mothers had completed a dietary survey. Blood pressure measurements of the middle-aged adults were analysed in conjunction with the maternal dietary information collected decades earlier. Blood pressure at age 40 years

appeared to be related to the balance of maternal intake of protein and carbohydrate during pregnancy. Where the mother's pregnancy intake of animal protein was relatively low (up to 50 grams per day), the offspring's blood pressure at age 40 was inversely related to the percentage of energy intake derived from this source, and carbohydrate intake was simultaneously positively associated with blood pressure. Where the mother's intake of animal protein was high (more than 50 grams per day, which applied to approximately 20 per cent of mothers in the sample), the offspring's blood pressure at age 40 was positively related to the percentage of energy from this source, and carbohydrate intake was inversely associated with blood presure. These trends were statistically significant even with adjustment for mother's maximum antenatal blood pressure and the offspring's birth weight. The combination of low maternal protein intake and high carbohydrate intake also appeared to reduce placental weight, whereas high intakes of both animal protein and carbohydrate were linked to an enlarged placenta.

Thus, there is some epidemiological evidence directly connecting maternal nutrition with later blood pressure in the offspring. Further studies of this kind would be most interesting, and will be needed especially if more basic work leads to consensus that specific recommendations for pregnant women are warranted. However, factors besides maternal nutrition may be important, including maternal blood pressure, smoking, and pre-pregnancy circumstances (Paneth 1994; Morely, Leeson Payne, Lister, et al. 1995; Churchill, Perry & Beevers 1997). Existing data, sufficiently comprehensive to address questions of maternal nutrition and other underlying influences are rare, and full prospective studies will take time. These research questions may broken up into a number of smaller ones, using retrospectively established cohorts to look for relationships with birth measurements, and prospective studies to explore determinants of those birth measurements, bearing in mind that the birth measurements are, theoretically, only indicators of more fundamental physiological changes. Animal experiments are required to investigate the latter.

Answers thus lie in layered research, drawing on several disciplines, which exemplifies the proper context for contemporary epidemiological research.

2.9   The aims of this thesis regarding blood pressure

The starting point for this thesis was a cross-sectional study of cardiovascular risk factors in children, conducted by Dr Richard Cockington, Dr Ian Hamilton-Craig, Dr John Boulton and Mrs Anthea Magarey, during 1984-85 (described in Chapter 4). The study was known as the Adelaide Children's Hospital Family Heart Study. All of the children were born during 1975-76 in the Queen Victoria Hospital in Adelaide, South Australia, where detailed measurements of new-born babies were routinely made. The availability of both birth measurements and cardiovascular risk assessments meant that it was possible to investigate the fetal origins of raised blood pressure in this cohort, using existing data.

In addition, a follow-up study was undertaken of the individuals who had, as children, participated the Adelaide Children's Hospital Family Heart Study. Their cardiovascular risk factor status was re-assessed during 1995-96 when they were about 20 years of age. This enabled relationships between birth characteristics and blood pressure to be examined at a second time point.

Thus this thesis addresses the following research questions in relation to the origins of elevated blood pressure:

1. Is birth weight related to blood pressure at age 8 in a cohort of children born and living in Australia?

2. Are other birth measurements related to blood pressure values for these children? In particular, is there evidence that blood pressure is related to the following birth

phenotypes: low birth weight relative to placental weight; thinness, possibly accompanied by a small head circumference; shortness with a large head relative to chest?

3.   Is birth weight related to blood pressure values of cohort members in early adulthood?

4.   Are other birth measurements related to the adult blood pressure values? In particular, is there evidence that blood pressure is related to the following birth phenotypes: low birth weight relative to placental weight; thinness, possibly accompanied by a small head circumference; shortness with a large head relative to chest?

5.   If it exists, is the relationship between birth weight and blood pressure amplified with age?

These questions are addressed taking into account established influences on childhood and adult blood pressure and also socio-economic status. The research methods are described in Chapter 4. Results concerning children are presented in Chapter 5 and results concerning the same individuals in early adulthood are presented in Chapter 6.

Chapter 3
Literature review: blood lipids

3.1 Blood lipids as risk factors for cardiovascular disease

According to Fraser (1986), it was known from the early 19th century that cholesterol was a component of arterial atheromatous deposits, which logically led to the idea that cholesterol in the blood might promote the development of these deposits, thereby having a role in ischaemic heart disease. Thus plasma cholesterol was one of the variables measured from the outset in the large-scale prospective observational studies that sought an understanding of the causes of cardiovascular disease. Both the Framingham Study (Dawber, Kannel, Rovotskie, et al. 1959) and the Seven Countries Study (Keys 1980) showed that serum cholesterol concentration was positively associated with the risk of cardiovascular disease.

Law, Wald and Thompson (1994) recently reviewed the evidence for an association between serum cholesterol concentration and ischaemic heart disease. More than 60 cohort studies providing information about the relationship were identified, but Law and colleagues confined their attention to the 10 largest studies (concerning men only). A log-linear relationship was evident in each study, meaning that any absolute change in serum cholesterol concentration was associated with a certain percentage change in risk of ischaemic heart disease. Specific results were given for a decrease in serum cholesterol concentration of 0.6 mmol/L, this being about 10 per cent of the average serum cholesterol concentration in western populations. This decrease was associated with a decrease in risk of death from ischaemic heart disease ranging from 6 to 26 per cent (unadjusted). As explained by Law and colleagues, these estimates would be depressed by regression dilution bias arising from random fluctuations in baseline cholesterol measurements (analogous to the situation for blood pressure, discussed previously).

The estimates would also be affected by a form of bias Law, Wald, Wu, et al. (1994) called the surrogate dilution effect. In principle, this bias arises because a reduction in serum cholesterol concentration achieved by some intervention corresponds to a greater reduction in risk than indicated by observational studies: a difference of 1 mmol/L in serum cholesterol in an observational study corresponds to a difference of around 0.67 mmol/L in low density lipoprotein (LDL) cholesterol, whereas interventions generally act through LDL cholesterol, and a 1 mmol/L reduction in serum cholesterol then corresponds to a 1 mmol/L reduction in LDL cholesterol, and has a larger impact on risk through this latter factor (see below).

Thus Law, Wald and Thompson (1994) adjusted their figures describing the relationship between serum cholesterol concentration and ischaemic heart disease risk for the influences of regression dilution bias and the surrogate dilution effect (with corrected estimates being about 60 per cent greater than those obtained in unadjusted analyses). An interaction with age was also apparent, the relationship progressively diminishing with age. In summary then, the 10 largest cohort studies indicated that each decrease in serum cholesterol concentration of 0.6 mmol/L was associated with decreases in ischaemic heart disease risk of 54 per cent at age 40 years, 39 per cent at age 50 years, and 27 per cent at age 60 years.

Most of the evidence relating serum cholesterol concentrations to cardiovascular disease has been obtained from studies of men. In cohort studies that included both men and women the relationship among women has sometimes been weaker than that observed for men (Law, Wald & Thomspon 1994). Some authors have interpreted this as a real difference in relative risk, however, Law and colleagues considered results for women and concluded that apparent differences in the relationship were due to greater regression dilution bias in data pertaining to women, and that the relationship was in fact very similar for men and women. Recently published results of a very large follow-up study (23,000 men and 26,000 women) undertaken in the Netherlands

by Verschuren and Kromhout (1995) showed associations of similar magnitude in men and women (although women have lower absolute risks than men through their lower distribution of cholesterol).

Results of randomised controlled trials are consistent with results of observational studies. La Rosa (1995) re-examined the early trials, which on the whole had not been viewed as particularly successful, and reported that meta-analysis showed drug-induced cholesterol reductions of 20-25 per cent to be associated with statistically significant reductions in cardiovascular disease morbidity and mortality. Law, Wald and Thompson (1994) reviewed 28 randomised controlled trials, that met specific criteria for size and quality, in which serum cholesterol concentration had been reduced either by drugs, diet or ileal bypass surgery. A dose-response relationship was apparent, and the risk of ischaemic heart disease was further reduced with increases in the length of time over which the reduction in cholesterol was sustained. Overall, each decrease of 0.6 mmol/L in serum total cholesterol among men aged around 60 years was associated with a 10 per cent reduction in the risk of fatal ischaemic heart disease and a 21 per cent reduction in the risk of non-fatal myocardial infarction.

Interestingly, in some populations serum cholesterol may even be a better predictor of cardiovascular risk than blood pressure, in the longer term. Pekkannen, Tervahauta, Nissinen, et al. (1993) analysed data from 30 years of follow up of 1,619 Finnish men and found that baseline systolic blood pressure only predicted coronary heart disease deaths in the first two decades of follow up, whereas baseline serum cholesterol continued to correlate with disease risk in the third decade. This is in contrast to the 30 year results from the original Framingham Study (Stokes, Kannel, Wolf, et al. 1987).

Cholesterol in the blood is carried in different lipoprotein particles and these also received attention as possible determinants of cardiovascular disease when it became possible to measure them. Keys (1980) regretted that lipoprotein fractionation had not

been undertaken in the Seven Countries study, explaining that it had been ruled out because of the expense and practical difficulties, in the face of its uncertain value. These contraints very likely applied in many other studies, which probably accounts for the smaller volume of work concerning these factors.

LDL is the major cholesterol-carrying particle, and second-wave results from the Framingham Study showed that it, too, was positively associated with cardiovascular disease risk (Kannel, Castelli & Gordon 1979). Further supportive evidence has been provided by numerous epidemiological studies, clinical trials, and genetic studies (Austin 1992). At the same time, high density lipoprotein (HDL) cholesterol has a protective effect, being inversely related to cardiovascular disease risk (Betteridge 1989), and the ratio of HDL to LDL cholesterol provides further information about disease risk, some have argued superior to that provided by total cholesterol or by either lipoprotein value alone (Fraser 1986). Like total and LDL cholesterol, triglyceride concentration is positively related to cardiovascular disease risk (Garber & Anvins 1994).

There has been, however, a great deal of controversy about whether these factors have separate influences on cardiovascular disease risk. For example, Pocock, Shaper, Phillips, et al. (1986) collated evidence from 7 large prospective studies and made a strong case for HDL cholesterol not having any independent role in cardiovascular disease, and Barter (1991) drew on evidence from biological research to argue that HDL cholesterol was merely a marker for some other causal factor (possibly triglyceride-rich lipoproteins).

The debate about independent influences remains unresolved but appears to be receiving less attention, being replaced by growing consensus that independence is not the important issue. Instead, it is argued that - independent or not - information regarding lipoproteins and triglyceride enables more accurate prediction of

cardiovascular risk, which is of most concern (National Institutes of Health 1992; Castelli, Anderson, Wilson, et al. 1992; Austin 1992; Stein & Gotto 1992; Kannel & Wilson 1992; Schaefer 1993; Branchi, Rovellini, Fiorenza, et al. 1994; Tenkanen, Pietila, Manninen, et al. 1994).

It is not the purpose of this thesis to contribute to the debate about the independence of these risk factors. In the context of this thesis, it is sufficient that these factors are indicative of cardiovascular risk. Thus serum total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride are all outcomes of interest in this thesis.

3.2 Influences on lipid concentrations in adults

In adults, serum cholesterol concentrations tend to rise with age and differ between males and females. In general, levels of adverse lipids are higher, while those of protective factors are lower, in males than females, with differences diminishing after the age of menopause (La Rosa 1992; Junger, Walldius, Holme, et al. 1992).

Body weight and fatness are related to lipid concentrations in adults. Early on, the Framingham Study showed that body mass index was positively associated with serum cholesterol concentration, and subsequently demonstrated that weight gain was accompanied by increases in serum cholesterol values, while weight loss was associated with decreases (Higgins, Kannel, Garrison, et al. 1988). Many other studies have consistently found that body mass index is positively associated with serum total cholesterol and LDL cholesterol, and inversely associated with HDL cholesterol, and that weight change influences lipid concentrations (for example Criqui, Frankville, Barrat-Conor, et al. 1983; Kromhout 1983; Thelle, Shaper, Whitehead, et al. 1983; Sedgwick, Thomas, Davies, et al. 1990; Van Horn, Ballew, Liu, et al. 1991). Through a study that involved ascertainment of body fat percentage

by hydrostatic weighing, Segal, Dunaif, Gutin, et al. (1987) confirmed that body composition rather than body weight was the factor determining serum lipids.

Alcohol consumption, lipid concentrations and cardiovascular disease risks appear to be related in a complex manner, with interactions probable, and the now well-established increase in cardiovascular disease risk at very low as well as high levels of alcohol consumption a source of further snarling (Paunio, Virtamo, Gref, et al. 1996). Nevertheless, data from many populations indicate that there are direct effects of alcohol intake on serum lipids, with consumption being either negatively or not correlated with total cholesterol and LDL cholesterol, sometimes positively correlated with triglyceride, but quite consistently positively correlated with HDL cholesterol (Castelli, Doyle, Gordon, et al. 1977; Thelle, Shaper, Whitehead, et al. 1983; Stamford, Matter, Fell, et al. 1984; Masarei, Puddey, Rouse, et al. 1986; Contaldo, D'Arrigo, Carandente, et al. 1989; Haarbo, Hassage, Schlemmer, et al. 1990).

Cigarette smoking appears to promote poor lipid profiles, often being associated with increased concentrations of total cholesterol, LDL cholesterol and triglyceride, and invariably being associated with decreased concentrations of HDL cholesterol (Thelle, Shaper, Whitehead, et al. 1983; Stamford, Matter, Fell, et al. 1984; Haarbo, Hassage, Schlemmer, et al. 1990; Handa, Tanaka, Shindo, et al. 1990). The emergence of adverse effects of cigarette smoking on serum lipids has been documented in members of the Bogalusa Heart Study who took up smoking during adolescence (Freedman, Srinivasan, Shear, et al. 1986), and the gradual disappearance of effects in adults who stopped smoking has also been described (Shennan, Seed & Wynn 1985).

Oral contraceptive use by women can have undesirable effects on serum lipids. The two main components of oral contraceptives actually have opposing influences, with the adverse tending to dominate (Mishell 1991). Fotherby's (1985) consolidation of this literature suggested that any effects occurred shortly after a woman began using

oral contraceptives, and were maintained but were not progressive. The extent of effects depended on the nature of the oral contraceptive, with low dose and triphasic formulations least likely to influence lipids. Early and more recent data from the Bogalusa Heart Study disclose an adverse influence of oral contraceptives on lipids in young women using modern oral contraceptive formulations (Webber, Hunter, Baugh, et al. 1982; Webber, Hunter, Johnson, et al. 1991).

Exercise is popularly believed to have favourable effects on blood cholesterol. However, there appears to be only a modest amount of high-quality research in this area, with results that are by no means as conspicuous or as consistent as the popular response implies. As summarised by Sedgwick, Thomas, Davies, et al. (1989), cross-sectional studies have tended to support the relationship, but longitudinal studies have not, and a role of exercise over and above its influence on body weight is quite uncertain. In complete agreement are Taylor and Ward (1993), who critically appraised the literature applying to women. They found that many of the studies were scientifically weak and had not taken body weight into account. The only reliable evidence of a relationship was among young women who undertook very high levels of exercise.

Illustrative Australian data are provided by a national (cross-sectional) survey of almost 8,000 adults (Bauman & Owen 1991). Self-reported habitual exercise level was associated with concurrent measurements of total serum cholesterol for men, and with HDL cholesterol and triglyceride for both men and women. Whether these associations persisted after adjustment for body mass index was not reported. In an exceptionally thorough longitudinal study of 1,000 Australian adults undertaken around the same time, Sedgwick, Thomas and Davies (1993) found no independent relationships between change in fitness and changes in serum lipids in men, and none in women apart from a very small improvement in the ratio of HDL to total cholesterol.

Although his review of the literature found no evidence for an overall effect of exercise on total cholesterol concentration, Superko (1991) suggested that there may be a threshold of physical activity above which lipids may be favourably influenced. The threshold was thought to lie around the equivalent of 10 miles of jogging per week, a level of exercise uncommon in the Australian population (Sedgwick, Thomas, Davies, et al. 1989).

The evidence for an influence of diet on serum lipid concentrations is sturdier, although the degree to which effects are mediated by body weight is again uncertain. The elements of diet that have received most attention in this context are total fat, saturated fat and cholesterol. As outlined by Fraser (1986), experimental work showing that dietary cholesterol, and both type and quantity of dietary fat, contributed to serum cholesterol concentrations in male human subjects was conducted in the United States during the 1950s and 1960s. Supportive epidemiological evidence was not readily forthcoming, however. The Seven Countries Study and other cross-cultural studies found some evidence of relationships at the population level, but studies within populations, including the Framingham Study and extended data from the Seven Countries Study, could not demonstrate associations at the individual level. There is, therefore, still a substantial body of opinion against a causal role for diet (Jacobs, Anderson & Blackburn 1979; Shaper 1996).

The previous lack of evidence within populations may have been due to insensitive dietary assessment methods, as some later publications (Thorogood, Roe, McPherson, et al. 1990; Bolton-Smith, Woodward, Smith, et al. 1991), including another from the Framingham Study (Sonnenberg, Posner, Belanger, et al. 1992), have presented modest correlations between elements of diet, particularly fat intake, and serum lipid concentrations. Amidst the continuing debate a new development appears in the work of Esrey, Joseph and Grover (1996) which shows direct associations between the percentages of energy intake as total fat, saturated fat, and mono-unsaturated fat, and

the outcome of death from coronary heart disease, independent of total energy intake and serum lipids, among members of a United States cohort who were less than 60 years of age.

Influences of other components of diet, notably dietary fibre, milk and protein, have been proposed but investigated to a far lesser extent, with results unconvincing (Fraser 1986). Coffee drinking has been implicated as an adverse influence on serum lipids in cross-sectional studies, although effects are very small and a causal relationship is unsubstantiated (Thelle 1991).

Thus influences on adult blood lipids, that need to be considered as potential confounding factors in the context of an investigation of a new determinant, are: sex, age, body fatness, alcohol consumption, smoking habit, oral contraceptive use among women, and possibly dietary fat intakes and exercise level (these last possibly not contributing information additional to that contained in indices of body size).

3.3   The significance of childhood lipid profiles

As with blood pressure, serial measurements of lipid concentrations display continuity over time. Labarthe, Eissa and Varas (1991) summarised the research concerning tracking of lipid values, finding it less plentiful than that for blood pressure, but nevertheless sufficient to demonstrate tracking of total cholesterol and LDL cholesterol from 6 months of age, and tracking of HDL cholesterol and triglyceride concentrations from one year of age.

The Bogalusa and Muscatine Studies - the seminal longitudinal studies of cardiovascular risk factors in children - have yielded detailed and concordant data showing tracking of blood lipids through childhood and adolescence and into the third decade (Webber, Srinivasan, Wattigney, et al. 1991; Mahoney, Lauer, Lee, et al.

1991). In both studies, tracking was most prominent for total cholesterol and LDL cholesterol. For example, in the Bogalusa Heart Study around 50 per cent of the children with LDL cholesterol in the highest quartile still had values within that quartile 12 years later, while the corresponding figure for HDL cholesterol was closer to 40 per cent.

Further evidence that childhood lipid concentrations provide insight regarding later cardiovascular disease comes from autopsy studies in which atherosclerotic lesions have been documented in children and young adults who died from violent causes, and found to be related to post-mortem lipid levels (Stary 1989). Through the Bogalusa Heart Study, atherosclerotic lesions in children and young adults have even been related to lipid values measured prior to death (Freedman, Wattigney, Srinivasan, et al. 1993).

Thus plasma lipid concentrations in childhood are indicative of lipid profiles in later life. They therefore provide information about the likelihood of experiencing cardiovascular disease in later life. Moreover, as many authors have recognised, this continuity in lipid measurements strongly suggests that poor lipid profiles have aetiological origins in pre-adult life (Berenson, Wattigney, Bao, et al. 1995).

3.4 Influences on lipid concentrations in children

Labarthe, Eissa and Varas (1991), in reviewing the natural history of cholesterol in childhood, found very few longitudinal studies that documented lipid concentrations (absolute values rather than tracking coefficients) over more than a few years. Thus most of the information on concentrations during childhood comes from piecing together results of cross-sectional studies. Cholesterol concentrations appear to rise sharply during infancy, then are fairly stable from around 2 years of age until puberty, when values decrease for a time. This general pattern applies to both sexes, but

Labarthe and colleagues noted considerable differences between populations in the ages at which the pre-adolescent peak and the adolescent trough occur. Recently published data from cohorts of children followed over long periods of time bear this out (Boulton, Magarey & Cockington 1995; Twisk, Kemper & Mellenbergh 1995). As summarised by Kwiterovich (1991), the changes that take place around the time of puberty are likely to be a consequence of sexual maturation and hormonal changes.

Body weight and body fat influence lipid concentrations in children. The Bogalusa Heart Study showed that generalised obesity in children (elevated weight for height) was associated with relatively high concentrations of total cholesterol, LDL cholesterol, and triglyceride, and reduced concentration of HDL cholesterol. Furthermore, the distribution of body fat was also important, truncal body fat in particular being associated with a poor lipid profile (Freedman, Srinivasan, Harsha, et al. 1989; Kikuchi, Srinivasan, Harsha, et al. 1992). Similar results have emerged from other studies of children (for example Resnicow & Morabia 1990; Sangi, Mueller, Harrist, et al. 1992).

Diet and exercise are often discussed in the context of modifying lipid concentrations in children. Enthusiasm for these approaches seem to arise partly from generalising presumed relationships in adults (see section 3.2), and partly as a logical response to the evidence linking body fatness and lipid profiles in children. As moderators of body weight, children's diet and exercise are likely to influence their lipid profiles, and this forms the basis of most recommendations (for example American Health Foundation 1989; Dietitians' Association of Australia and the Australian College of Paediatrics 1995). Whether these approaches work in practice is questionable, however, as Labarthe, Eissa and Varas (1991) reviewed studies of interventions to reduce blood cholesterol concentrations in children (most with an emphasis on improved diet, some including a program of physical activity) and found the majority

to be of poor quality, many lacking a control group, so that the evidence was overall quite unconvincing.

Data pertaining to children, that support relationships with diet and exercise which are independent of body weight, are rare. Srinivasan, Webber and Berenson (1989) summarised the dietary literature, remarking on the very strong associations between dietary components and serum lipids found in early childhood, and the apparent absence of any relationships from school age. It was suggested that difficulties in accurately assessing the diets of children might have contributed to the lack of findings. Recent Australian work indicates that there may be small independent effects. Gliksman, Lazarus and Wilson (1993) surveyed some 1,000 Australian children aged 12 to 15 years and found no associations between dietary fat variables and serum lipids in boys, while in girls there were small associations which were likely to have persisted after adjustment for body mass index (although this exact analysis was not reported). Vandongen, Jenner, Thompson, et al. (1995) conducted a randomised controlled trial of nutrition and fitness programs in more than 1,000 10 to 12 year olds living in Western Australia. The interventions succeeded in improving fitness and diet but, apart from an association between fiber intake and blood cholesterol in boys, were not directly associated with any changes in cholesterol.

Thus, influences on blood lipids in mid-childhood, that need be considered as potential confounding factors in the context of an investigation of a new determinant, are: sex, age, and body fatness. Independent influences of diet and exercise are unlikely to be identifiable, even if they actually exist.

3.5 Birth characteristics and later lipid concentrations

Since blood lipids, along with blood pressure, are primary clinical risk factors for cardiovascular disease, they have also been a focus of research undertaken by Barker

and colleagues to explain the association between birth weight and death from cardiovascular disease. Internationally, however, work on this subject is far less extensive than that for blood pressure. Apart from four studies by Barker and colleagues (three in Britain and one in India), only five investigations were identified in a systematic search of the literature published to the end of 1996.

To recap, Barker and his colleagues developed the theory that adult cardiovascular events have aetiological origins in fetal life chiefly through work with three British cohorts. These cohorts were defined retrospectively using collections of old birth records. They are referred to by the geographic locations in which the births occurred: Hertfordshire, Preston and Sheffield.

In Sheffield there were in fact two groups of subjects, one comprising persons born 1907-24 and the other persons born 1939-40. The Sheffield birth records were very detailed, containing birth weight, placental weight, length, head circumference, chest circumference and abdominal circumference. Assessment of serum lipids was undertaken for 219 members of the 1939-40 cohort when members were aged 50 to 53 years, this sample representing about half of those who still lived in Sheffield (Barker, Martyn, Osmond, et al. 1993).

For both men and women of Sheffield, birth weight, adjusted for length of gestation, was inversely associated with concentrations of total cholesterol and LDL cholesterol, although the trends were of borderline statistical significance. Stronger (and statistically significant) inverse associations were present between abdominal circumference at birth and concentrations of total cholesterol and LDL cholesterol. For example, as abdominal circumference increased from 11.5 inches (29 cm) to 13 inches (33 cm), total cholesterol fell from 6.7 mmol/L to 6.1 mmol/L. The relationships with abdominal circumference increased in magnitude upon adjustment for duration of gestation, and were mirrored by weaker inverse associations between other birth

dimensions (birth length, head circumference and chest circumference) and lipid profile around 50 years of age. Concentrations of HDL cholesterol and triglyceride were not related to birth measurements (Barker, Martyn, Osmond, et al. 1993).

The relationships seen in the Sheffield cohort, between birth measurements and serum lipids at age 50 years, were strengthened by adjustment for current smoking habit and alcohol consumption. They were more prominent than relationships between current body mass index and serum lipid concentrations, and they were manifest within each category of social class. Similar patterns of association were said to be present in unpublished data from the Preston cohort (Barker, Martyn, Osmond, et al. 1993).

In the Hertfordshire cohort, separate studies were undertaken to assess serum lipid concentrations in men and women (Fall, Barker, Osmond, et al. 1992; Fall, Osmond, Barker, et al. 1995). This was because the Hertfordshire cohort was the first to be traced by Barker and colleagues, and efforts were initially concentrated on men to make the task simpler (as most men kept the same name for life). Results for men and women were different.

Of men born in east Hertfordshire during 1920-30, almost 1,200 were still living there in the late 1980s, and 485 participated in a study of serum lipids (Fall, Barker, Osmond, et al. 1992). For this cohort, birth weight was the only recorded birth measurement. Birth weight was not related to lipid concentrations in the whole sample, but a relationship was apparent within a subgroup of men who had experienced a certain type of infant feeding. (In fact, manner of infant feeding was itself related to adult lipid profile, as men who had been breast fed and not weaned by one year, as well as men who had been exclusively bottle fed, had higher concentrations of total cholesterol and LDL cholesterol than the remaining men.) Birth weight was positively related to serum concentrations of total cholesterol and LDL cholesterol, among men who had been breast fed and not weaned by one year. There

was a simultaneous inverse relationship with weight at one year, so that the highest cholesterol concentrations were found among men (breast fed and not weaned by one year) who had been relatively large at birth and relatively small at one year. This pattern was not subject to confounding by age, smoking habit, alcohol consumption or social class (at birth or current). These relationships were not apparent among men who had been weaned by one year (those solely breast fed and those both breast and bottle fed).

Among 297 women of east Hertfordshire, seen sometime later at around 64 years of age, birth weight was positively associated with HDL cholesterol concentration, and inversely associated with triglyceride concentration. These relationships were not a product of social class differentials. Other lipid concentrations were not related to birth weight, and there were no relationships with weight at one year. There were no differences in lipid profiles in subgroups based on manner of infant feeding (Fall, Osmond, Barker, et al. 1995).

One other study in Britain contains data concerning birth measurements and adult lipid profiles. Frankel, Elwood, Sweetnam, et al. (1996) followed up 1,258 men from Caerphilly and five surrounding Welsh towns, who had been recruited to a study of heart disease in 1979-83, primarily to examine relationships between birth weight and incident coronary heart disease. The men had ascertained their birth weight from their mother or a close female relative, and total cholesterol, HDL cholesterol and triglyceride had been assessed at approximately 50 years of age. Mean lipid values for men in each quartile of birth weight were presented in a table, although these results were not specifically described. Total cholesterol and triglyceride appear to fall slightly with increasing birth weight category, but no trend is evident for HDL cholesterol. These trends were manifestly not statistically significant.

Evidence from outside Britain is limited. There appears to be one study each of: Jamaican children, Swedish adolescents, young adults living in Croatia, 30 year olds in Texas, Swedish men aged 50-60 years, and men and women aged 38 to 60 years in India. Results for these studies, summarised below, are equivocal.

Forrester, Wilks, Bennett, et al. (1996) reported data pertaining to 610 Jamaican school children aged 6 to 9 years, for whom maternal hospital records provided information on birth weight, placental weight, length and head circumference. In this sample, serum cholesterol concentration was inversely associated with birth length, after adjustment for sex, age and current weight (although this relationship did not persist after adjustment for placental weight). Socioeconomic status did not account for this finding. Other birth measurements were not related to cholesterol concentration.

Almost 900 Swedish adolescents were studied by Bergstrom, Hernell, Persson, et al. (1995). Among boys, both weight and length at birth were inversely correlated with current HDL cholesterol, although these relationships were not statistically significant when current size was taken into account. No relationships with birth measurements were reported for girls. However, adolescent boys and girls with cholesterol values in the highest quartile seemed to have grown relatively poorly during infancy and childhood, as indicated by their heights in these phases.

Among almost 200 Croatians aged approximately 20 years, birth weight - the only birth measurement available for analysis - was not related to current plasma lipid concentrations (Kolacek, Kapetanovic, Zimolo, et al. 1993). Total cholesterol was higher in males breast fed for less than 3 months than in males breast fed for a longer period. Also, in comparisons of subgroups based on relative weight during early childhood and adulthood, the highest cholesterol and LDL cholesterol concentrations

were found among males who had been leanest in the first three years of life and had become the fattest adults.

Likewise, there was little evidence of associations between birth weight and lipid concentrations at age 30 in a sample of 564 men and women from San Antonio, Texas, although low birth weight was linked to clustering of conditions associated with the insulin resistance syndrome, which include dyslipidaemia (Valdez, Athens, Thompson, et al. 1994). Specifically, the sample comprised male and female Mexican Americans and non-Hispanic whites for whom lipids were assessed. Birth weight was obtained from birth certificates. The only statistically significant result for any of the four sex by race subgroups was an inverse relationship between birth weight and plasma triglyceride among non-Hispanic white men.

In a study of Swedish men aged 50 to 60 years, that was primarily concerned with insulin concentrations, Lithell, McKeigue, Berglund, et al. (1996) noted that there were no relationships between birth weight or ponderal index and either HDL cholesterol or triglyceride in adulthood.

Finally, Stein, Fall, Kumaran, et al. (1996) recently reported results of a study in India, similar to those undertaken in Hertfordshire, Preston and Sheffield. More than 500 men and women born in the Holdsworth Memorial Hospital in Mysore during 1934-54 were followed up in the early 1990s. Stein and colleagues were primarily concerned with relationships between birth dimensions and coronary heart disease in adulthood, ascertained by electrocardiogram and the Rose Questionnaire. Birth length was found to be inversely related to incipient coronary heart disease. Lipids were considered as possible mediating factors in this relationship, but links between birth dimensions and lipids were not examined directly. In this context, no associations between birth measurements and lipids were apparent.

3.6 Interpretation

Results concerning birth dimensions and later lipid concentrations are by no means as coherent as those concerning blood pressure. The lipid results have not received the same degree of comment, either interpretive or critical, in the international literature.

To summarise, for the four groups where birth weight was the only birth measurement available (Hertfordshire, Caerphilly, Croatia, and San Antonio) there was no firm evidence of relationships between birth weight and total cholesterol or LDL cholesterol. Birth weight was positively associated with HDL cholesterol among Hertfordshire women, and inversely associated with triglyceride among both women in Hertfordshire and white men in San Antonio.

Of the five studies where other birth dimensions were available (Sheffield, Preston, Jamaica, Sweden, and India), the strongest results and arguments come from the Sheffield study. In that study, abdominal circumference at birth was inversely associated with concentrations of total and LDL cholesterol 50 years later. In their discussion, Barker, Martyn, Osmond, et al. (1993) emphasised the strength and specificity of this result and pointed to animal work which showed that undernutrition in late gestion led to disproportionate fetal growth. They speculated that poor growth of the liver in late gestation might underlie the observed association, and drew support for this suggestion from previous work showing that the liver was a site of synthesis of LDL cholesterol in late gestation, and that babies who were small for their gestational age had raised LDL cholesterol concentrations. Details of the mechanisms were not known, nor were causes of this particular form of reduced fetal growth.

In the published correspondence concerning the Sheffield paper, Mongrelli and Gardosi (1994) argued that attributing the main finding to impaired growth during late gestation was imprudent, because abdominal circumference was not a conventional

measure of impaired fetal growth; the standard measures were ponderal index, skinfold thickness, or the ratio of mid-arm circumference to head circumference. Barker, Fall, Martyn, et al. (1994) replied that they were not referring to the severe intrauterine growth retardation that was the province of clinicians, but to more common but less severe reduced growth found among babies of average birth weight.

Two of the measures of fetal growth listed by Mongrelli and Gardosi (1994) were not available to Barker, Martyn, Osmond et al. (1993). Ponderal index was, but relationships with this variable were not reported. These relationships would be of interest, not necessarily because ponderal index is a better measure of growth or thinness, simply because it is more widely available. The lack of replication of the abdominal circumference results would appear to inhibit further discussion. Replication is unlikely to be forthcoming because abdominal circumference at birth is a very rare measurement.

A broader context for further investigation of relationships between fetal growth and later lipid profiles is provided by Barker's detailed working hypothesis. As described already, Barker (1994; 1995) has proposed that different forms of poor fetal growth are manifest in different forms of physical appearance at birth. Two of these birth phenotypes are thinness, possibly accompanied by a small head circumference, and shortness with a large head relative to chest. Babies that have either appearance at birth, as well as babies with low weight relative to that of their placenta, are thought to have an elevated risk of cardiovascular disease in adult life, but possibly as a consequence of different underlying physiological abnormalities. Barker has suggested that the thin baby is especially predisposed to elevated cholesterol in later life.

In the light of the more detailed theory, the epidemiological results concerning birth dimensions and later lipids are more harmonious. In Sheffield and Preston the overall

picture is one of thin babies having poor lipid profiles later on. In Jamaica the short baby emerges as having high cholesterol, which contradicts Barker's specific prediction. On the other hand, it is consistent with the idea that both patterns of disproportion are important to later cardiovascular disease. Analyses concerning birth weight only might be expected to yield null results, since birth weight alone may not enable sufficient discrimination of the relevant patterns of poor fetal growth. Replication is an important part of the foundation for the generalisability of epidemiological evidence, however, and there are insufficent replications of any of these findings to be convinced that the associations hold meaning for general populations.

It should also be noted that the alternative explanations offered by critics in relation to the blood pressure findings are relevant here: relationships between birth dimensions and later lipid profiles may primarily be a reflection of adverse circumstances throughout life, or they may be a product of genetic influences. The same counter-arguments apply: Barker and his colleagues included assessment of social class in their studies and also took into account behaviours that might provide pathways for socio-economic influences on cardiovascular disease risk; and genes do not appear to be a major determinant of birth proportions.

Barker (1994) summarised evidence from animal studies showing that the early environment is capable of having a permanent impact on physiological systems. In relation to lipids, there is a considerable body of research concerning early post-natal influences, particularly infant feeding, on later lipid profiles. However, with regard to pre-natal influences, which are the focus of this thesis, there is only a small amount of relevant experimental work.

Two studies have examined the effect of restricted maternal diet on plasma lipids of the offspring, with different findings. McLeod, Nestel and Goldrick (1973) found no

effect of maternal protein restriction prior to and during pregnancy on plasma cholesterol concentrations of rat pups following birth. Lucas, Baker, Desai, et al. (1996) set up four different feeding groups: a control group wherein the mothers were normally fed throughout pregnancy and lactation, a group in which the dams were fed a low protein diet during pregnancy and lactation, a group where the dams had a low protein diet during pregnancy but the pups were crossed to normally fed mothers following birth, and a group where the pregnant rats were normally fed but the pups were crossed to protein restricted mothers following birth. At 6 months of age, mean cholesterol, HDL and triacylglycerol concentrations for each experimental group were lower than the corresponding mean values for the control pups. These differences were greater for male than female pups. The mean values of plasma lipids for each of the experimental groups were similar. This latter study therefore found an influence of maternal nutrition on plasma lipids of the offspring, but the effect was not in the direction proposed by Barker and, at least in rats, there was no distinction between effects of maternal malnutrition imposed pre-natally or post-natally.

There appear to be no other animal studies specifically testing effects of poor fetal growth or maternal undernutrition on lipid concentrations of the offspring. Such work is currently being undertaken in Adelaide (Owens, Kind, Sohlstrom, et al. 1996).

Further epidemiological investigations of whether birth dimensions, particularly those corresponding to specific phenotypes, are associated with later lipid profiles are in order. As well as being of interest in their own right, results of such studies might eventually allow a meta-analysis of the kind undertaken by Law and Shiell (1996) concerning blood pressure, whereupon it may be more confidently known whether any relationships have general relevance.

3.7 The aims of this thesis regarding blood lipids

As mentioned previously, the starting point for the data used in this thesis was a cross-sectional study of cardiovascular risk factors in children, conducted by Dr Richard Cockington, Dr Ian Hamilton-Craig, Dr John Boulton and Mrs Anthea Magarey, during 1984-85 (described fully in Chapter 4). The study was known as the Adelaide Children's Hospital Family Heart Study. All of the children were born during 1975-76 in the Queen Victoria Hospital in Adelaide, South Australia, where detailed measurements of new-born babies were routinely made. The availability of both birth measurements and cardiovascular risk assessments meant that it was possible to investigate the fetal origins of later lipid profiles in this cohort.

In addition, a follow-up study was undertaken of the individuals who had, as children, participated in the Adelaide children's Hospital Family Heart Study. Their cardiovascular risk factor status was re-assessed during 1995-96 when they were about 20 years of age. This enabled relationships between birth characteristics and lipid concentrations to be investigated at a second time point.

This thesis addresses the following research questions in relation to the origins of adverse lipid profiles:

1. Is birth weight related to blood lipid concentrations at age 8 in a cohort of children born and living in Australia?

2. Are other birth characteristics related to blood lipid concentrations for these children? In particular, is there evidence that lipid profiles are related to the following birth phenotypes: low birth weight relative to placental weight; thinness, possibly accompanied by a small head circumference; shortness with a large head relative to chest?

3. Is birth weight related to blood lipid concentrations of cohort members in early adulthood?

4. Are other birth characteristics related to adult blood lipid concentrations? In particular, is there evidence that lipid profiles are related to the following birth phenotypes: low birth weight relative to placental weight; thinness, possibly accompanied by a small head circumference; shortness with a large head relative to chest?

These questions are addressed taking into account established influences on childhood and adult lipid profiles and also socio-economic status. The research methods are described in Chapter 4. Analyses relevant to these research questions are presented in Chapter 5 (results from childhood) and Chapter 6 (results in early adulthood).

Chapter 4
Methods

4.1 Overview

A study of cardiovascular risk factors in 8 year old children was conducted at the Adelaide Children's Hospital, South Australia, in 1984-85. The study sample was drawn from children born in the Queen Victoria Hospital in Adelaide, South Australia, during 1975-76. The 856 children who participated in that study formed a cohort that has been maintained to the present time.

The current study has two parts. In the first part, new analyses were undertaken using data collected in the study at age 8, to which were added data from hospital birth records. For the second part, a follow up of cohort members was undertaken to collect new data pertaining to cardiovascular risk factors at 20 years of age.

4.2 The study at age 8

The study at age 8 was undertaken by Dr Richard Cockington, Dr Ian Hamilton-Craig, Dr John Boulton and Mrs Anthea Magarey, to document and investigate influences on cardiovascular risk factors in children, with a view to making recommendations regarding screening. Two thousand children who were born sequentially in the Queen Victoria Hospital between June 1975 and July 1976 were deemed eligible to be involved in the study. This sampling frame was specified because cord blood had been collected for these children and it was thought that this might be a basis for additional analyses, although in the end this was not possible because the cord samples could not be linked to individual study participants.

Hospital records for 1,952 of the 2,000 listed births, providing information about the families, were located in 1984. Tracing was undertaken using the telephone directory, the electoral roll and newspaper advertisements, and contact was eventually made with the families of 1,138 children. The families of 856 children (75% of those traced and invited) agreed to participate in the study. A quarter of the families that declined involvement did not live in the Adelaide metropolitan area at that time (Boulton, Cockington, Hamilton-Craig, et al. 1995).

Participating children attended the Adelaide Children's Hospital for a physical examination and a blood test during 1984-85. Measurements were conducted according to a World Health Organisation protocol (World Health Organisation 1980). Weight was measured to the nearest 100 grams using beam balance scales, with the child lightly clothed but shoeless. Height was measured to the nearest centimetre using a Harpenden stadiometer. Biceps, triceps, subscapular and supra-iliac skinfolds were measured using Harpenden skin callipers. Blood pressure was ascertained using a standard mercury sphygmomanometer, with the child lying down and a cuff size appropriate to the circumference of the arm. Two measurements of blood pressure were made, separated by a 10 minute rest period, with diastolic pressure read at the 4th Korotkoff phase. A single nurse made all of the measurements for all of the subjects.

A blood sample was obtained by venipuncture with the child lying down, having fasted for 12 hours. Serum total cholesterol, triglyceride and HDL cholesterol were measured by standard enzymatic techniques (Allain, Poon, Chan, et al. 1974). LDL cholesterol was derived by the Friedwald-Fredrickson formula (Friedwald, Levy & Fredrickson 1972).

Parents were asked to complete a questionnaire that sought information concerning their education and occupation, among other things. The questionnaire was completed by all but 2 mothers and by almost 90 per cent of the fathers.

Results of the study at age 8, addressing the original aims, have been reported by the original investigators (Boulton, Cockington, Hamilton-Craig, et al. 1985). The data sets were generously made available for the new analyses undertaken for this thesis.

4.3 Birth data

Information relating to the births of the cohort members was obtained from records held by the Queen Victoria Hospital. This was undertaken for the majority of subjects during 1991 by Dr Andrew Miller, and was completed in 1995-96 as part of the work towards this thesis. Birth records were eventually located for 823 of the 826 singleton subjects. (The records showed that 4 of the 830 subjects considered singletons in the data sets from age 8 had, in fact, been part of a twin pair *in utero*, although the twin had not survived; these subjects are considered to be twins in the present study.)

Details abstracted from the birth records were: mother's age (in years), duration of gestation (in weeks), birth weight (in grams), placental weight (in grams), head circumference (in centimetres), chest circumference (in centimetres), and length (in centimetres). Duration of gestation had been calculated from the date of the last menstrual period. The placentas had been weighed untrimmed and without blood being expressed. Chest circumference was measured at the level of the nipples. Of the 823 records retrieved, 794 (96%) contained complete details. Birth weight was missing in 1 case, placental weight in 22 cases, head circumference in 4, chest in 2, and length in 5.

As described earlier, study subjects were a sample of children born in the Queen Victoria Hospital during 1975-76. There were 1,144 other children who satisfied the study selection criteria but did not take part, either because they were unable to be traced or because they declined the invitation to be involved. A search for the hospital records of these non-participating children was also undertaken during 1995-96 as part

of the work towards this thesis. This search was difficult due to the scant details concerning the non-participating families, however, records for 776 children (68%) were found. Details abstracted for comparison with study participants were: sex of the child, birth weight, gestational age at birth, and the mother's age at the time of giving birth.

4.4 Analysis of the data at age 8

Birth details were added to the existing data from the study of cardiovascular risk factors in children (Boulton, Cockington, Hamilton-Craig, et al. 1995) for a series of analyses to investigate associations between birth dimensions and both blood pressure and blood lipids at age 8. Twins were excluded from these analyses because they experience uterine conditions that are different from singletons, in particular, twins experience additional growth restriction.

The averages of the two readings made of systolic and diastolic pressure were used in the analyses. The blood pressure values and the lipid concentrations were treated as continuous variables. All birth characteristics were also treated as continuous variables.

Confounding by size at 8 years was explored using several indices of body size and fatness. These were weight, height, body mass index (defined as weight divided by the square of height), and the sum of the four skinfold thicknesses. Adjustments to control for confounding by current size were made before relationships with birth characteristics were investigated.

Associations between birth characteristics and both blood pressure and blood lipids at age 8 were investigated using linear regression analyses, with adjustment for confounding variables. The validity of regression models was checked by examining

the distribution of residuals using plots of the standardised residuals versus the predicted outcome and probability plots.

For clarity of presentation, some results have been presented using tables of mean values. These tables serve to illustrate patterns of association, but in all cases results of inferential testing (p values or confidence intervals) are based on the outcome variables in their original continuous scale of measurement.

Relationships between birth weight and the outcome variables were investigated among all singleton children and among those born at term (more than 37 weeks of gestation). Separate relationships for each of the following birth dimensions were also examined among those born at term: head circumference, chest circumference, length, and placental weight.

In order to test Barker's hypotheses concerning the importance of certain birth phenotypes, joint effects of specific birth characteristics were investigated. The three phenotypes were: low birth weight relative to placental weight; thinness, possibly accompanied by a small head circumference; shortness with a large head relative to chest. These were modelled using the relevant combinations of birth characteristics. Thinness was represented by ponderal index (the ratio of birth weight (in grams) to the cube of birth length (in centimetres), multiplied by 1,000). The ratio of head to chest circumference was constructed for use in the third scenario. These analyses were confined to children born at term, since body proportions of the fetus vary with gestational age, and the phenotypes refer to term babies.

The influence of socio-economic status on relationships between birth and outcome variables was examined. Two indicators of socio-economic status at age 8 were used: the mother's educational attainment (primary, some secondary, completed secondary, or tertiary) and the father's occupational status according the Congalton four-point

scale (A to D) (Congalton 1969). These indicators were treated as categorical variables in all regression analyses (the reference category for mother's education was some secondary education; class C was used as the reference category for father's occupation). (For robustness, the category with the highest frequency was chosen as the reference category in most instances.)

4.5 The follow up at age 20

Contact with cohort members was maintained by Dr Richard Cockington after the study at age 8. Each subject was sent a birthday card and a Christmas card every year. The cards contained a request for notification of any change of address, and a tear-off section and a reply-paid envelope to facilitate this. Newsletters were also distributed from time to time.

A follow-up study was conducted during 1995-96, when the cohort members were approximately 20 years of age. Letters of invitation were sent to the last known address of all subjects. The letter was accompanied by a form whereby subjects could indicate their willingness or otherwise to participate and, in the former case, their preferred appointment times. A reply-paid envelope was supplied for the return of this form. Copies of letters and forms sent to the subjects may be found in Appendix A.

A reminder letter and another reply form were sent to individuals not responding the first letter within approximately two weeks. Where no reply was forthcoming, telephone contact was attempted. Tracing was undertaken where telephone contact was not achieved, firstly through an alternate contact person listed in the study database, and where this was unsuccessful, through the telephone directory and the electoral roll.

Of the 856 original cohort members, 2 were deceased and 9 had withdrawn by 1995, when the follow up began. Ultimately, only 21 (2%) of the remaining 845 subjects were unable to be traced. Thus, over an 18 month period, 824 subjects were located and invited to participate in the follow up, and 605 of these subjects (73%) eventually did so; this represents 71% of the original cohort. Of the 223 subjects who declined participation, 83 (37%) did not live in Adelaide at the time of the follow up.

Participating subjects attended the Women's and Children's Hospital (the institution resulting from the amalgamation of the Queen Victoria Hospital and Adelaide Children's Hospital) in 1995-96. Wherever possible, morning appointments were made, and subjects were asked to fast from 8 pm of the night before their appointment. A questionnaire was mailed to subjects prior to the appointment, with a request to complete as many items as possible and bring it to the hospital. A copy of the questionnaire may be found in Appendix B. (Note that not all questions were intended for use within this thesis.)

At the hospital, written consent was obtained from each subject. The study questionnaire was checked for completeness and subjects were assisted with any unanswered items. The questionnaire contained (with permission) questions administered in the most recent Risk Factor Prevalence Study of the National Heart Foundation of Australia, concerning oral contraceptive use, smoking habit, alcohol consumption, discretionary salt practices, and exercise behaviour (Risk Factor Prevalence Study Management Committee 1990).

The study questionnaire also included (with permission) the Short Fat Questionnaire, which is a 17 item checklist developed in Australia by Dobson, Blijlevens, Alexander, et al. (1993) to rapidly assess dietary fat consumption and assign subjects a ranking, rather than an actual measure of fat intake. The checklist concerns methods of cooking meat and vegetables, use of sauces or spreads that are relatively high in fat, weekly

frequency of eating various foods with relatively high fat content, and usual practices regarding type of milk consumed, meat fat, and chicken skin. Each response to a checklist item receives a score between 0 and 4, and a total score is obtained from the sum. This checklist has been validated against a full food frequency questionnaire and used in a community survey, and is recommended for epidemiological studies seeking to rank subjects according to their fat intake behaviour.

Several indicators of the subject's socio-economic background were included in the study questionnaire. Subjects were asked about their educational attainment and also about their current occupation, although it was recognised that the latter was unlikely to provide a useful measure of socio-economic background, since at age 20 many subjects would be studying at tertiary institutions and working part-time in jobs requiring low levels of skills. As seen in Chapter 2, educational attainment was the strongest socio-economic correlate of cardiovascular risk factors in the United States but the extent to which this would apply in a relatively young sample with good access to education is uncertain. Therefore, additional means of characterising the subject's socio-economic background were used.

Information was requested concerning parents' education, occupation and area of residence, in order to assess the current socio-economic circumstances of the family. Based on the postcode of the area of residence, the family was later assigned an Index of Relative Disadvantage and an Index of Economic Resources, as calculated by the Australian Bureau of Statistics (McLennan 1990), explained in greater detail below. These Indexes were used in preference to parents' education and occupation in analyses because they were broader measures, available in continuous rather than categorical form. Questions about the family income were not included because this was felt to be too intrusive and not appropriate information to seek through a son or daughter.

Indices of socio-economic status based on area of residence have been created by the Australian Bureau of Statistics using census data (McLennan 1990). Five indices summarising different aspects of the socio-economic conditions in an area are available, of which the Index of Relative Socio-Economic Disadvantage and the Index of Economic Resources were most relevant to this cohort and the planned analyses. Essentially, the Index of Relative Socio-Economic Disadvantage reflects the extent to which low income families with low educational attainment and high unemployment are concentrated in an area, while the Index of Economic Resources amalgamates information on household income, home and car ownership. Subjects were assigned index values on the basis of the postcode of the family residence. Where parents or the subject did not live together, the highest index of the parents was used.

Subjects were also asked to provide the name of the suburb or town in which the family lived when the subject was born. Using the relevant postcode, subjects were later assigned an Index of Relative Socio-economic Disadvantage and an Index of Economic Resources for their family at the time of their birth. Although these Indexes were created some 15 years after the subjects were born, because they are relative measures and most areas have stable profiles in a relative sense, the Indexes would still provide a reasonable ranking of the family's socio-economic circumstances at an earlier time.

To continue with events at the hospital, a physical examination was conducted in a similar manner to the examination at age 8. The nurse who made all of the measurements for all of the subjects was, in fact, the same nurse who had seen all of the children at 8 years. Subjects were asked to remove their shoes and any heavy clothing before measurements of weight and height were made. Weight was measured to the nearest 100 grams using digital scales and height was measured to the nearest centimetre using a Holtain stadiometer. Waist and hip circumferences were measured to the nearest centimetre using a clinical tape measure. Biceps, triceps, subscapular

and supra-iliac skinfold thicknesses were measured to the nearest 0.1 millimetre using Harpenden skin callipers.

Blood pressure was measured following the recommendations of Jamieson, Webster, Philips, et al. (1990) and the procedures used in the National Heart Foundation's Risk Factor Prevalence Surveys which were based on the World Health Organisation's MONICA (Monitoring of Trends and Determinants of Cardiovascular Disease) protocol (Bennet 1994). The subject sat quietly with legs uncrossed for at least five minutes before the blood pressure readings were made. Measurements were taken from the left arm, using a cuff size appropriate to the arm circumference, with an automated blood pressure recorder (Dinamap model 845XT). Two measurements were made, separated by a five minute rest period. As almost all of the physical examinations took place in the morning, effects of time of day on blood pressure were avoided (Padfield, Jyothinagaram, Watson et al. 1990; Muller & Toffler 1991).

A fasting blood sample was obtained by antecubital venipuncture from those subjects who consented to this (95% of the 605 participants). Plasma total cholesterol, HDL cholesterol and triglyceride concentrations were measured by the Department of Chemical Pathology at the Women's and Children's Hospital using standard enzymatic methods (Allain, Poon, Chan, et al. 1974). The laboratory's coefficient of variation for the assay of plasma total cholesterol was 2.7% and that for triglyceride was 3.4%. LDL cholesterol concentration was calculated using the Friedwald-Fredrickson formula (Friedwald, Levy & Fredrickson 1972).

Subjects were offered breakfast after the assessments, various companies having kindly donated supplies of breakfast food. Copies of the blood test results were sent to the subjects with a letter thanking them for their participation. Appropriate management of lipid abnormalities was arranged by Dr Richard Cockington.

4.6 Repeatability of measurements

The reproducibility of the anthropometric and blood pressure measurements made in the follow up at age 20 was formally investigated. For 29 university students of comparable age to the study subjects (age range 17 to 25 years, mean of 20 years, for the students), clinical measurements were made according to the protocol for the main study by the same research nurse. The measurements were repeated on a second occasion, between 1 and 11 days later (mean delay of 4 days).

The mean of the differences between the two readings made for each subject was calculated for each variable, along with a repeatability coefficient (Bland & Altman 1986). This coefficient is the value below which the absolute difference between repeated readings may be expected to lie with 95 per cent probability (British Standards Institution 1979), analagous to a confidence interval.

The mean differences and repeatability coefficients for measurements of body size were as follows: for height the mean difference was 0.2 cm with a repeatability coefficient of 1.2 cm; for weight the mean difference was less than 0.1 kg with a repeatability coefficient of 1.6 kg; for waist circumference the mean difference was 0.2 cm with a repeatability coefficient of 2.5 cm; and for hip circumference the mean difference was 0.2 cm with a repeatability coefficient of 2.5 cm. For the skinfold thicknesses the results were: for biceps a mean difference of less than 0.1 mm and a repeatability coefficient of 0.9 mm; for triceps a mean difference of 0.1 mm and a repeatability coefficient of 1.8 mm; for subscapular a mean difference of 0.1 mm and a repeatability coefficient of 1.2 mm; and for suprailiac a mean difference of 0.2 mm and a repeatability coefficient of 1.9 mm.

As in the main study, blood pressure values on each occasion were based on the average of two readings made 5 minutes apart. For systolic blood pressure the mean

of the differences between the two averages was 2.1 mm Hg with a repeatability coefficient of 15 mm Hg. For diastolic pressure the mean difference was 0.6 mm Hg with a repeatability coefficient of 12 mm Hg.

These coefficients were similar to those (calculated from published data) for successive follow-up examinations within the Bogalusa Heart Study (Foster & Berenson 1987) and the Second National Health and Nutrition Examination Survey (NHANES II) (Marks, Habicht & Mueller 1989). Of note, the repeatability coefficient for systolic blood pressure in the Bogalusa Heart Study was approximately 13 mm Hg while that for diastolic pressure was about 12 mm Hg. The authors of these North American studies considered their results to demonstrate good precision and reproducibility of measurements and high quality data.

4.7   Analysis of the data at age 20

Blood pressure and blood lipids were again the outcomes of interest at age 20. The averages of the two readings of systolic and diastolic pressure were used in the analyses. As before, the blood pressure values, the lipid concentrations, and the birth measurements were treated as continuous variables. Associations were investigated using multiple linear regression analyses, with adjustment for confounding variables. These analyses were undertaken in the same manner as for the age 8 data (detailed in section 4.4).

Influences of behavioural and socio-economic factors on relationships between birth and outcome variables were examined. The behavioural factors were: smoking status, alcohol consumption, discretionary salt practices, relative fat intake, exercise level, and oral contraceptive use (for women only). Socio-economic status at birth, during childhood, and at the present time was considered.

On the basis of their response to the study questionnaire, each subject was classified as either a current smoker or a non-smoker. This was treated as a categorical variable in all analyses (with non-smoking as the reference category).

Alcohol consumption was assessed through two questions, one concerning weekly frequency of drinking (non-drinker, less than once per week, 1 to 2 days per week, 3 to 4 days per week, 5 to 6 days per week, daily) and the other about the usual number of drinks consumed on a day when alcohol was drunk (1 or 2, 3 or 4, 5 to 8, 9 to 12, 13 to 20, more than 20). Responses to these two questions were combined to classify the subjects according to the number of drinks consumed per week (none, up to 8 drinks, up to 16 drinks, up to 24 drinks, a total of more than 24 drinks), which was treated as a categorical variable in all regression analyses (with consumption of up to 8 drinks per week used as the reference category). (In theory, some combinations of weekly frequency and drinks per session would lead to an ambiguous classification of weekly consumption; the National Heart Foundation (National Heart Foundation of Australia and Australian Institute of Health 1991) overcame this problem by developing a index of risk drinking. In the present study, a more direct measure of intake was required, so the categories presented above were used and where there was ambiguity, subjects were assigned to the highest category they could possibly fall into.)

As explained earlier, a ranking of fat intake was derived from the Short Fat Questionnaire. It was treated as an ordinal variable in all analyses.

Habitual physical activity was ascertained from two questions, following the procedures of Bauman and Owen (1991) in their analysis of National Heart Foundation data. Exercise level was classified as aerobic if the subject reported undertaking at least 3 sessions, of more than 45 minutes duration, of vigorous physical activity in the past two weeks. Exercise level was classified as moderate if the subject

undertook some vigorous exercise, but less than the amount required for the aerobic classification. The subject was considered to be inactive if he or she reported no deliberate physical activity of any type in the past two weeks. This variable was treated as categorical in all analyses (with inactivity as the reference category).

Women were asked to indicate whether or not they were currently using oral contraceptives. This variable was treated as categorical in all analyses (with non-use as the reference category).

Socio-economic status at birth, characterised by the family's Index of Relative Socio-Economic Disadvantage and Index of Economic Resources, was treated as a continuous variable in all analyses. Mother's education and father's occupation from the study at age 8 were used again to indicate socio-economic status during childhood; both were categorical variables and, as before, were represented by a set of indicator variables in all analyses (with some secondary education used as the reference category for mother's education and class C used as the reference category for father's occupation). Current socio-economic status was depicted by the subject's educational attainment (some high school, completed high school, some tertiary education, completed tertiary qualification), the current Index of Relative Socio-economic Disadvantage of the subject's family, and the current Index of Economic Resources of the subject's family; the former, being categorical, required a set of indicator variables (with some tertiary education as the reference category), while the latter two measures were treated as continuous.

Finally, amplification of the magnitude of effects seen at age 8 and again at age 20 was assessed by examining the interaction between birth weight and time of observation using a generalised estimating equation with exchangeable correlations and a robust estimation of the variance-covariance matrix (Diggle, Liang & Zeger 1994).

Data entry was carried out through the dSurvey data entry package (dSurvey 1993). Most statistical analyses were undertaken using SPSS-X (SPSS Inc. 1988). The amplification analyses were undertaken using STATA (Stata Corporation 1993) and the graphs were drawn using SYGRAPH (Systat Inc. 1990).

Chapter 5
Results for the cohort at age 8

5.1 The cohort established at age 8

There were 826 singleton subjects in the sample of children who took part in the study of cardiovascular risk factors at age 8. The analyses reported in this thesis concern only these singleton children, of whom there were 433 boys and 393 girls. At examination, the children had a mean age of 9 years (sd 0.5 years), which is somewhat older than 8 because the study took several years to complete.

As described in the methods, study participants were a sample of children born in the Queen Victoria Hospital during 1975-76. Children who took part in the study were similar to those who satisfied the selection criteria but did not take part (either because they were unable to be traced or because they declined the invitation to be involved) in terms of sex, gestational age at birth, birth weight, and mother's age at the time of giving birth. These comparisons are presented in Table 5.1.1. (Tables for each section may be found at the end of that section.)

In addition, the distribution of birth weight for the group of children studied is very similar to that for all singleton babies born in South Australia during 1981 (mean 3387 g, sd 557 g), which was the first year for which statewide birth statistics were compiled. The statewide distribution of birth weight for term births has been stable since 1981 (A Chan, Senior Medical Consultant, Pregnancy Outcome Unit, South Australian Health Commission, personal communication, August 21st, 1995).

The birth characteristics of the study group are summarised in Table 5.1.2. The majority of the children were born at term, with only 57 (7%) being born before 37 weeks of gestation, and 7 born after 42 weeks of gestation.

Size, blood pressure and blood lipids for the cohort at age 8 (published previously by the original collaborators) are summarised in Table 5.1.3. Boys and girls had similar distributions of blood pressure and blood lipids. As shown in the table, there were a few missing values for most variables. Since missing values across variables came from different subjects, all subjects were retained and subsequent analyses were undertaken using all cases with complete information for that particular model.

Father's occupational status and mother's educational attainment provide an indication of the socio-economic background of the child. Distributions of these indicators are presented in Tables 5.1.4 and 5.1.5. In South Australia at about that time, 28% of men in the workforce had jobs with the lowest grade of Congalton occupational status ranking (Nixon & Pearn 1984). Within the cohort, however, only 14% of fathers were assigned this ranking. Children from the poorest socio-economic circumstances are therefore under-represented in the cohort, but they are nevertheless present in sufficient numbers to enable meaningful comparisons within the cohort.

Table 5.1.1

Comparison of study subjects and non-participants

Variable	Cohort members n = 826			Non-participants n = 776		
	mean	(sd)	range	mean	(sd)	range
Birth weight (g)	3381	(554)	1220 - 5120	3302	(554)	1170 - 5100
Gestation (weeks)	39	(2)	26 - 44	39	(2)	28 - 44
Mother's age (years)	23	(5)	15 - 45	26	(5)	15 - 43
Male	52	%		51	%	

Table 5.1.2

Birth characteristics of the cohort

Birth characteristic	mean	(sd)	n
Birth weight (g)	3381	(554)	822
Placental weight (g)	563	(114)	801
Head circumference (cm)	34	(2)	819
Chest circumference (cm)	34	(2)	821
Length (cm)	50	(3)	818
Ponderal index (g/cm^3 x 1000)	27	(3)	817
Head : chest circumference	1.03	(0.06)	819
Gestation (weeks)	39	(2)	822

Table 5.1.3

Size and cardiovascular risk factors at age 8

Variable	Boys			Girls		
	mean	(sd)	n	mean	(sd)	n
Weight (kg)	31	(6)	431	31	(6)	392
Height (cm)	134	(6)	431	133	(6)	393
Systolic pressure (mm Hg)	101	(11)	432	102	(12)	393
Diastolic pressure (mm Hg)	61	(9)	428	61	(9)	393
Total cholesterol (mmol/L)	4.4	(0.8)	428	4.6	(0.8)	391
LDL cholesterol (mmol/L)	2.8	(0.7)	432	3.0	(0.8)	388
HDL cholesterol (mmol/L)	1.4	(0.4)	431	1.3	(0.4)	389
HDL : LDL cholesterol	0.5	(0.3)	430	0.5	(0.3)	388
Triglyceride (mmol/L)	0.5	(0.3)	432	0.6	(0.3)	391

Table 5.1.4

Socio-economic background of the cohort at age 8: father's occupational status

Congalton status ranking of father's occupation

	n	%
A (highest)	72	11
B	231	34
C	277	41
D (lowest)	95	14
Missing or not applicable	151	-
Total	826	100

Table 5.1.5

Socio-economic background of the cohort at age 8: mother's education

Mother's educational attainment

	n	%
Primary school	63	8
Some high school	306	38
Completed high school	247	30
Tertiary education	194	24
Missing value	16	-
Total	826	100

5.2 Blood pressure at age 8

At age 8, blood pressure distributions for boys and girls were very similar. For boys, the mean systolic pressure was 101 mm Hg (sd 11 mm Hg) while that for girls was 102 mm Hg (sd 12 mm Hg). For both boys and girls, the mean diastolic pressure was 61 mm Hg (sd 9 mm Hg). As discussed by Boulton, Cockington, Hamilton-Craig et al. (1995), these distributions are similar to those found elsewhere for children of corresponding age.

Both systolic and diastolic pressure were weakly correlated with indices of current size and fatness, including weight, height, body mass index and the sum of the skinfold thicknesses. The strongest correlations were with weight (for systolic pressure Pearson's r = 0.34, p < 0.01, and for diastolic pressure Pearson's r = 0.30, p < 0.01).

Since weight at age 8 was not only correlated with blood pressure but also with birth weight (Pearson's r = 0.23, p < 0.01), it potentially confounded associations between birth weight and blood pressure. Adjustment for weight at age 8 was therefore made in all subsequent analyses. The other indices of current size were no longer related to blood pressure after adjustment for weight, and so were no longer considered as potential confounders. This was also true for sex and age.

Relationships between birth weight and blood pressure were weak and not statistically significant. A one kilogram increase in birth weight was associated with a decrease in systolic pressure of 1.0 mm Hg (95% CI -0.4 to 2.3) and with a decrease in diastolic pressure of 0.5 mm Hg (95% CI -0.5 to 1.6), after adjustment for current weight. These relationships became weaker when duration of gestation was taken into account. Among those born at term, a one kilogram increase in birth weight was associated with a decrease in systolic pressure of 0.7 mm Hg (95% CI -1.0 to 2.4) and with a decrease

in diastolic pressure of 0.5 mm Hg (95% CI -0.9 to 1.8), after adjustment for current weight.

Relationships between blood pressure at age 8 and other birth dimensions were investigated among those who had been born at term (more than 37 weeks of gestation). The birth dimensions considered were head circumference, chest circumference, length, and placental weight. Head circumference was inversely related to systolic pressure, adjusted for weight at age 8 (partial regression coefficient for head circumference = -0.52, p = 0.05). There were no other statistically significant relationships for single birth characteristics.

Three more complex anthropometric indicators of fetal growth restriction were investigated in relation to blood pressure at age 8. These birth characteristics were: low birth weight relative to placental weight; thinness, possibly accompanied by a small head circumference; shortness with a large head circumference relative to chest.

Among those born at term, there were simultaneous effects of placental weight and birth weight on blood pressure at age 8. At any birth weight, blood pressure tended to rise with increasing placental weight. At any placental weight, blood pressure tended to fall with increasing birth weight. Therefore, the highest blood pressures were found among those children who had the largest placentas and the lowest birth weights, and vice versa. For diastolic pressure, there was an increase of 0.7 mm Hg for each 100 g increase in placental weight (95% CI = 0.0 to 1.4) and a decrease of 1.4 mm Hg for each 1 kg increase in birth weight (95% CI = -0.3 to 3.1). For systolic pressure the pattern was similar but not statistically significant: an increase of 0.4 mm Hg for each 100 g increase in placental weight (95% CI = -0.4 to 1.3) and a decrease of 1.3 mm Hg for each 1 kg increase in birth weight (95% CI = -0.9 to 3.5). Tables 5.2.1 and 5.2.2 illustrate these results by presenting the mean systolic and diastolic pressures for

children grouped according to tertiles (thirds of the distributions) of placental weight and birth weight.

There was no effect of ponderal index (thinness) at birth, either alone or in conjunction with head circumference, on blood pressure at age 8. Nor were there simultaneous effects of length (shortness) and the ratio of head circumference to chest on blood pressure at age 8.

Finally, the possible influence of socio-economic status on relationships between birth measurements and blood pressure at age 8 was examined. Blood pressure at age 8, adjusted for current weight, was not associated with father's occupational status. However, both systolic and diastolic pressure, adjusted for current weight, were associated with mother's education ($p = 0.05$ for the addition of maternal education to the model in each case).

There was some degree of association between birth weight and mother's education: a linear regression of birth weight on a set of indicator variables for maternal education revealed that the mean birth weights of children born to mothers with some high school education was lower than the means for all other education levels ($p = 0.10$ for the model). Birth weight was not associated with father's occupational status at age 8.

The magnitudes of the relationships between birth characteristics and blood pressure were not affected by adjustment for mother's education. Nor were there any changes when father's occupational status was taken into account, as expected, since this variable does not satisfy the conditions for potential confounding. Tables 5.2.3 and 5.2.4 demonstrate the weak inverse relationships between birth weight and blood pressure at every level of mother's education, in the presence of stronger associations between maternal educational level and blood pressure at age 8.

Table 5.2.1

Mean systolic pressure (mm Hg) at age 8 adjusted for current weight according to birth weight and placental weight groups, for children born at term; numbers in each cell are shown in parentheses

Placental weight (g)	Birth weight (g)			
	≤ 3200	3201 - 3600	> 3600	Total
≤ 500	101.2 (130)	100.8 (78)	99.6 (20)	100.5
501 - 600	101.8 (68)	101.4 (106)	100.2 (80)	101.1
> 600	102.9 (22)	102.5 (61)	101.3 (178)	102.2
Total	102.0	101.6	100.3	(743)

Table 5.2.2

Mean diastolic pressure (mm Hg) at age 8 adjusted for current weight according to birth weight and placental weight groups, for children born at term; numbers in each cell are shown in parentheses

Placental weight (g)	Birth weight (g)			
	≤ 3200	3201 - 3600	> 3600	Total
≤ 500	61.0 (128)	60.5 (78)	60.1 (20)	60.1
501 - 600	61.5 (68)	61.0 (106)	59.5 (80)	60.7
> 600	63.1 (22)	62.6 (61)	61.0 (178)	62.2
Total	61.9	61.4	59.8	(741)

Table 5.2.3

Mean systolic pressure (mm Hg) at age 8 adjusted for current weight according to birth weight and maternal education groups, for children born at term; numbers in each cell are shown in parentheses

Mother's education	Birth weight (g)			
	≤ 3200	3201 - 3600	> 3600	Total
Primary school	103.2 (14)	103.0 (15)	102.5 (30)	102.9
Some high school	102.7 (86)	102.6 (87)	102.0 (99)	102.4
Completed high school	101.0 (64)	100.9 (77)	100.3 (90)	100.8
Tertiary education	101.0 (54)	100.9 (65)	100.3 (65)	100.8
Total	102.0	101.9	101.3	(750)

Table 5.2.4

Mean diastolic pressure (mm Hg) at age 8 adjusted for current weight according to birth weight and maternal education groups, for children born at term; numbers in each cell are shown in parentheses

Mother's education	Birth weight (g)			
	≤ 3200	3201 - 3600	> 3600	Total
Primary school	64.5 (14)	64.2 (15)	63.3 (30)	64.0
Some high school	62.0 (86)	61.6 (87)	60.8 (99)	61.5
Completed high school	61.4 (66)	61.0 (77)	60.1 (90)	60.8
Tertiary education	60.7 (54)	60.3 (65)	59.5 (65)	60.2
Total	62.2	61.8	61.0	(748)

5.3 Blood lipids at age 8

As shown in Table 5.1.3, almost all subjects had complete data concerning total cholesterol, LDL cholesterol, HDL cholesterol, the ratio of HDL to LDL cholesterol, and triglyceride. Both the ratio of HDL to LDL cholesterol and triglyceride exhibited marked right skewness, so the natural logarithms of these variables were used in all analyses.

At age 8, lipid profiles of boys and girls were a little dissimilar, as seen in Table 5.1.3. Since birth measurements are related to sex, with male babies tending to be larger, and since the sex differences in lipid profiles persisted after current size was taken into account, an adjustment for sex was made in all analyses. There were no sex by birth measurement interactions, so models stratified by sex were not required.

Measurements of current size were weakly related to the lipid values independently of sex (for example, for weight and total cholesterol, partial correlation coefficient = 0.12, $p < 0.01$). As seen in the previous section, measurements of current size were also correlated with birth dimensions, so adjustment for current size was necessary in order to examine independent effects of birth characteristics on lipids. Again, adjustment for weight at age 8 was an efficient approach to controlling confounding from this source.

After adjustment for sex and current weight, there was a slight maldistribution of birth weight over the time of the follow up examination, with children who were older at the time they were examined having slightly lower birth weights than those who were seen close to their eighth birthday (partial correlation coefficient = -0.08, $p = 0.03$ for birth weight and age at examination). Since lipid values are related to age, it was necessary to make an adjustment for this factor. Thus in all subsequent analyses, adjustments were made for sex, age in months, and current weight.

Birth weight was not related to any of the lipid values at age 8 in regression models adjusting for sex, current weight and age. This did not change when duration of gestation was also considered. Nor were there any statistically significant relationships between single birth dimensions (head circumference, chest circumference, length, placental weight) and the lipid fractions.

Three birth phenotypes were investigated in relation to lipid fractions at age 8. As before these were: low birth weight relative to placental weight; thinness, possibly accompanied by a small head circumference; shortness with a large head circumference relative to chest. These analyses were again confined to children who had been born at term.

In linear regression analyses with lipid fractions as the outcomes, no joint effects of birth weight and placental weight were evident.

Associations between ponderal index at birth and lipid values at age 8 were apparent, however. Children whose ponderal index at birth had been low tended to have raised concentrations of total cholesterol and LDL cholesterol. In addition, they tended to have lower concentrations of HDL cholesterol and lower ratios of HDL to LDL cholesterol than children with higher ponderal indices. These relationships are summarised in Table 5.3.1. Ponderal index was not related to the logarithm of triglyceride at age 8.

In absolute terms the influence of ponderal index on lipid values, although statistically significant or almost so, was small. Due to the loss of information when data were collapsed into categories, tables of mean values within tertiles (or higher quantiles) did not illustrate the relationships found in regression analyses using individual data.

There was no simultaneous linear effect of head circumference, in addition to ponderal index, on lipids at 8 years. However, the effect of ponderal index on total cholesterol, LDL cholesterol and the ratio of HDL to LDL cholesterol was increased in those whose head was small at birth (circumference of 33 cm or less), after adjustment for sex, age and current weight. (For this subset, with total cholesterol as the outcome, the partial regression coefficient for ponderal index = -0.049, p = 0.08. In the case of LDL cholesterol, the partial regression coefficient for ponderal index = -0.072, p = 0.01, and in the case of the logarithm of the ratio of HDL to LDL cholesterol, the partial regression coefficient for ponderal index = 0.039, p = 0.01.)

In addition, there was evidence of joint effects of length and the ratio of head circumference to chest at birth, such that for babies whose head was large in relation to their chest, shortness at birth was associated with elevated concentrations of total and LDL cholesterol at age 8. This pattern emerged when an interaction term was included in the regression models. To elaborate, the regression models showed that, overall, controlling for the ratio of head circumference to chest, length was positively related to total cholesterol and LDL cholesterol at age 8. Ponderal index and length are inversely related, so this overall relationship is consistent with the dominant influence of ponderal index, reported above. Likewise, controlling for length, the ratio of head circumference to chest was positively related to these lipid fractions. When the interaction of length and the ratio of head circumference to chest was added to the model, it could be seen that for babies whose head to chest ratio exceeded 1.08 (which in this sample corresponded to the highest quintile of head to chest ratio) there was an inverse relationship between length and both total cholesterol and LDL cholesterol. In other words, in the babies with a relatively large head, shortness at birth was associated with elevated concentrations of total and LDL cholesterol at age 8. These results are summarised in Tables 5.3.2 and 5.3.3.

The surfaces described by the regression equations, involving an interaction term, are illustrated in Figures 5.3.1 and 5.3.2. (Figures may be found after the corresponding table at the end of the section.) The figures show that there is a positive relationship between birth length and later lipid concentrations when the head is relatively small to normal in size, but the relationship with birth length is reversed when the head is relatively large.

Turning to socio-economic status, there were no associations between the lipid fractions at age 8 and mother's education, after adjustment for the child's sex, age and current weight. However, LDL cholesterol, HDL cholesterol and the ratio of HDL to LDL cholesterol were associated with father's occupational status ($p < 0.02$ for the addition of father's occupational status to the model in each case).

As seen previously, there was some degree of association between birth weight and mother's education, but no association between birth weight and father's occupational status. Likewise, there was some degree of association between ponderal index at birth and mother's education ($p = 0.07$ for the model) but no association between ponderal index and father's occupational status.

Thus socio-economic status, as indicated by mother's education or father's occupational status, did not meet the conditions required for it to potentially confound relationships between birth measurements and lipid fractions at age 8. As expected, therefore, adjustment for either indicator of socio-economic status did not affect the magnitudes of the relationships reported in this section.

Table 5.3.1

Relationships between ponderal index at birth and lipid concentrations at age 8 adjusted for sex, age and current weight, for children born at term

Dependent variable	Partial regression coefficient	Standard error	p value
Total cholesterol	- 0.018	0.010	0.08
LDL cholesterol	- 0.023	0.010	0.02
HDL cholesterol	- 0.009	0.005	0.07
HDL : LDL cholesterol (logarithm of)	- 0.015	0.006	< 0.01

Note.
The regression coefficient may be interpreted as the increase in the dependent variable associated with a one unit increase in ponderal index.

Table 5.3.2

Relationship between total cholesterol at age 8 adjusted for sex, current weight and age, and both length and the ratio of head circumference to chest at birth, for children born at term

Independent variable	Partial regression coefficient	Standard error	p value
Birth length	0.512	0.252	0.04
Head : chest circumference at birth	24.392	12.260	0.05
Interaction of length and head : chest	- 0.472	0.245	0.05

Total cholesterol = 0.231 * sex + 0.413 * age + 0.005 * weight

+ 0.512 * birth length + 24.392 * head : chest

- 0.472 * birth length * head : chest

- 26.132

Figure 5.3.1

Total cholesterol at age 8 as a function of birth length and relative head size, for children born at term
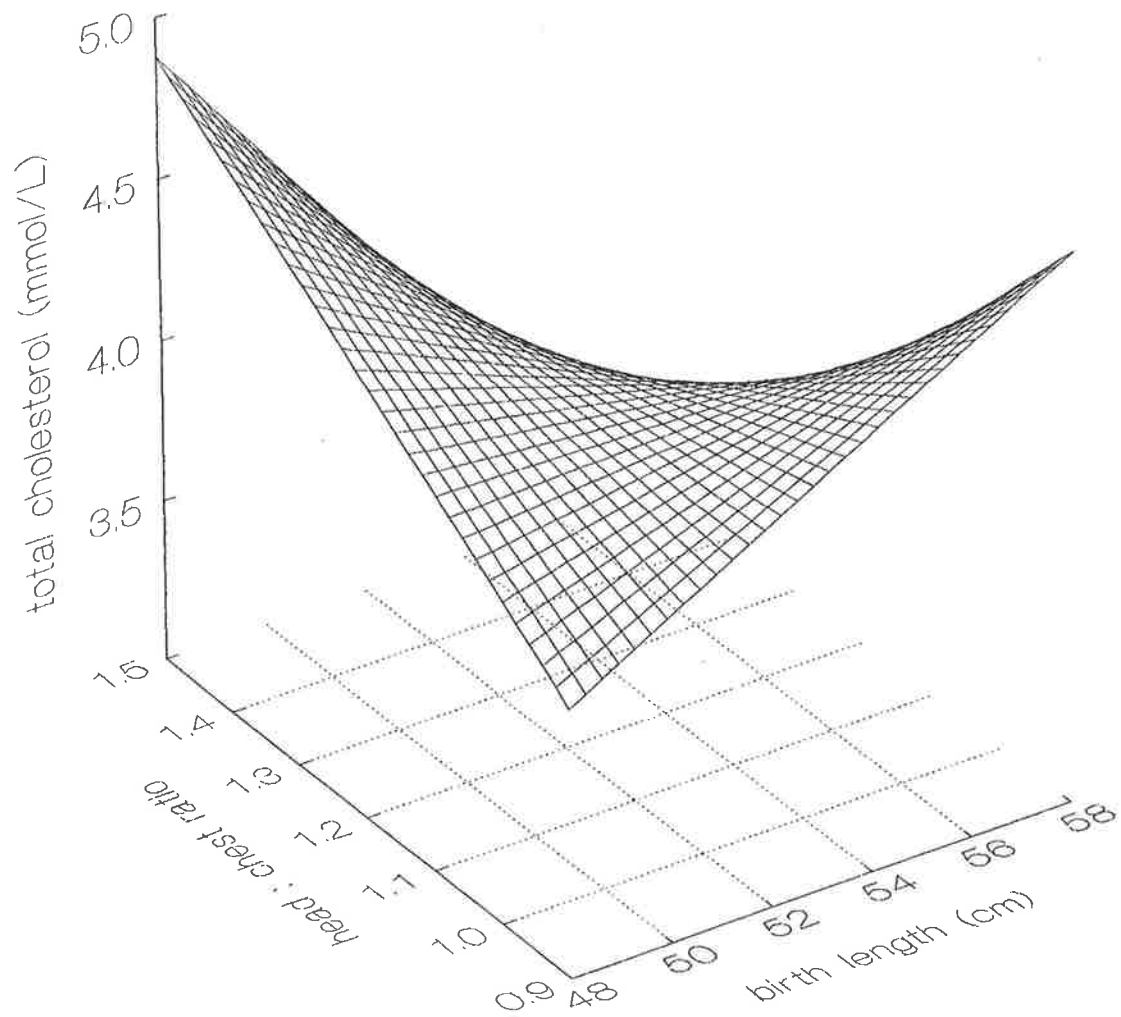
Table 5.3.3

Relationship between LDL cholesterol at age 8 adjusted for sex, current weight and age, and both length and the ratio of head circumference to chest at birth, for children born at term

Independent variable	Partial regression coefficient	Standard error	p value
Birth length	0.558	0.238	0.02
Head : chest circumference at birth	26.566	11.584	0.02
Interaction of length and head : chest	- 0.515	0.232	0.03

LDL cholesterol = 0.234 * sex + 0.362 * age + 0.007 * weight

+ 0.558 * birth length + 26.556 * head : chest

- 0.515 * birth length * head : chest

- 29.661

Figure 5.3.2

LDL cholesterol at age 8 as a function of birth length and relative head size, for children born at term
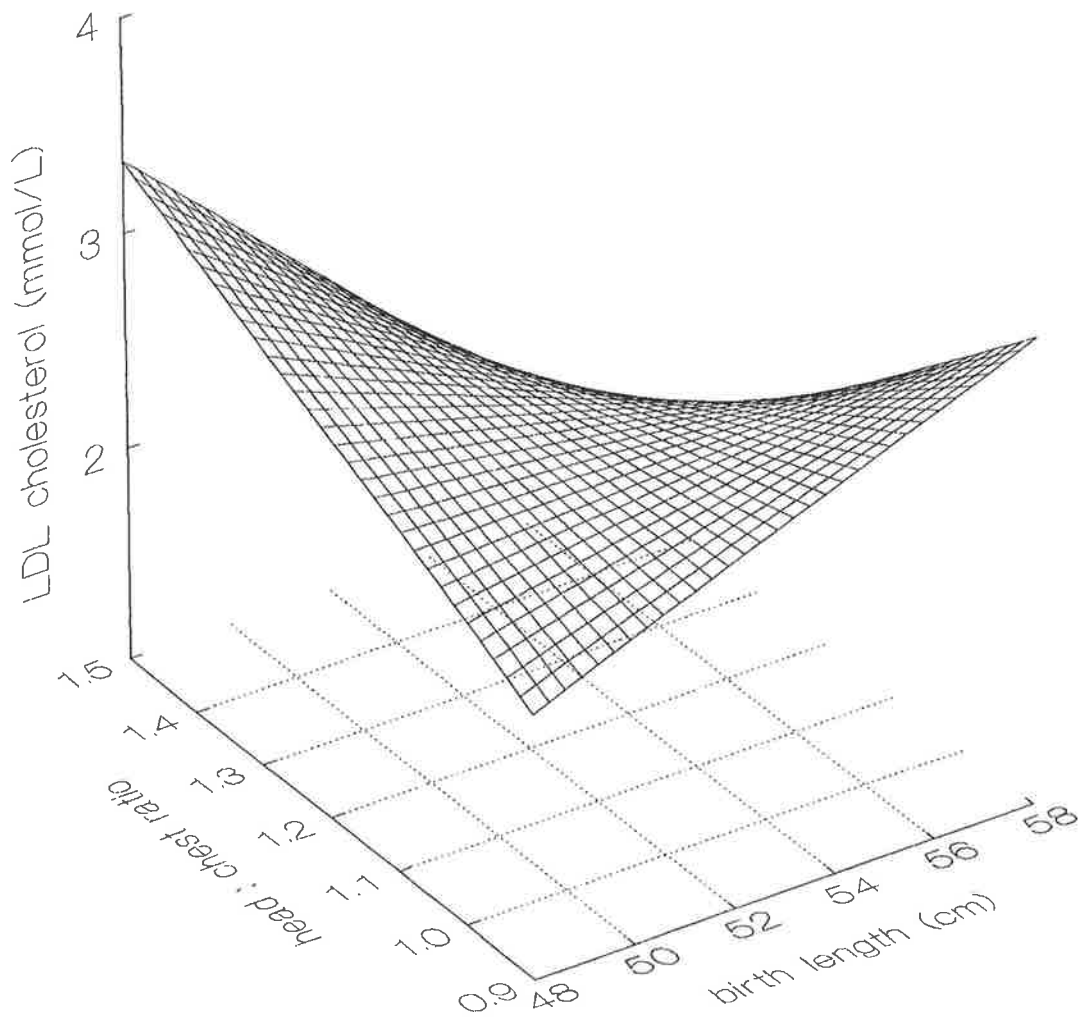
Chapter 6
Results for the cohort at age 20

6.1 The cohort at age 20

Of the 826 singleton subjects involved in the study at age 8, a total of 584 (71%) participated in the follow up at age 20. Before the follow up began, 2 of the original subjects had died and 9 had withdrawn. Of the remaining 231 subjects who did not take part in the follow up, 21 could not be traced, 82 were contacted but no longer lived in Adelaide, and 128 lived in Adelaide but declined participation.

Among the 584 (singleton) young adults who took part in the follow up, there were 297 males and 287 females. Both the males and females had a mean age of 19.7 years (sd 0.3 years) at the time of their follow up examination.

Comparisons of cohort members who participated in the follow up and those who did not, in terms of the characteristics at birth and at 8 years that are most important within this thesis, are presented in Table 6.1.1. (As before, tables for each section may be found at the end of that section.) Participants and non-participants had different distributions of sex and socio-economic indices. While 73% of the female cohort members took part in the follow up, males were less likely to participate, with 69% finally being involved, so the proportion of males differs between the participants and non-participants. Also, as might be expected, subjects with the lowest socio-economic status, as indicated by the father's occupational status or the mother's educational attainment at the time of the age 8 study, were less likely to take part in the follow up than subjects in more favourable socio-economic circumstances. Nevertheless, participants and non-participants were similar with respect to birth weight, length of gestation, and cardiovascular risk factor profiles at 8 years.

Characteristics of the 20 year olds who took part in the follow up are summarised in Table 6.1.2. The cardiovascular risk factor profiles of the young men and women are different, with women having slightly higher mean lipid values than men, but markedly lower mean systolic pressure. Missing values for the lipids occurred because 29 subjects did not wish to have a blood test.

For comparison, Table 6.1.3 shows summary statistics derived from the National Heart Foundation's 1989 Risk Factor Prevalence Study, for men and women aged 20 to 24 years (from the publication by the Risk Factor Prevalence Study Management Committee 1990). Mean values of size and cardiovascular risk factors in the Adelaide cohort are similar to those from the national survey, but the national standard deviations tend to be greater, perhaps because of the greater age range. In the national sample, as in the Adelaide cohort, women had higher mean values of total cholesterol and HDL cholesterol compared with men of the same age, but lower mean systolic pressure.

Occupational status of the cohort members at the time of the follow up is shown in Table 6.1.4. Almost half of the subjects were studying full-time, with only a third having full-time jobs. Thus for the cohort, as for this age group more generally, occupational classification or status ranking does not necessarily capture the subject's broader socio-economic circumstances.

Instead, the socio-economic background of the cohort members at age 20 is described by the subject's level of education and by two indices derived from the postcode of the subject and his or her parents (as detailed in the methods), the Index of Relative Socio-economic Disadvantage and the Index of Economic Resources. Distributions of these socio-economic indicators are presented in Tables 6.1.5 to 6.1.7. Overall, 80% of cohort members had completed high school, with the majority of these subjects going on to undertake further education (Table 6.1.5). This is another reflection of the fact,

noted at age 8, that subjects from families with high socio-economic status are somewhat over-represented within the cohort. In general, approximately 70% of students in South Australia complete high school and approximately 50% of school-leavers undertake some form of tertiary education (Austalian Bureau of Statistics 1992).

For the two area socio-economic indices, the numbers of subjects with an index value in each of four categories are displayed in Tables 6.1.6 and 6.1.7. The categories are based on the quartiles for South Australia (McLennan 1990), so the fact that more than a quarter of cohort members fall into the highest category in each instance is another demonstration of the overall relatively high socio-economic status of cohort members. However, there are still sufficient numbers of low socio-economic status subjects within the cohort for meaningful analysis, particularly as the actual index values rather than the quartile classifications are used in the analyses.

Behaviours that potentially influence the subject's cardiovascular risk are summarised in Tables 6.1.8 to 6.1.11. Approximately one third of the subjects were current smokers, the rate being only slightly higher in males than in females (Table 6.1.8). Most cohort members reported moderate consumption of alcohol (up to 16 drinks per week), although more than 10% of subjects reported not drinking alcohol at all, and 40 males reported high weekly alcohol consumption (Table 6.1.9). Patterns of smoking and drinking were almost identical to those found among Adelaide-based 20 to 29 year olds in the National Heart Foundation's 1989 Risk Factor Prevalence Survey, where 32% of men and 28% of women smoked, and 11% of men and 16% of women did not drink alcohol (National Heart Foundation of Australia and Australian Institute of Health 1991).

A minority of cohort members reported that they always added salt to their food or usually ate fat on meat (Table 6.1.10). These rates were lower than those for

Adelaide-based 20 to 29 year olds in the National Heart Foundation's 1989 Risk Factor Prevalence Survey, where 17% of men and 12% of women reported always adding salt to food, and 16% of men and 6% of women reported usually eating the fat on meat (National Heart Foundation of Australia and Australian Institute of Health 1991).

Short Fat Questionnaire scores, used to assess relative fat intake, had a distribution within this cohort (Table 6.1.10) similar to that obtained in the community survey conducted when the Short Fat Questionnaire was developed (Dobson et al. 1993). In the community survey, the mean score was 23 (sd = 8).

More than half of the men and 40% of the women in the cohort reported amounts of exercise that were classified as aerobic (Table 6.1.11). These rates are high compared with data from the National Heart Foundation's 1983 Risk Factor Prevalence Survey, reported by Bauman and Owen (1991). In that survey, approximately 30% of men and 20% of women aged 25 to 35 years undertook aerobic exercise. (These figures do not provide the most apt comparison, since the subjects are older than cohort members, but they are the best Australian data available.) Approximately 20% of the 25 to 35 year olds reported being inactive, whereas 34% of cohort members were classified as such. Thus cohort members who exercised were more likely to report doing high levels of exercise than moderate exercise, whereas in the community (in a slightly older age group), those who exercised seemed to prefer moderate rather than aerobic levels of physical activity.

Table 6.1.1

Comparison of follow up participants and non-participants

| Variable | Participants in the follow up at age 20 | | | Cohort members who did not participate in the follow up | | |
| | n = 584 | | | n = 242 | | |
	mean	(sd)	range	mean	(sd)	range
At birth:						
Birth weight (g)	3363	(564)	1220 - 5120	3424	(530)	1300 - 4670
Gestation (weeks)	39	(2)	28 - 44	39	(2)	26 - 44
At age 8:						
Systolic pressure (mm Hg)	101	(12)	65 - 145	102	(11)	78 - 135
Diastolic pressure (mm Hg)	61	(9)	37 - 98	61	(9)	30 - 89
Total cholesterol (mmol/L)	4.5	(0.8)	2.0 - 7.6	4.6	(0.9)	2.1 - 8.9
LDL cholesterol (mmol/L)	2.9	(0.7)	0.6 - 6.4	2.9	(0.9)	0.8 - 7.4
HDL cholesterol (mmol/L)	1.3	(0.4)	0.5 - 3.4	1.3	(0.4)	0.6 - 2.6
HDL/LDL cholesterol ratio	0.5	(0.3)	0.1 - 2.6	0.5	(0.2)	0.1 - 1.9
Father's occupation in lowest Congalton status category (D)	13 %			18 %		
Mother had no high school education	6 %			11 %		
Male	51 %			56 %		

Table 6.1.2

Size and cardiovascular risk factors at age 20

Variable	Men			Women		
	mean	(sd)	n	mean	(sd)	n
Weight (kg)	76	(13)	297	64	(14)	287
Height (cm)	179	(6)	297	165	(6)	287
Systolic pressure (mm Hg)	125	(9)	297	115	(9)	287
Diastolic pressure (mm Hg)	71	(8)	297	70	(7)	287
Total cholesterol (mmol/L)	4.3	(0.8)	290	4.6	(0.9)	265
LDL cholesterol (mmol/L)	2.6	(0.7)	290	2.8	(0.8)	265
HDL cholesterol (mmol/L)	1.2	(0.3)	290	1.4	(0.3)	265
HDL/LDL cholesterol ratio	0.5	(0.3)	290	0.5	(0.2)	265
Triglyceride (mmol/L)	1.0	(0.5)	290	0.9	(0.4)	265

Table 6.1.3

Summary statistics from the National Heart Foundation's 1989 Risk Factor Prevalence Study, for subjects aged 20 to 24 years

Variable	Men			Women		
	mean	(sd)	n	mean	(sd)	n
Weight (kg)	75	(16)	386	61	(12)	381
Height (cm)	177	(8)	386	164	(8)	381
Systolic pressure (mm Hg)	124	(16)	386	112	(12)	392
Diastolic pressure (mm Hg)	75	(12)	386	69	(9)	392
Total cholesterol (mmol/L)	4.6	(1.1)	334	4.9	(1.1)	270
HDL cholesterol (mmol/L)	1.2	(0.4)	334	1.5	(0.4)	270
Triglyceride (mmol/L)	1.0	(0.5)	334	0.9	(0.5)	270

Notes.
Data from the Risk Factor Prevalence Study Management Committee (1990).
Standard deviations have been derived from the published standard errors of means.
For women, the lipid values have been calculated by weighting the separate information for those taking and not taking the oral contraceptive pill.

Table 6.1.4

Occupational status of cohort members at age 20

Category of work or study	n	% of cohort
Working full-time	172	29
Working part-time	187	32
Unemployed	64	11
Home duties	24	4
Studying full-time	253	43
Studying part-time	42	7

Note.
Subjects could nominate more than one category, so the column
percentages do not sum to 100.

Table 6.1.5

Socio-economic background of the cohort at age 20:

subject's educational attainment

Highest level of education attained	n	%
Some high school	114	20
Completed high school	136	23
Some tertiary education	302	52
Completed tertiary education	30	5
Missing value	2	-
Total	584	100

Table 6.1.6

Socio-economic background of the cohort at age 20: Area Index of Relative Socio-economic Disadvantage

Area Index of Relative Socio-economic Disadvantage, allocated to the South Australian quartiles

	n	%
1 (most disadvantaged)	48	9
2	144	26
3	169	30
4 (least disadvantaged)	198	35
Missing value	25	-
Total	584	100

Table 6.1.7

Socio-economic background of the cohort at age 20: Area Index of Economic Resources

Area Index of Economic Resources, allocated to the South Australian quartiles

	n	%
1 (least economic resources)	39	7
2	129	23
3	158	28
4 (most economic resources)	244	43
Missing value	14	-
Total	584	100

Table 6.1.8

Smoking status at age 20

Smoking status	Men		Women	
	n	%	n	%
Non-smoker	205	69	209	73
Smoker	92	31	78	27
Total	297	100	287	100

Table 6.1.9

Weekly alcohol consumption at age 20

Usual number of drinks consumed in a week	Men		Women	
	n	%	n	%
None (non-drinker)	32	11	45	16
Up to 8 drinks	134	45	185	65
9 to 16 drinks	63	21	41	14
17 to 24 drinks	28	9	10	4
More than 24 drinks	40	14	5	2
Missing value	0	-	1	-
Total	297	100	287	100

Table 6.1.10

Salt and fat consumption practices at age 20

Dietary practice	Men	Women
Almost always add salt to food	7 %	8 %
Usually eat most fat on meat	9 %	2 %
Mean Short Fat Questionnaire score	26 (sd 7)	22 (sd 7)

Table 6.1.11

Level of exercise at age 20

Usual level of exercise	Men		Women	
	n	%	n	%
None	79	27	113	40
Moderate	52	18	55	20
Aerobic	157	55	113	40
Missing value	9	-	7	-
Total	297	100	287	100

6.2 Blood pressure at age 20

At age 20, distributions of blood pressure and associations with birth characteristics were different for males and females, so separate analyses were carried out for each sex.

Among the young men, associations between birth characteristics and blood pressure were potentially distorted by the influences of current size and age, these variables being associated with both birth and blood pressure measurements. Of the size variables (weight, height, body mass index, sum of skinfold thicknesses, and waist to hip ratio), weight was most strongly correlated with blood pressure (for systolic pressure Pearson's $r = 0.25$, $p < 0.01$) and adjustment for weight at age 20 controlled for confounding by current size. (Although body mass index was correlated with blood pressure almost as strongly as weight, and is typically used in studies of adult blood pressure, adjustment for body mass index did not provide adequate control for confounding.) Hence all blood pressure analyses for males were adjusted for both weight and age at the time of the follow up examination.

In men, birth weight was inversely related to systolic pressure at age 20, adjusted for weight and exact age. A one kilogram increase in birth weight was associated with a decrease in systolic pressure of 2.3 mm Hg (95% CI 0.5 to 4.2). However, this effect was diminished and no longer statistically significant when duration of gestation was considered. Among those born at term, a one kilogram increase in birth weight was associated with a decrease in systolic pressure of 1.3 mm Hg (95% CI -1.0 to 3.6). Birth weight was not associated with diastolic pressure at age 20.

Among males born at term, there were no statistically significant relationships between blood pressure and either placental weight, head circumference, chest circumference, or length, when these birth dimensions were considered separately. Also, there were

no joint effects of birth characteristics representing the three phenotypes: low birth weight relative to placental weight; thinness, possibly accompanied by a small head circumference; shortness with a large head relative to chest.

Associations between blood pressure and both behavioural and socio-economic factors, for males, are displayed in Table 6.2.1. These are presented as correlations derived from regression models. (In the case of categorical variables, mean blood pressure levels in each category were also examined to assess potential confounding.) Most associations were of small magnitude and not statistically significant. Of the variables that were to some degree correlated with blood pressure ($r > 0.1$), two were also associated with birth weight, but only weakly: educational attainment at age 20 (coefficient of multiple correlation = 0.14, $p = 0.09$) and alcohol consumption at age 20 (coefficient of muliple correlation = 0.11, $p = 0.35$). As expected, therefore, no relationships between birth characteristics and blood pressure were masked by negative confounding by smoking status, alcohol consumption, discretionary salt practices, relative fat intake, or exercise level. Nor did any relationships emerge when socio-economic status was taken into account (indicated either by the subject's educational attainment, or by the family's area measures of relative disadvantage and economic resources, current or at birth, or by the father's occupation or mother's education when the subject was aged 8).

Turning to the young women, associations between their birth characteristics and blood pressure at age 20 were potentially influenced by current size. Adjustment for body mass index did not provide adequate control for this source confounding; adjustment for both weight and height (absolute size rather than relative weight for height) was required. There was no differential distribution of age at follow up across birth measurements, so age was not a source of confounding in this case. Hence all blood pressure analyses for females were adjusted for weight and height at age 20.

In women, birth weight was inversely related to both systolic and diastolic pressure at age 20. A one kilogram increase in birth weight was associated with a decrease in systolic pressure of 5.0 mm Hg (95% CI 3.3 to 6.7) and with a decrease in diastolic pressure of 2.0 mm Hg (95% CI 0.5 to 3.4). The relationship with systolic pressure persisted when duration of gestation was taken into account, although the relationship with diastolic pressure was diminished to the extent that it became statistically non-significant. Among those born at term, a one kilogram increase in birth weight was associated with a decrease in systolic pressure of 4.4 mm Hg (95% CI 2.1 to 6.7) and with a decrease in diastolic pressure of 1.1 mm Hg (95% CI -0.8 to 3.0).

Among females born at term, there were separate inverse relationships between systolic pressure at age 20, adjusted for current weight and height, and head circumference, chest circumference, and length at birth. Results of the multiple linear regression analyses are summarised in Table 6.2.2. Placental weight, the other birth measurement considered singly, was not related to systolic pressure. These associations were not apparent for diastolic pressure.

Still considering females born at term only, there was weak evidence of simultaneous effects of placental weight and birth weight on systolic pressure at age 20. As in the age 8 data, systolic pressure tended to rise with increasing placental weight and, simultaneously, fell with increasing birth weight. The relationship with placental weight did not achieve conventional statistical significance, perhaps reflecting the decreased sample size available at age 20, but the effect of birth weight was stronger in the joint model than when birth weight was considered alone. In the joint model, a one kilogram increase in birth weight was associated with a decrease in systolic pressure of 5.7 mm Hg (95% CI 2.8 to 8.6) and a 100 gram increase in placental weight was associated with an increase in systolic pressure of 0.8 mm Hg (95% CI -1.9, 3.7). Table 6.2.3 attempts to illustrate these results; the loss of information when the data

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were collapsed into categories obscured the weak effect of placental weight observed in the continuous data. These joint effects were not evident for diastolic pressure.

In addition, ponderal index at birth was inversely related to systolic pressure at age 20 (partial regression coefficient = -0.345, p = 0.04). When head circumference and ponderal index were entered together in a regression model, both birth dimensions were simultaneously negatively associated with systolic pressure, although the effect of ponderal index did not achieve statistical significance. (For head circumference the partial regression coefficient = -0.97, p = 0.01; for ponderal index the partial regression coefficient = -0.25, p = 0.13.) These effects were not evident for diastolic pressure.

Inclusion of birth length, the ratio of head circumference to chest at birth, and their interaction, in a model for systolic pressure at age 20 showed that for babies whose head was large in relation to their chest, shortness at birth was associated with elevated blood pressure in early adulthood, whereas among babies whose head to chest ratio was low, length was positively associated with blood pressure at age 20 (and these babies tended to have low ponderal index, so this finding is consistent with the joint effects described above). These results did not achieve statistical significance, but testing for interactions generally requires a very large sample size, so this may primarily reflect a lack of power in the available sample. The same pattern of joint effects, of similar magnitude, was evident for diastolic pressure. These results are summarised in Tables 6.2.9 and 6.2.10 and the regression equations are illustrated in Figures 6.2.1 and 6.2.2 (which may be found immediately after the corresponding tables).

Associations between blood pressure and both behavioural and socio-economic factors, for females, are displayed in Table 6.2.4. As for men, most associations were of small magnitude and not statistically significant. Inclusion of behavioural or

socio-economic variables in the models did not change the magnitude of associations between birth dimensions and blood pressure. The relationship between birth weight and systolic pressure was evident in each socio-economic stratum, however these strata were defined, as demonstrated in Tables 6.2.5 to 6.2.8.

Table 6.2.1

Relationships between behavioural or socio-economic variables and blood pressure at age 20, for males

Variable	Systolic pressure		Diastolic pressure	
	r	p	r	p
Smoking status *	0.05	0.39	< 0.01	0.97
Weekly alcohol consumption *	0.13	0.16	0.09	0.46
Discretionary salt practices *	0.13	0.08	0.14	0.04
Short Fat Questionnaire score	- 0.12	0.03	- 0.04	0.52
Exercise level *	0.16	0.03	0.09	0.35
Educational attainment *	0.06	0.77	0.10	0.39
Area index of relative disadvantage at age 20	0.01	0.82	0.02	0.74
Area index of economic resources at age 20	0.01	0.87	0.01	0.91
Father's occupational status when subject was aged 8 *	0.12	0.32	0.04	0.94
Mother's educational attainment when subject was aged 8 *	0.05	0.90	0.08	0.57
Birth area index of relative disadvantage	- 0.03	0.59	0.05	0.38
Birth area index of economic resources	- 0.02	0.68	0.05	0.42

* For these variables the correlation coefficient represents the coefficient of multiple correlation for a set of indicator variables, and the p value is that for the model.

Table 6.2.2

Relationships between birth dimensions and systolic pressure at age 20 adjusted for current weight and height, for females born at term

Independent variable	Partial regression coefficient	Standard error	p value
Head circumference at birth	- 1.081	0.350	< 0.01
Chest circumference at birth	- 0.760	0.272	< 0.01
Length at birth	- 0.690	0.251	< 0.01

Note.
The regression coefficient may be interpreted as the increase in systolic pressure associated with a one unit increase in the independent variable.

Table 6.2.3

Mean systolic pressure (mm Hg) at age 20 adjusted for current weight and height, according to birth weight and placental weight groups, for females born at term; numbers in each cell are shown in parentheses

Placental weight (g)	Birth weight (g)			
	≤ 3200	3201 - 3600	> 3600	Total
≤ 500	117 (64)	113 (26)	112 (4)	114
501 - 600	117 (29)	114 (36)	113 (20)	115
> 600	117 (7)	114 (25)	112 (56)	114
Total	117	114	112	(261)

Table 6.2.4

Relationships between behavioural or socio-economic variables and blood pressure at age 20, for females

Variable	Systolic pressure		Diastolic pressure	
	r	p	r	p
Smoking status *	0.04	0.47	0.10	0.10
Weekly alcohol consumption *	0.14	0.15	0.10	0.42
Discretionary salt practices *	0.05	0.74	0.07	0.52
Short Fat Questionnaire score	- 0.01	0.84	- 0.02	0.77
Exercise level *	0.10	0.25	0.03	0.87
Educational attainment *	0.04	0.93	0.07	0.69
Area index of relative disadvantage at age 20	< 0.01	0.94	- 0.07	0.35
Area index of economic resources at age 20	< 0.01	0.88	- 0.04	0.46
Father's occupational status when subject was aged 8	0.03	0.97	0.03	0.97
Mother's educational attainment when subject was aged 8	0.13	0.20	0.10	0.39
Birth area index of relative disadvantage	- 0.07	0.25	- 0.02	0.71
Birth area index of economic resources	- 0.13	0.03	- 0.09	0.14

* For these variables the correlation coefficient represents the coefficient of multiple correlation for a set of indicator variables, and the p value is that for the model.

Table 6.2.5

Mean systolic pressure (mm Hg) at age 20 adjusted for current weight and height, according to birth weight and educational attainment groups, for females born at term; numbers in each cell are shown in parentheses

Highest level of education attained	Birth weight (g)			
	≤ 3200	3201 - 3600	> 3600	Total
Some high school	116 (18)	113 (15)	112 (35)	113
Completed high school	117 (19)	113 (14)	112 (17)	114
Some tertiary education	117 (60)	114 (53)	113 (37)	115
Completed tertiary education	115 (5)	112 (4)	111 (5)	113
Total	116	113	112	(262)

Table 6.2.6

Mean systolic pressure (mm Hg) at age 20 adjusted for current weight and height, according to birth weight and mother's educational attainment when subject was aged 8, for females born at term; numbers in each cell are shown in parentheses

Mother's education when subject was aged 8	Birth weight (g)			
	≤ 3200	3201 - 3600	> 3600	Total
Primary school	114 (7)	111 (4)	110 (8)	112
Some high school	117 (36)	114 (28)	113 (26)	115
Completed high school	116 (30)	113 (27)	112 (36)	115
Tertiary education	118 (28)	115 (24)	114 (13)	116
Total	116	113	112	(257)

Table 6.2.7

Mean systolic pressure (mm Hg) at age 20 adjusted for current weight and height, according to birth weight and birth area disadvantage groups, for females born at term; numbers in each cell are shown in parentheses

Birth area index of relative socio-economic disdavantage	Birth weight (g)			
	≤ 3200	3201 - 3600	> 3600	Total
1 (most)	115 (12)	112 (7)	111 (10)	113
2	117 (23)	114 (30)	113 (30)	115
3	118 (35)	115 (21)	114 (29)	116
4 (least)	116 (22)	112 (26)	111 (13)	113
Total	117	113	112	(266)

Table 6.2.8

Mean systolic pressure (mm Hg) at age 20 adjusted for current weight and height, according to birth weight and birth area economic resources groups, for females born at term; numbers in each cell are shown in parentheses

Birth area index of economic resources	Birth weight (g)			
	≤ 3200	3201 - 3600	> 3600	Total
1 (least)	116 (10)	113 (4)	112 (7)	114
2	117 (33)	114 (34)	113 (31)	115
3	117 (32)	114 (23)	113 (22)	114
4 (most)	116 (25)	113 (26)	111 (13)	113
Total	116	113	112	(260)

Table 6.2.9

Relationship between systolic pressure at age 20 adjusted for current weight and height, and both length and the ratio of head circumference to chest at birth, for females born at term

Independent variable	Partial regression coefficient	Standard error	p value
Birth length	7.40	5.22	0.16
Head : chest circumference at birth	386.91	250.18	0.12
Interaction of length and head : chest	- 7.91	5.09	0.12

systolic pressure = 0.18 * weight + 0.27 * height

+ 7.40 * birth length + 386.91 * head : chest

- 7.91 * birth length * head : chest

- 302.61

Figure 6.2.1

Systolic pressure at age 20 as a function of birth length and relative head size, for females born at term
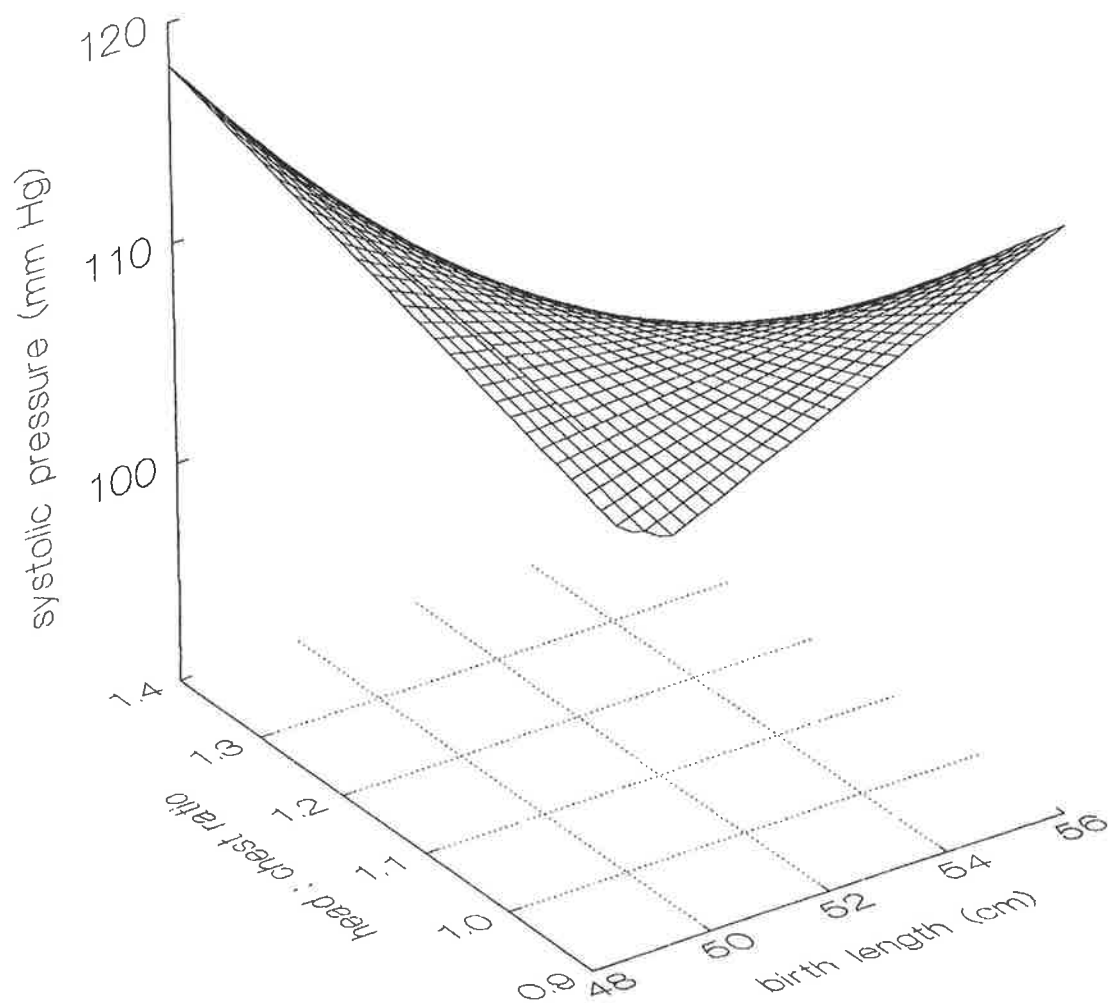
Table 6.2.10

Relationship between diastolic pressure at age 20 adjusted for current weight and height, and both length and the ratio of head circumference to chest at birth, for females born at term

Independent variable	Partial regression coefficient	Standard error	p value
Birth length	6.77	4.28	0.12
Head : chest circumference at birth	333.66	205.37	0.11
Interaction of length and head : chest	- 6.74	4.18	0.11

diastolic pressure = 0.05 * weight + 0.23 * height

+ 6.77 * birth length + 333.66 * head : chest

- 6.74 * birth length * head : chest

- 306.01

Figure 6.2.2

Diastolic pressure at age 20 as a function of birth length and relative head size, for females born at term
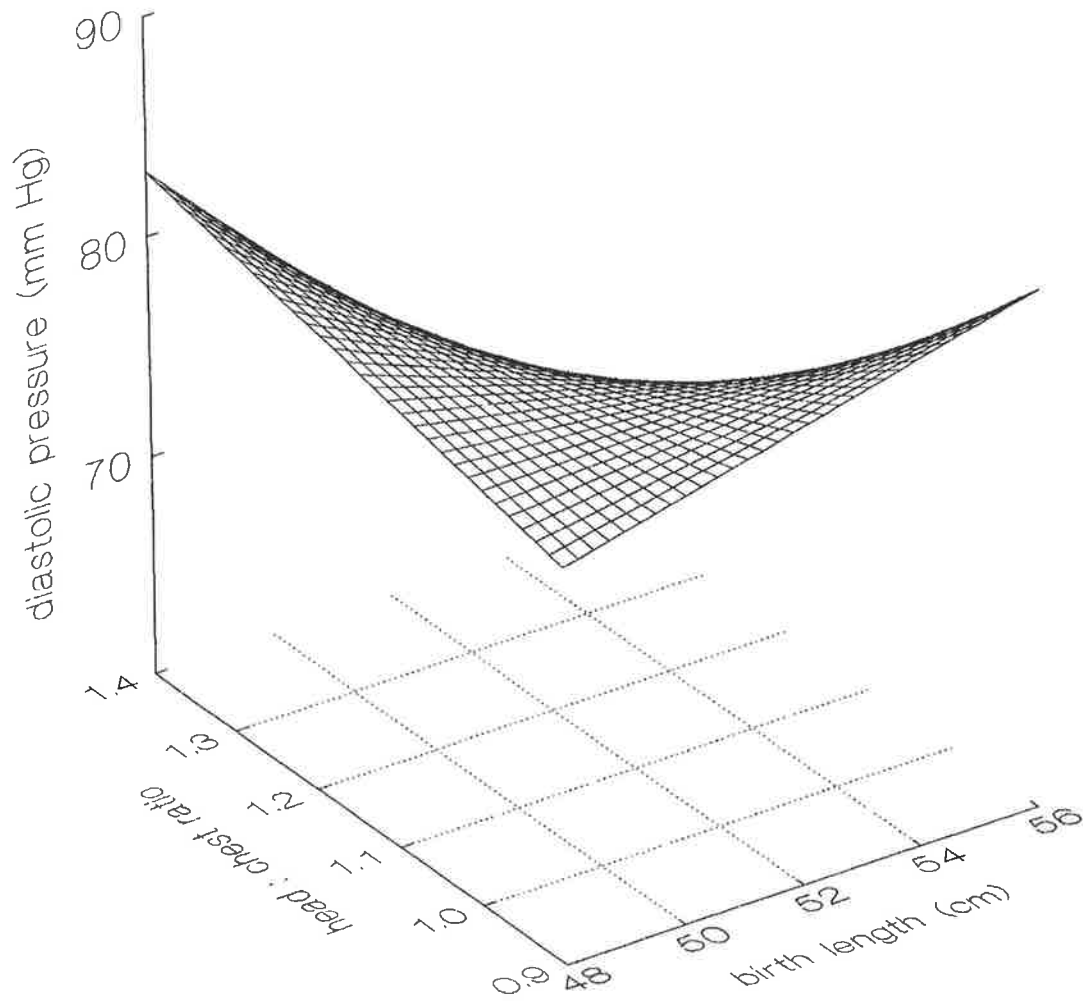
6.3 Blood lipids at age 20

At age 20, distributions of lipids and confounding factors for relationships between birth characteristics and lipids were different for males and females, so separate analyses were carried out for each sex. As before, distributions of the ratio of HDL to LDL cholesterol and triglyceride exhibited marked right skewness, so the natural logarithms of these variables were used in all analyses.

Among the young men, associations between birth characteristics and lipid fractions were likely to be influenced by current size and age, since these variables were associated with both birth and lipid measurements. Body mass index was correlated with most lipid concentrations more strongly than the other size measurements, and adjustment for body mass index controlled for confounding by current size on this occasion. Simultaneous adjustments for body mass index and age at the time of follow up were therefore made in all lipid analyses for males at age 20.

In men, with one exception, birth weight was not related to lipid concentrations at age 20, adjusted for body mass index and age, either considering all births or those born at term only. The possible exception was an inverse association between birth weight and the logarithm of triglyceride apparent among all births (partial regression coefficient = -0.00008, p = 0.08) but diminished and not statistically significant among those born at term (partial regression coefficient = -0.00007, p = 0.20).

Among men born at term, head circumference at birth was inversely related to total cholesterol and LDL cholesterol and positively related to the the ratio of HDL to LDL cholesterol, with details given in Table 6.3.1. Head circumference was not associated with HDL cholesterol or triglyceride. Neither chest circumference nor length at birth were associated with lipid concentrations at age 20. There was one statistically

significant association for placental weight, that being with the logarithm of the ratio of HDL to LDL cholesterol (partial regression coefficient = 0.0004, p = 0.05).

Joint effects of variables representing the three birth phentoypes were examined: low birth weight relative to placental weight; thinness, possibly accompanied by a small head circumference; shortness with a large head relative to chest. There was some evidence linking both of the latter two phenotypes to concentrations of total and LDL cholesterol at age 20, as described below. There was no evidence of effects on HDL cholesterol or triglyceride.

Among men born at term, ponderal index was inversely related to concentrations of total cholesterol and LDL cholestrol and positively related to the ratio of HDL to LDL cholesterol, adjusted for age and body mass index. Results of the multiple linear regression analyses are summarised in Table 6.3.2. Ponderal index was not related to HDL cholesterol or triglyceride.

Ponderal index and head circumference at birth were simultaneously inversely related to total cholesterol, LDL cholesterol and the ratio of HDL to LDL cholesterol. None of these relationships achieved statistical significance, however. (In the case of total cholesterol the partial regression coefficient for ponderal index = -0.029, p = 0.12, and the partial regression coefficient for head circumference = -0.052, p = 0.13. With LDL cholesterol as the outcome, the partial regression coefficient for ponderal index = -0.024, p = 0.14, and the partial regression coefficient for head circumference = -0.05, p = 0.08. Considering the logarithm of HDL to LDL cholesterol, the partial regression coefficient for ponderal index = 0.012, p = 0.18, and the partial regression coefficient for head circumference = 0.023, p = 0.17.)

Concerning the third phenotype, there was good evidence of an interaction between birth length and the ratio of head circumference to chest, in relation to total cholesterol

at age 20. The complicated effect was the same as that seen at age 8: for babies whose head was large in relation to their chest, shortness at birth was associated with elevated cholesterol, while for babies with a relatively small head circumference, length was positively related to later cholesterol concentration. These results are summarised in Table 6.3.3 and the regression equation, involving an interaction term, is depicted in Figure 6.3.1. Although not statistically significant, this pattern was also evident for LDL cholesterol, as shown in Table 6.3.4 and Figure 6.3.2.

Associations between lipid fractions and both behavioural and socio-economic factors, for males, are presented in Tables 6.3.5 to 6.3.7. As before, these are presented as correlations derived from regression models. (In the case of categorical variables, mean lipid concentrations in each category were also inspected to assess potential confounding.) In relation to total cholesterol, LDL cholesterol and the ratio of HDL to LDL cholesterol, most associations were of small magnitude. There were some slightly stronger relationships for HDL cholesterol and triglyceride, although the correlation of greatest magnitude, that between smoking status and triglyceride concentration, was still quite small ($r = 0.23$). Since none of these variables were even moderately correlated with birth characteristics, the potential for confounding by these variables is theoretically limited. In practice, inclusion of behavioural or socio-economic variables in the models did not change the magnitude of any of the previously reported associations between birth measurements and lipid fractions.

Turning now to the young women, associations between their birth characteristics and lipid fractions at age 20 were potentially influenced by current size, but not age at the time of follow up. As in the blood pressure analysis for females at age 20, adjustment for body mass index was not a satisfactory means of dealing with confounding by current size, and once again, adjustment for both weight and height was appropriate. This was done in all subsequent analyses.

In women, birth weight was not related to any of the lipid fractions at age 20, adjusted for weight and height. This was the case whether or not duration of gestation was taken into consideration. Among the women who had been born at term, there were no associations between any of the other birth dimensions considered separately.

However, there was some evidence of joint effects of birth dimensions representing the third phenotype, the baby that is short with a large head relative to its chest, on LDL cholesterol. The pattern was the same as that seen previously at age 8 (for total and LDL cholesterol) and in the men at age 20 (for total and LDL cholesterol): when head circumference was large in relation to chest, length was inversely associated with LDL cholesterol, but for babies with a relatively small head, length was positively associated with LDL cholesterol. The magnitude of the effect was similar to that seen in men, although in women the findings did not achieve statistical significance. These results, from a model including an interaction term for birth length and the ratio of head to chest circumference, are summarised in Table 6.3.8 and illustrated in Figure 6.3.3.

Associations between lipid fractions and both behavioural and socio-economic factors, for females, are presented in Tables 6.3.9 to 6.3.11. The strongest associations were with oral contraceptive use, which had an adverse effect on lipid profiles. However, neither this variable nor any of the others confounded associations between birth characteristics and lipid fractions.

Table 6.3.1

Relationships between head circumference at birth and lipid concentrations at age 20 adjusted for current body mass index and age, for males born at term

Dependent variable	Partial regression coefficient	Standard error	p value
Total cholesterol (mmol/L)	- 0.068	0.032	0.04
LDL cholesterol (mmol/L)	- 0.066	0.029	0.02
Logarithm of HDL : LDL cholesterol	0.029	0.016	0.08

Note.
The regression coefficient may be interpreted as the mean or expected increase in lipid concentration associated with a one unit increase in head circumference.

Table 6.3.2

Relationships between ponderal index at birth and lipid concentrations at age 20 adjusted for current body mass index and age, for males born at term

Dependent variable	Partial regression coefficient	Standard error	p value
Total cholesterol (mmol/L)	- 0.038	0.018	0.03
LDL cholesterol (mmol/L)	- 0.033	0.016	0.04
Logarithm of HDL : LDL cholesterol	0.016	0.009	0.06

Note.
The regression coefficient may be interpreted as the mean or expected increase in lipid concentration associated with a one unit increase in ponderal index.

Table 6.3.3

Relationship between total cholesterol at age 20 adjusted for current body mass index and age, and both length and the ratio of head circumference to chest at birth, for males born at term

Independent variable	Partial regression coefficient	Standard error	p value
Birth length	1.099	0.392	< 0.01
Head : chest circumference at birth	51.967	19.138	< 0.01
Interaction of length and head : chest	- 1.046	0.380	< 0.01

Total cholesterol = 0.017 * age + 0.053 * body mass index

+ 1.099 * birth length + 51.967 * head : chest

- 1.046 * birth length * head : chest

- 51.948

Figure 6.3.1

Total cholesterol at age 20 as a function of birth length and relative head size, for males born at term

Table 6.3.4

Relationship between LDL cholesterol at age 20 adjusted for current body mass index and age, and both length and the ratio of head circumference to chest at birth, for males born at term

Independent variable	Partial regression coefficient	Standard error	p value
Birth length	0.603	0.357	0.09
Head : chest circumference at birth	28.923	17.445	0.10
Interaction of length and head : chest	- 0.577	0.347	0.10

LDL cholesterol = 0.142 * age + 0.052 * body mass index

+ 0.603 * birth length + 28.923 * head : chest

- 0.577 * birth length * head : chest

- 31.694

Figure 6.3.2

LDL cholesterol at age 20 as a function of birth length and relative head size, for males born at term

Table 6.3.5

Relationships between behavioural or socio-economic variables and total cholesterol and LDL cholesterol at age 20, for males

Variable	Total cholesterol		LDL cholesterol	
	r	p	r	p
Smoking status *	0.04	0.47	0.03	0.66
Weekly alcohol consumption *	0.09	0.49	0.06	0.76
Discretionary salt practices *	0.03	0.86	0.02	0.93
Short Fat Questionnaire score	0.01	0.81	0.04	0.53
Exercise level *	0.03	0.85	0.03	0.87
Educational attainment *	0.09	0.47	0.06	0.80
Area index of relative disadvantage at age 20	- 0.03	0.58	- 0.02	0.78
Area index of economic resources at age 20	- 0.01	0.86	- 0.01	0.86
Father's occupational status when subject was aged 8 *	0.10	0.48	0.07	0.71
Mother's educational attainment when subject was aged 8 *	0.17	0.04	0.16	0.06
Birth area index of relative disadvantage	< 0.01	0.97	- 0.02	0.78
Birth area index of economic resources	0.02	0.78	< 0.01	0.95

* For these variables the correlation coefficient represents the coefficient of multiple correlation for a set of indicator variables, and the p value is that for the model.

Table 6.3.6

Relationships between behavioural or socio-economic variables and HDL cholesterol and the ratio of HDL to LDL cholesterol at age 20, for males

Variable	HDL cholesterol		HDL : LDL cholesterol (logarithm of)	
	r	p	r	p
Smoking status *	0.04	0.51	0.02	0.70
Weekly alcohol consumption *	0.16	0.06	0.11	0.35
Discretionary salt practices *	0.04	0.82	0.02	0.93
Short Fat Questionnaire score	0.05	0.36	0.01	0.91
Exercise level *	0.05	0.71	0.03	0.89
Educational attainment *	0.16	0.07	0.08	0.61
Area index of relative disadvantage at age 20	- 0.10	0.09	- 0.08	0.18
Area index of economic resources at age 20	- 0.13	0.03	- 0.08	0.18
Father's occupational status when subject was aged 8 *	0.15	0.12	0.12	0.29
Mother's educational attainment when subject was aged 8 *	0.08	0.62	0.10	0.38
Birth area index of relative disadvantage	0.05	0.42	0.02	0.73
Birth area index of economic resources	0.06	0.33	0.02	0.76

* For these variables the correlation coefficient represents the coefficient of multiple correlation for a set of indicator variables, and the p value is that for the model.

Table 6.3.7

Relationships between behavioural or socio-economic variables and triglyceride concentration at age 20, for males

Variable	Triglyceride (logarithm of)	
	r	p
Smoking status *	0.23	< 0.01
Weekly alcohol consumption *	0.18	0.03
Discretionary salt practices *	0.05	0.67
Short Fat Questionnaire score	- 0.13	0.03
Exercise level *	0.08	0.41
Educational attainment *	0.09	0.50
Area index of relative disadvantage at age 20	0.08	0.20
Area index of economic resources at age 20	0.11	0.06
Father's occupational status when subject was aged 8 *	0.07	0.75
Mother's educational attainment when subject was aged 8 *	0.03	0.96
Birth area index of relative disadvantage	< 0.01	0.90
Birth area index of economic resources	< 0.01	0.96

* For these variables the correlation coefficient represents the coefficient of multiple correlation for a set of indicator variables, and the p value is that for the model.
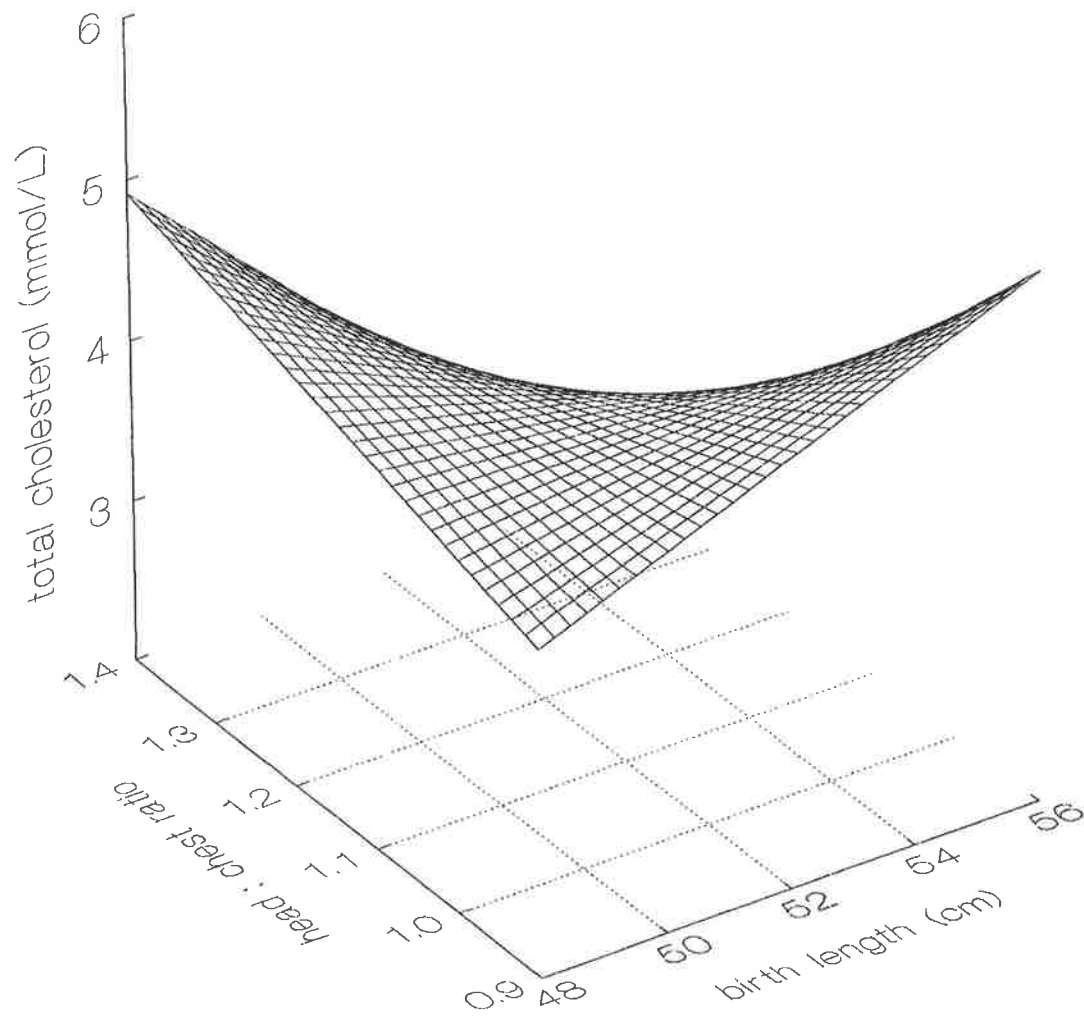
Table 6.3.8

Relationship between LDL cholesterol at age 20 adjusted for current weight and height, and both length and the ratio of head circumference to chest at birth, for females born at term

Independent variable	Partial regression coefficient	Standard error	p value
Birth length	0.684	0.530	0.20
Head : chest circumference at birth	34.827	25.756	0.17
Interaction of length and head : chest	- 0.675	0.524	0.20

LDL cholesterol = 0.007 * weight - 0.017 * height

+ 0.684 * birth length + 34.827 * head : chest

- 0.675 * birth length * head : chest

- 30.277

Figure 6.3.3

LDL cholesterol at age 20 as a function of birth length and relative head size, for females born at term
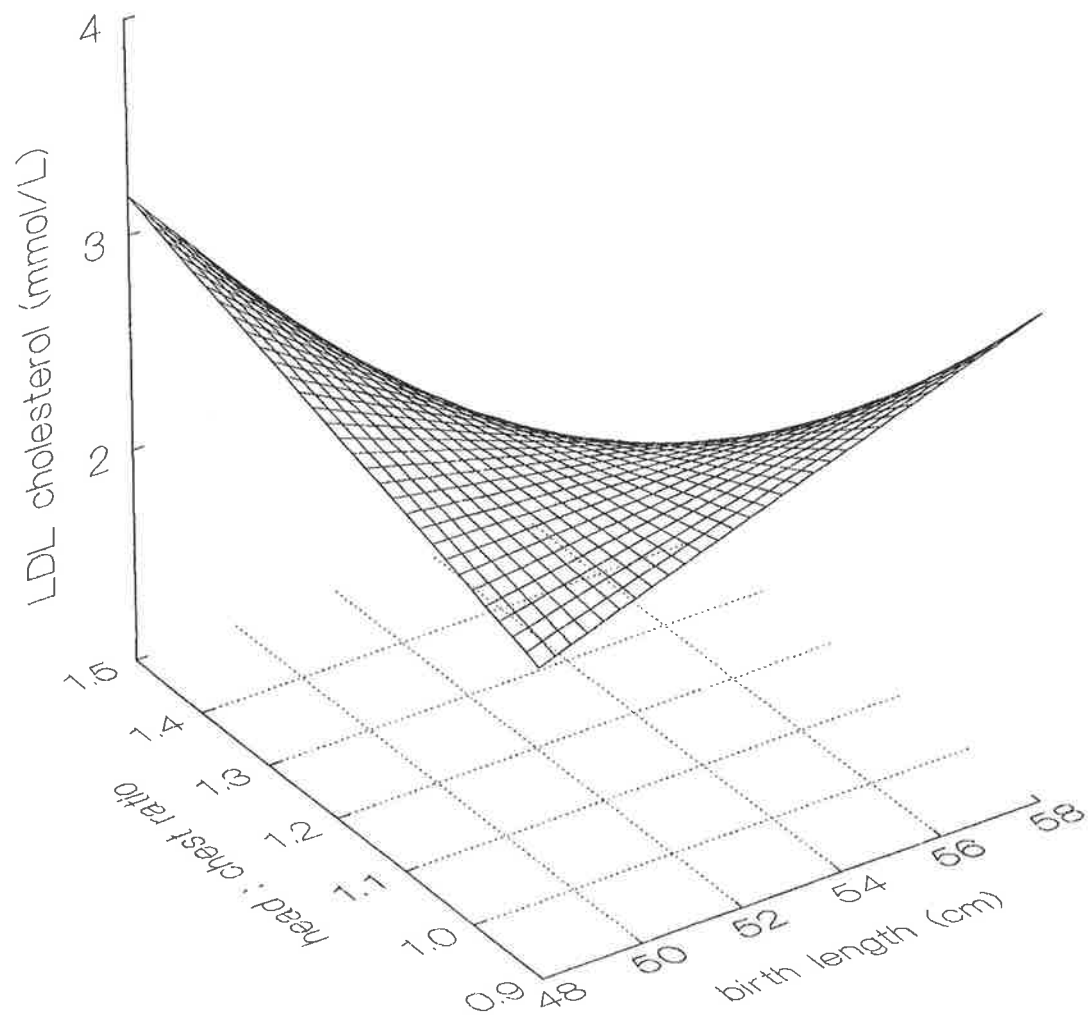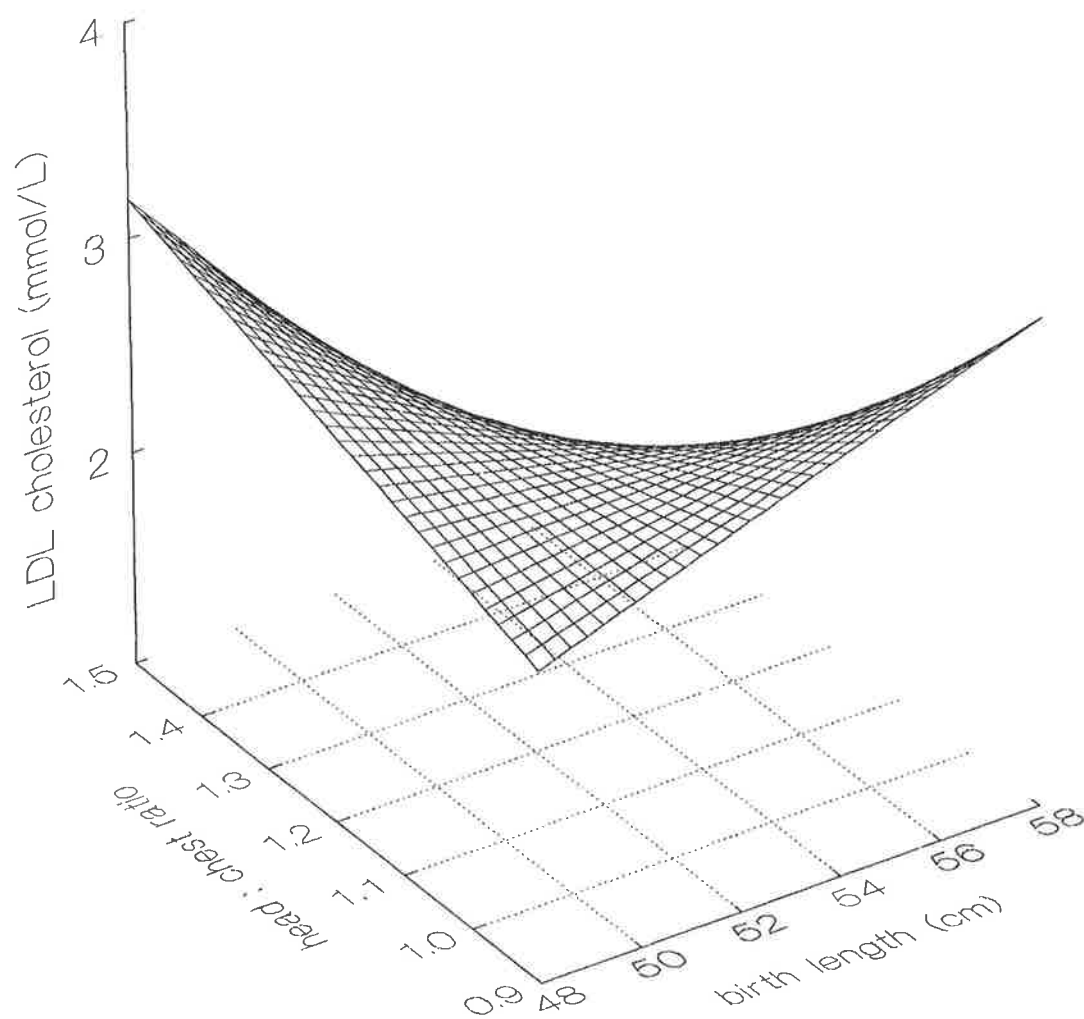
Table 6.3.9

Relationships between behavioural or socio-economic variables and total cholesterol and LDL cholesterol at age 20, for females

Variable	Total cholesterol		LDL cholesterol	
	r	p	r	p
Oral contraceptive use *	0.23	< 0.01	0.23	< 0.01
Smoking status *	0.02	0.71	< 0.01	0.98
Weekly alcohol consumption *	0.10	0.48	0.08	0.66
Discretionary salt practices *	0.09	0.35	0.12	0.14
Short Fat Questionnaire score	0.11	0.08	0.05	0.34
Exercise level *	0.09	0.39	0.11	0.21
Educational attainment *	0.06	0.84	0.06	0.34
Area index of relative disadvantage at age 20	- 0.06	0.34	- 0.06	0.34
Area index of economic resources at age 20	- 0.04	0.49	- 0.05	0.45
Father's occupational status when subject was aged 8 *	0.08	0.69	0.09	0.64
Mother's educational attainment when subject was aged 8 *	0.11	0.38	0.13	0.25
Birth area index of relative disadvantage	- 0.06	0.30	- 0.08	0.22
Birth area index of economic resources	- 0.06	0.33	- 0.05	0.38

* For these variables the correlation coefficient represents the coefficient of multiple correlation for a set of indicator variables, and the p value is that for the model.

Table 6.3.10

Relationships between behavioural or socio-economic variables and HDL cholesterol and the ratio of HDL to LDL cholesterol at age 20, for females

Variable	HDL cholesterol		HDL : LDL cholesterol (logarithm of)	
	r	p	r	p
Oral contraceptive use *	- 0.07	0.32	- 0.20	< 0.01
Smoking status *	- 0.03	0.59	- 0.02	0.79
Weekly alcohol consumption *	0.20	0.01	0.12	0.31
Discretionary salt practices *	0.14	0.07	0.18	0.93
Short Fat Questionnaire score	0.05	0.36	0.01	0.01
Exercise level *	0.08	0.41	0.03	0.89
Educational attainment *	0.08	0.60	0.07	0.74
Area index of relative disadvantage at age 20	0.01	0.88	0.08	0.21
Area index of economic resources at age 20	- 0.01	0.91	0.06	0.33
Father's occupational status when subject was aged 8 *	0.11	0.48	0.12	0.41
Mother's educational attainment when subject was aged 8 *	0.08	0.66	0.10	0.45
Birth area index of relative disadvantage	0.10	0.10	0.14	0.02
Birth area index of economic resources	0.07	0.25	0.11	0.08

* For these variables the correlation coefficient represents the coefficient of multiple correlation for a set of indicator variables, and the p value is that for the model.

Table 6.3.11

Relationships between behavioural or socio-economic variables and triglyceride concentration at age 20, for females

Variable	Triglyceride (logarithm of)	
	r	p
Oral contraceptive use *	0.33	< 0.01
Smoking status *	0.08	0.17
Weekly alcohol consumption *	0.04	0.95
Discretionary salt practices *	0.06	0.63
Short Fat Questionnaire score	- 0.06	0.35
Exercise level *	0.08	0.47
Educational attainment *	0.09	0.58
Area index of relative disadvantage at age 20	0.03	0.64
Area index of economic resources at age 20	0.04	0.57
Father's occupational status when subject was aged 8 *	0.18	0.06
Mother's educational attainment when subject was aged 8 *	0.05	0.90
Birth area index of relative disadvantage	0.02	0.77
Birth area index of economic resources	- 0.01	0.83

* For these variables the correlation coefficient represents the coefficient of multiple correlation for a set of indicator variables, and the p value is that for the model.

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6.4 Amplification of effects

The last question to be addressed through analysis of data collected at age 20 was whether effects seen at age 8 were not only present, but amplified, at age 20. This analysis is relevant to the relationship between birth weight and blood pressure among females, and to the relationship between ponderal index and lipids among males, where effects were evident at both time points.

With regard to blood pressure, an effect of birth weight was seen at both age 8 and age 20 among females. At age 8 a one kilogram increase in birth weight was associated with a 1.0 mm Hg decrease in systolic pressure (section 5.2), while at age 20 the same increase in birth weight was associated with a 5.0 mm Hg decrease in systolic pressure (section 6.2). The null hypothesis here is that these effects (regression coefficients) are essentially the same, when the different distributions of blood pressure at the two ages are taken into account. The alternative hypothesis is that the underlying effects are of a different size.

This hypothesis was tested by examining the interaction between birth weight and time of observation using a generalised estimating equation with exchangeable correlations and a robust estimation of the variance-covariance matrix (Diggle, Liang & Zeger 1994). Analysis was restricted to the 287 females who had data for both time points, and adjustments were made for weight at age 8, and for weight and height at age 20, as in the previous analyses of this outcome variable. The effect of birth weight on systolic blood pressure was found to be greater at age 20 than at age 8 (coefficient for the interaction of birth weight and time of observation = -0.0031, p = 0.02).

Considering diastolic pressure, the relationship with birth weight was not statistically significant at age 8, with the best estimate of effect being that a one kilogram increase in birth weight was associated with a 0.5 mm Hg decrease in diastolic pressure

(section 5.2). At age 20, the same increase in birth weight was associated with a decrease in diastolic pressure of 2.0 mm Hg (section 6.2). The formal test of whether these effects are of different size, carried out in the manner described above, found no statistically significant difference between them (coefficient for the interaction of birth weight and time of observation = -0.0014, p = 0.22).

Among males, there was evidence of relationships between ponderal index and total cholesterol, LDL cholesterol and the ratio of HDL to LDL at both 8 and 20 years (sections 5.3 and 6.3). Tests of the amplification of these effects were undertaken using data for the 297 males who were seen at both time points, in the manner described above, with adjustment for age in months and weight at age 8, and adjustment for age in months and body mass index at age 20. There were no statistically significant differences in the magnitudes of the effects at age 8 and age 20.

Chapter 7
Discussion

7.1 Overview of results

In this Australian cohort, there was evidence of relationships between birth dimensions and later blood pressure. There was also evidence that birth characteristics were related to later lipid profiles.

At age 8, for boys and girls together, relationships between birth weight and blood pressure were weak and not statistically significant: among those born at term, a one kilogram increase in birth weight was associated with a decrease in systolic pressure of 0.7 mm Hg (95% CI -1.0 to 2.4), after adjustment for current weight. However, there was some evidence of simultaneous effects of birth weight and placental weight, the latter variable being positively associated with blood pressure at age 8. Head circumference at birth was inversely related to blood pressure in mid-childhood, but neither thinness nor shortness at birth were observed to predict blood pressure at this time.

At age 20, among males, there was little evidence of relationships between birth dimensions and current blood pressure. Among those born at term, a one kilogram increase in birth weight was associated with a decrease in systolic pressure of 1.3 mm Hg (95% CI -1.0 to 3.6), after adjustment for current weight and age; as the confidence interval shows, this relationship was not statistically significant.

In contrast, among females at age 20 there was considerable evidence that birth characteristics were related to current blood pressure. Among those born at term, a one kilogram increase in birth weight was associated with a decrease in systolic pressure of 4.4 mm Hg (95% CI 2.1 to 6.7), after adjustment for current weight and

height. Amplification of the relationship between birth weight and systolic pressure had occurred between age 8 and age 20. In addition, there was evidence that each of the birth phenotypes specified by Barker were linked to later blood pressure. Placental weight was positively related to blood pressure when considered simultaneously with birth weight (although this relationship did not achieve statistical significance). Thinness at birth, as indicated by ponderal index, was associated with elevated blood pressure in early adulthood. There was also a suggestion (not statistically significant) that blood pressure at age 20 was elevated among women who had been short at birth with a large head circumference compared to their chest.

Blood lipids were also assessed during childhood and in early adulthood. At age 8, for boys and girls together, thinness at birth was associated with elevated total cholesterol and LDL cholesterol concentrations, and with relatively low HDL cholesterol. Those who had been short at birth with a large head circumference relative to their chest also tended to have elevated concentrations of total and LDL cholesterol. These relationships were observed among children born at term, after adjustment for sex, current weight and age.

At age 20, the relationships between birth characteristics and concentrations of total and LDL cholesterol that were seen at age 8 were again evident in young men born at term, after adjustment for current weight and age. Thus both shortness and thinness at birth were linked to elevated total and LDL cholesterol concentrations in young men. However, these patterns were not observed among women at age 20, with the possible exception of an association (not statistically significant) between the short birth phenotype and LDL cholesterol, adjusted for current weight and height.

The magnitudes of the associations between birth dimensions and later blood pressures and blood lipids were not affected by socio-economic status, nor were relationships at age 20 influenced by current behaviours relevant to cardiovascular risk factors,

including smoking habit, alcohol consumption, discretionary salt practices, relative fat intake, and exercise level. Current body size was taken into account in some form in all analyses to control for confounding from this source.

Some of the results tendered here did not achieve conventional statistical significance. Whether or not these results constitute supportive evidence is a matter of judgement. The view that non-statistically-significant findings are noteworthy is taken here when positive results (with a likelihood of being false positive of up to 20 per cent) arose from analyses guided by *a priori* hypotheses and from analyses in which power (and hence the ability for a genuine effect to reach conventional statistical significance) was greatly compromised through stratification or modelling of interactions. This broader interpretation of the nature of evidence follows from many discussions of the role of significance tests in epidemiology which highlight the dependence of p-values on the sample size, the inappropriateness of mechanically applying p-values as decision rules, and the greater importance of the magnitude of the effect (see Poole 1987). Adopting the stance of Susser (1977), Rothman (1986) and others, the probability value indicates the likelihood that a finding was due to chance under the conditions of the null hypothesis and, as such, is informative even when the conventional 0.05 significance level is not attained.

7.2 Limitations of study design

This study had two parts. In the first part, new analyses were undertaken using existing data from a cohort established when members were aged 8. For the second part, a follow up of cohort members was undertaken to collect new data pertaining to cardiovascular risk factors at age 20. Aspects of the study design that need to be considered now are the nature of the cohort, the completeness of the follow up, and the quality of the data.

The cohort was based on births in the Queen Victoria Hospital, in Adelaide, South Australia, during 1975-76. Use of one hospital has the limitation that the hospital may only capture part of the relevant population and not the full spectrum. At that time, the Queen Victoria Hospital was the biggest maternity hospital in South Australia. It was a private hospital but both private and public patients delivered there, in roughly equal proportions. The hospital had a tertiary role in the mid-1970s, which led to the formation of a high risk pregnancy service in 1978, but high risk cases would have contributed to a small fraction of the cohort.

The cohort established at age 8 comprised less than 50 per cent of those children notionally able to become members. Nevertheless, in terms of sex, gestational age at birth, birth weight, and mother's age at the time of giving birth, cohort members were similar to those who could have been included in the cohort but for various reasons were not. Cohort members also appeared to be similar to newborns in South Australia as a whole with repect to the distribution of birth weight. The study subjects would thus seem to be similar to the wider community with regard to birth characteristics, the independent or exposure variables in this study.

Cardiovascular risk factor profiles of study subjects at age 8 and age 20 were similar to those of other samples at comparable ages, suggesting that with regard to the outcome variables the cohort was also not unlike the wider community. However, in other respects the cohort was not representative of general population. In particular, the proportion of subjects from relatively high socio-economic backgrounds was considerably greater within the cohort than in South Australia generally. This discrepancy was evident at age 8 and became more marked over time, as non-participation at age 20 was greatest among subjects of low socio-economic status. Despite the under-representation of individuals from the poorest circumstances, there were still sufficient numbers of such subjects to enable meaningful comparisons within the cohort.

By age 20, only one per cent of subjects enrolled in the cohort at age 8 had withdrawn or died. At the end of the follow up study, only two per cent of the remaining cohort members could not be traced; the remainder were all invited to participate in the follow up and 73 per cent chose to do so. This represents a considerable achievement, greatly facilitated by the contact with cohort members that Dr Richard Cockington maintained over the intervening years. By way of comparison, Shean, de Klerk, Armstrong et al. (1994) reported on a contemporary Australian longitudinal study in which 12-year-old school children given anti-smoking education were enrolled. In the follow up undertaken 7 years later, 68 per cent of the original participants were traced and 53 per cent of those traced responded to a survey about smoking behaviour.

Although cohort members who took part in the follow up at age 20 had slightly different distributions of sex and childhood socio-economic factors compared with non-participants, these groups were similar with respect to previously recorded variables of primary interest, including birth weight and cardiovascular risk factors at age 8.

Overall, therefore, the cohort appears to be reasonably representative of the wider community in terms of the main exposure variables and the outcomes of interest at age 8 and age 20. The cohort is unlikely to be representative in other respects, as indicated by the documented over-representation of individuals from families with relatively high social position. However, the analyses reported in this thesis are based on comparisons within the cohort. Bias will only have been introduced if the relationships of interest are different among individuals born in another hospital, or different among those who did not become cohort members although they were born in the Queen Victoria Hospital in the required time period, or different among cohort members who did not participate at age 20. The occurrence of systematic differences in these groups seems unlikely.

Another consideration relating to the nature of the cohort is the sample size and the implications of this for statistical power to detect effects of interest. With regard to the straightforward analyses of effects of birth weight on blood pressure at age 8, a sample of approximately 780 is theoretically required to detect a 2 mm Hg difference in systolic pressure per kilogram change in birth weight with power of 80 per cent (based on the conventional 0.05 level of statistical significance, a birth weight distribution with mean 3380 g, sd 550 g, and a blood pressure distribution with mean 101 mm Hg, sd 11 mm Hg) (Machin & Campbell 1987). At age 20, a sample of approximately 190 is theoretically required to detect a 4 mm Hg difference in systolic pressure per kilogram change in birth weight (based on the same birth weight distribution but a blood pressure distribution with mean 120 mm Hg, sd 9 mm Hg). Power was thus theoretically adequate at both ages. (Stratification by sex at age 20 meant that the effective sample size was approximately 290.) However, tests of interactions demand a large sample size to maintain power at 80 per cent, commonly estimated as at least 4 times the size needed to detect the univariate effects (Breslow & Day 1987). Thus the samples available had limited power to detect interaction effects, which, as explained earlier, is why the emergence of such patterns was considered noteworthy even when conventional statistical significance was not achieved.

The remaining issue of study design concerns the quality of the data. The exposure variables were based on measurements made at birth, obtained from hospital records. Complete details were retrieved for 96 per cent of subjects, but the measurements were routinely made, outside of a research context. It seems likely, however, that some degree of standardisation of measurements would have been gained through basing the study on births in one hospital in a narrow period of time. Random errors and imprecision in birth measurements will have the consequence of diluting effects of interest; the extent of this potential problem cannot be ascertained.

The first part of the present study involved re-analysis of existing data pertaining to study subjects at 8 years of age. These data, primarily values of blood pressure and blood lipids, are presumed to be of high quality since they were collected in a research setting, for a project conducted in collaboration with the World Health Organisation. The main limitation entailed in the use of this existing data is an absence of information on factors which may be potential confounders in the current study. In particular, information about childhood diet and exercise would have been desirable. This lack is probably not important, however, as the literature review suggested that any influences of these factors on childhood blood pressure and blood lipids would be difficult to discern, and would probably be encapsulated in the measurements of body size. Other investigators of relationships between birth measurements and cardiovascular risk factors in childhood have not seen a need to take childhood behaviours into consideration.

In the follow up at age 20, cardiovascular risk factors were assessed as well as relevant behavioural practices. The repeatability study showed that the anthropometric measurements and the blood pressure readings were of high quality, and the lipid measurements were made to international standards. The blood pressure readings may suffer from being made in a clinical setting with a blood test impending (Stewart & Padfield 1994; Pickering 1996), but home visits (Aylett 1996) to avoid possible "white coat" effects were not feasible within the study resources.

Another limitation of the data at age 20 relates to the behavioural practices which were of interest as potential confounding variables. Smoking habit, alcohol consumption, discretionary salt practices, relative fat intake and exercise level were all ascertained through responses to a questionnaire. As well as being based on self-reports, the classifications available through this means were in most instances fairly broad. Thus the behavioural data are arguably susceptible to bias and lacking in sensitivity. In defence, the compromise struck between accuracy and resources (of the investigator

and the subjects) was based on epidemiological precedents: the questions and classifications were standard ones, developed, validated, and used in analyses elsewhere (Risk Factor Prevalence Study Management Committee 1990; Dobson, Blijlevens, Alexander, et al. 1993).

Multiple indicators of socio-economic economic status were used to characterise the social position of the subject and his or her family at three different time points. Each indicator has its strengths and limitations in the present context. Standard classifications of education and occupation, which have well-established validity as indicators of socio-economic status and allow comparisons with other samples, were used. However, since relatively few categories are available within these variables, the indices may be rather insensitive, and the potential for residual confounding remains. The indicators based on the postcode of residence allowed much finer discrimination between subjects, but could have been blunted through being pertinent to an area, with the possibility remaining that the subject's family was atypical of households in the area. Despite this inherent problem, socio-economic indices based on area of residence have been informative in a range of health contexts in Australia (Gordon, Christie & Robinson 1989; Slade, Spencer, Davies, et al. 1996; Jonas, Roder & Chan 1992; Shelly, Irwig, Simpson, et al. 1994), and several authors have argued that area measures capture an important independent aspect of socio-economic status (Carstairs & Morris 1989; Locker 1993).

Birth weight was only weakly related to measures of socio-economic status in the present study. Other Australian studies of births in roughly the same era yield mixed findings with regard to the strength of this relationship (Lumley, Correy, Newman, et al. 1985a; Morrison, Najman, Williams, et al. 1989; Jonas, Roder & Chan 1992). As discussed by Bell and Lumley (1992), this may be explained by an interaction between social position and maternal smoking, with the influence of socio-economic status on

pregnancy outcomes in contemporary Australian society being modest overall but quite dramatic among smokers (Lumley, Correy, Newman, et al. 1985b).

Since birth weight did not vary greatly with socio-economic status in the present study, it was unlikely that relationships between birth dimensions and later cardiovascular risk factors would simply reflect the continued influence of adverse social circumstances. That relationships between birth dimensions and later cardiovascular risk factors prevailed regardless of which index of socio-economic status was taken into account provides further grounds for believing that the relationships did not arise solely through covariation of both factors with socio-economic status.

7.3 Concordance with previous results and the fetal origins theory

An inverse relationship between birth weight and blood pressure in both childhood and adulthood has been substantiated in studies from around the world, as reviewed by Law and Shiell (1996). In the present study, the relationship between birth weight and systolic pressure at age 8 was weaker than the average for children from the meta-analysis of Law and Shiell. In view of the amount of existing evidence, the weakness of the effect in the present study may indicate some problem with the data available, rather than an absence of a genuine effect. Considerable random error in birth weight or blood pressure measurements or residual confounding are possible explanations which should be borne in mind when evaluating the evidence for other aspects of the fetal origins theory.

At age 20 there was a clear relationship between birth weight and blood pressure for females, of about the same magnitude as seen in other samples of adults in the review of Law and Shiell (1996). The effect for males was much weaker. This may have been because there is considerable individual variation in the age at which full biological maturity is achieved, with males tending to lag behind females (Tanner

1990). Judging from their physical appearance, a proportion of males in the cohort had not completed adolescent growth, so that perturbations in blood pressure that occur during adolescence (Lever & Harrap 1992) may have persisted. Another possibility is that males may have been affected to a greater extent than females by the conditions under which the blood pressure readings were made. The repeatability study cannot assess this possibility since the sample of males therein was small and no-one in that study was facing a blood test. Within the cohort, young men were informally observed to have been more apprehensive and more likely to feel faint than young women, and the difference between the first and the second blood pressure readings tended to be greater in males than females (for systolic pressure the mean difference among males was 2.8 ± 8.3 mm Hg, while that for females was 2.4 ± 7.6 mm Hg) possibly implying a larger degree of random error in blood pressure values for males. Again, since the accumulated international evidence supports the existence of an inverse relationship between birth weight and blood pressure in males, the weakness of the effect within this study may serve to indicate possible situation or age-related problems.

Among females, the relationship between birth weight and blood pressure was stronger at age 20 compared with age 8. This is the first longitudinal study to examine the development of this relationship between childhood and early adulthood. It is theoretically possible that this finding is an artefact of more accurate measurement of blood pressure at the later age, and to some extent this may be the case, given that the relationship at age 8 was weaker than expected from the literature. However, even if the magnitude of the effect at age 8 was closer to that seen in other samples of children, it would still be less than half the size of the effect observed at age 20. It is interesting that the detailed examination of amplification by Whincup, Cook, Papacosta, et al. (1995), in which blood pressure was assessed in a group of children at age 5 to 7 years and again at age 9 to 11 years, revealed amplification only in connection with

systolic pressure and more pronounced amplification in girls than in boys. This was basically the case in the present study also.

Turning to the different phenotypes and their role in later blood pressure, there was some evidence from all children at age 8 and from females at age 20 that birth weight and placental weight jointly influenced later blood pressure, with discrepancies between the two associated with elevated blood pressure. The first reported occurrence of this pattern, in the Preston cohort (Barker, Bull, Osmond, et al. 1990), was the clearest finding and no subsequent investigation has corroborated the strength of that finding. Indeed, several studies of children found the opposite form of relationship between placental weight and blood pressure. The patterns seen in the present study are consistent with Barker's proposition, but only weak. Together with the inconsistent results from other studies, this makes it difficult to argue that there is important additional information about later blood pressure contained in placental weight. However, it may be that the conditions under which placental weight is an eloquent marker for later blood pressure abnormalities are not fully understood. It is also possible that effects may be amplified over time (although that was not the case in this study), so that studies of children and young adults fail to convey the importance of placental weight.

Neither thinness nor shortness at birth were linked to blood pressure at age 8. Given the general weakness of relationships with birth weight in this and other samples of children, this is perhaps not surprising. However, among females at age 20 there was good evidence that thinness at birth was associated with elevated blood pressure in later life. Shortness at birth was also associated with later blood pressure, but less clearly. To the extent that the shortness findings may be accepted as evidence, then Barker's proposal that both these phenotypes are linked to elevated blood pressure in later life is supported. These results are consistent with those from Preston (Barker, Godfrey, Osmond, et al. 1992). The three-dimensional figures presented herein

highlight the mathematical problem entailed in an investigation of effects of both shortness and thinness at birth occurring within one cohort, since both involve birth length but in opposing directions. Given this complicated situation, it is possible that both effects are actually present in other cohorts, but one tends to swamp the other, creating an apparent lack of consistency in findings.

Turning to blood lipids, the literature review disclosed a lack of coherence in existing results. Against this background, the findings of the present study offer some unifying insights. Thinness at birth was related to concentrations of total and LDL cholesterol in both childhood and early adulthood more strongly than the other birth phenotypes. This is in accordance with Barker's proposal that thinness at birth is most relevant to later lipid profiles. In the Sheffield cohort (Barker, Martyn, Osmond, et al. 1993), effects of both thinness and shortness at birth on later lipid profiles were present, with the effect of thinness dominant. To date, no study had confirmed both findings, but in the present study shortness at birth accompanied by a relatively large head was linked to elevated total and LDL cholesterol in later life. The three-dimensional diagrams displaying the joint relationship between length and relative head size at birth have a saddle form, with a channel of relatively low total or LDL cholesterol values running down the middle, suggesting that babies with symmetrical proportions - small or otherwise - were not at increased risk of elevated total or LDL cholesterol in later life. This may explain why birth weight has not been strongly related to lipid profiles in previous studies. Again, the opposing nature of the shortness and thinness relationships makes it possible that similar results have been overlooked in other studies, as the effects could easily obscure each other.

There were still several inconsistent and inexplicable aspects to these findings, however. Thinness at birth was positively related to HDL cholesterol in childhood but not in early adulthood, and effects of birth characteristics on lipid concentrations were largely absent in young women. The study of Hertfordshire women (Fall, Osmond,

Barker, et al. 1995) had previously linked birth weight to later HDL cholesterol, so there is a precedent for the present finding, but it is puzzling that a relationship was not evident at both time points. Based on the Sheffield study (Barker, Martyn, Osmond, et al. 1993), similar results for men and women would be expected, although results for men and women have differed in other studies. It is difficult to know how to interpret these results. They may point to unidentified confounding or they may reflect an absence of genuine effects and hence possibly explain differences in cardiovascular disease experience between men and women.

7.4 Implications

In the present study, effects of fetal growth, as indicated by birth dimensions, on later blood pressure and blood lipids were small, particularly at age 8. On the basis of similar findings, Taylor, Whincup, Cook, et al. (1997) argued that childhood obesity was a more important determinant of childhood blood pressure than birth size. However, as previously pointed out by Barker, Law and Osmond (1991), differences in blood pressure associated with variation in current body mass decrease with age, whereas relationships with birth characteristics appear to strengthen. In the Preston cohort at age 50, routine birth measurements predicted adult blood pressure better than current body measurements or any adult lifestyle factor (Barker, Bull, Osmond, et al. 1990). Similarly, in the Sheffield cohort, thinness at birth was related to serum lipids at age 50 more strongly than current body size (Barker, Martyn, Osmond, et al. 1993). Amplification of the relationship between birth weight and blood pressure observed among females in the present study supports the argument that fetal growth is increasingly pertinent to cardiovascular risk and thus small effects seen at relatively young ages are noteworthy.

At this stage of development of the fetal origins theory, the implications for further research are considerably greater than the implications for public health and clinical

practice. Nevertheless, implications other than for research deserve consideration. Broadly, these relate to our understanding of risk factors for cardiovascular disease and current and potential strategies for managing cardiovascular disease risk.

Under the adult lifestyle paradigm for chronic disease, adult behaviours are the primary factors which have an impact on the likelihood of experiencing a cardiovascular disease event. Established modifiable risk factors include body weight, smoking habit, fat consumption and exercise level. The fetal origins theory is not incompatible with a strong role for adult lifestyle factors, and for contemporary adult populations the lifestyle understanding should certainly continue to form the basis of prevention efforts.

Although the predisposition to cardiovascular disease associated with birth size cannot be changed for individuals now in adulthood, there is a case to be made that individuals have a right to this additional information about their risk. Targetted approaches to risk reduction are an established part of prevention policies and programs, and an early life element could be included within this. Those at higher risk of cardiovascular disease through low birth weight could at least be more aware of the need to monitor symptoms. Such people would also have more reason to act in relation to adult lifestyle factors that could still be modified to reduce the likelihood of a cardiovascular disease event. This would be beneficial even presuming that risks acquired at different stages of life are simply additive. New research which suggests that adult factors, particularly obesity, interact with birth size (Leon, Koupilova, Lithell, et al. 1996) makes the case for action based on early life markers a more powerful one.

The fetal origins theory has led to a greater appreciation of the way disease propensities are acquired over the whole of life, not solely through adult behaviours. To be sure, there had been considerable interest in cardiovascular risk factors in children from the

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early 1980s, but the focus was very much on specific behaviours such as exercise and eating habits. Debate surrounding the fetal origins theory has generated new research concerning the childhood socio-economic environment, in many cases showing a long-term impact, and the theory specifically draws attention to growth and health in very early life. There are suggestions in the literature (Barker 1994), not explored in this thesis, that catch-up growth after birth may ameliorate some of the disadvantages of poor fetal growth. In the event that further evidence bears this out, there will be renewed reason to support the already recognised need for good nutrition during childhood.

Even at this early stage, the fetal origins theory would seem to have some theoretical and practical implications relevant to the pre-birth period. Firstly, the theory encourages a reconceptualisation of the problem of low birth weight (and poor fetal growth more generally), from a short-term condition requiring acute management to one that appears to be relevant in the longer term. From this perspective, the continuum of birth weight is of more interest than cut-offs such as 2,500 grams which are presently emphasised. With this new understanding comes an overwhelming need to respond preventively and to place less reliance on drugs and technologies that can be applied around the time of birth to overcome a seemingly temporary health risk. A response to low birth weight and associated problems once it has occurred will not redress unobtrusive physiological changes that are thought to be responsible for increased risk of cardiovascular disease in the longer term.

Recommendations to pregnant women, with the aim of improving growth of the baby, cannot yet be made on the basis of the fetal origins theory. However, existing knowledge about the immediate threats to health and survival that low birth weight entails has already led to substantial efforts to prevent low birth weight. These efforts may well encompass some of the factors that may eventually be shown to underlie long-term adverse health outcomes. For example, maternal smoking is clearly and

strongly linked to low birth weight (Kramer 1987) and is addressed both routinely and through special programs, albeit with only partial success (Lumley 1987; 1991). Maternal smoking during pregnancy has recently been associated with elevated blood pressure in children at age 8 (Morely, Leeson Payne, Lister, et al. 1995), a finding which only reinforces the need to keep working on this well recognised but stubborn problem.

Barker and his colleagues suspect that maternal nutrition is a primary factor underlying poor fetal growth (Godfrey & Barker 1995). Components of maternal diet that specifically contribute to fetal growth have not thus far been clearly identified, although the balance between protein and carbohydrate intake may be important (Campbell, Hall, Barker, et al. 1996; Godfrey, Robinson, Barker, et al. 1996). A nutritious diet in a general sense has long been promoted for pregnant women but, like smoking cessation, may be hardest to achieve among women with the greatest need.

Responses directed towards individual pregnant women carry with them a danger of further medicalising pregnancy (Oakley 1982) by extending the range of individual behaviours, risk indicators and health outcomes which fall within the domain of routine medical practice. Furthermore, by stressing the importance of fetal growth for life-long health there is created an additional responsibility for potential mothers; failure in fulfilment of which may result in women being blamed for the poor health of their children. Romito and Hovelaque (1987) have discussed in depth how presenting information to pregnant women in order to address various risk factors for poor neonatal outcomes insidiously implies the women are responsible. These authors emphasise that a woman's ability to use such information is circumscribed by her society and there is, therefore, an over-riding social responsibility to improve the education and social position of women. Taking a more limited view of the circumstances necessary for women to be able to make use of information provided to

them, Elbourne, Oakley and Chalmers (1989) have demonstrated the importance of social and psychological support.

As with many public health problems, substantial improvements among those with the greatest need, including women in developing countries and women from ethnic minorities, especially indigenous groups, once again depends greatly on social and structural changes. Admittedly, for these communities there are many more immediate problems requiring attention, and the remote effects of poor fetal growth may well appear to be of lesser importance. In this context, the long-term consequences of poor fetal growth may provide a forceful reason to comprehensively address the education and living standards of these groups, rather than accepting a piecemeal approach to shorter-term problems. At this point it is worth reflecting on the fact that a direct connection between fetal growth and later cardiovascular disease risk would by no means deny a role for socio-economic status. Rather, the fetal origins theory may constitute new understanding of the paths by which adverse social and economic circumstances have such profound effects on health, and a reaffirmation of the need to address social inequalities.

There are many areas where further research in relation to the fetal origins theory would be fruitful. Broadly, studies are required to further clarify the role of fetal growth in later disease, to specify the underlying mechanisms, and to define opportunities for prevention.

There is still a need for epidemiological studies in diverse countries to investigate associations between indices of fetal growth and later risk factors or disease outcomes. Such studies should be directed towards understanding the inconsistencies present in the existing body of results, either elaborating on the conditions under which similar results are found or providing grounds for rejecting certain tenets of the fetal origins theory. As with any novel elucidation of aetiology, single studies are seldom

conclusive and evidence must be garnered from many sources. In this regard, another follow up of the Adelaide cohort may be informative. Of particular interest would be whether the patterns of association with birth characteristics seen at age 20 were maintained further into adulthood, whether differences in effects among males and females persisted, and whether amplification of effects occurred. In the light of the findings of Leon, Koupilova, Lithell, et al. (1996) interactions between early life and adult factors also warrant investigation, in this and other cohorts.

The fetal origins theory attributes associations between birth characteristics and later disease to poor growth before birth and concomitant changes in physiology. Maternal nutrition is thought to be an important determinant of fetal growth. Ideally, epidemiological work now needs to move beyond a focus on birth size to more direct assessments of connections with underlying factors, especially altered physiology. Research in this direction presents methodological challenges and is daunting simply in view of the resources required: the necessary data are unlikely to be available for existing cohorts and prospective studies are thus called for. These studies may also provide a means to investigate whether enhanced growth in early childhood is able to compensate for poor fetal growth, an exciting possibility.

Animal studies appear to be the key to rapid progress in further elaboration of the fetal origins theory. As well as offering the most rigorous tests of the programming hypothesis through experimental manipulation, animal experiments of course avoid confounding by social class and risk-related behaviours. Laboratory work is presently being undertaken to address the question of whether pre-natal programming of physiological function occurs, and to investigate which system, tissue, cellular or molecular determinants of function have contributed to this. At the same time, the types of maternal factors that can be modulated to produce altered fetal growth and function are being explored (Owens, Kind, Sohlstrom, et al. 1996; Jackson 1996). Animal studies also appear to be the most expedient approach to investigating the role

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of timing of adverse experiences during gestation and the circumstances under which reversal of effects may occur.

7.5 Conclusion

In this study, aspects of the fetal origins theory of cardiovascular disease were addressed in an Australian setting. The study investigated whether fetal growth, particularly disproportionate growth, was associated with cardiovascular risk factors in an Adelaide-based cohort.

Overall the findings were mixed and the study does not give unequivocal support to the fetal origins theory. Nevertheless, there was evidence that poor fetal growth was associated with later cardiovascular risk factors. In women, disproportions at birth as well as low birth weight were linked to elevated blood pressure in early adulthood. In men, disproportionate fetal growth, but not low birth weight, was linked to elevated concentrations of total and LDL cholesterol in early adulthood. Some of these associations were also evident in childhood, yielding a degree of consistency of results within the cohort. Moreover, the study is the first to provide evidence (in females) of amplification of the relationship between birth weight and blood pressure from childhood to early adulthood. Associations that emerged in the Adelaide cohort did not appear to be the product of confounding by behaviours that affect cardiovascular risk factors nor did they appear to be a consequence of social class variation.

With regard to Barker's (1995) suggestion that the thin baby is predisposed to later high blood pressure (and non-insulin dependent diabetes) whereas the short baby is at increased risk of high blood pressure and high cholesterol (and elevated fibrinogen), results from the Adelaide cohort do not support such a clear distinction. Thinness and shortness at birth were, under certain conditions, linked to both high blood pressure and high cholesterol.

This study possibly offers some insight regarding apparent inconsistencies in results from other studies. Both short and thin babies were prone to unfavourable cardiovascular risk factor profiles in the Adelaide cohort, and both birth phenotypes may be important in other cohorts, but the simultaneous identification of these effects is analytically problematic.

Further evidence from other adult cohorts containing detailed birth information, rather than birth weight alone, would be most desirable. In such cohorts it would be of particular interest to examine whether birth disproportions, but not low birth weight, were related to adult lipid concentrations. The similarity or otherwise of results for men and women also deserves further attention, since it may explain sex differences in cardiovascular disease experience.

This study does not provide information on underlying causes of the associations. Prospective studies of pregnant (or pre-pregnant) women are justifiable on the basis of the international evidence for a relationship between birth weight and blood pressure alone, but should also consider causes of birth disproportions. Close attention to animal studies is warranted, for more evidence of associations, possible mechanisms, and clues as to underlying influences.

Finally, the existing evidence from the Adelaide cohort is sufficiently intriguing for another follow up to be considered in the future. Consistency and amplification of results further into adulthood would be of considerable interest.

Appendix A

Letters and form sent to the study subjects at age 20

March 1995

Adelaide Children's Hospital Family Heart Study
Time to see you now!

Dear

I am writing to seek your continued support for the Adelaide Children's Hospital Family Heart Study. Your participation to date has provided valuable insights as to reasons why some people suffer from heart disease in later life, and once again I thank you for this.

Recent international research has raised a new possibility that the growth pattern of a baby before it is born (as indicated by its birth measurements), as well as growth in early childhood, is related to later blood pressure and risk of heart disease in adult life. This possibility is of great interest to Professor Jeffrey Robinson of the Department of Obstetrics and Gynaecology at the University of Adelaide. I mentioned some preliminary research on this topic from our data in past newsletters. Further analysis by Vivienne Moore, a PhD student of Professor Robinson's, has shown that in our study group at eight years blood pressure is related to birth size. This relationship was not found in the data collected from the small group at 15 years. We are keen to know whether this relationship reappears at age 19 to 20. With your assistance, we would like to be among the first in the world to investigate this relationship in a group of children followed through to adulthood.

Together with Professor Robinson and Vivienne Moore, I would like to continue research on this important question, and am pleased to inform you that we have been successful in obtaining funding to support this research. **We are therefore seeking your co-operation in the next round of examinations which are being conducted this year.**

What is involved

At this stage, we would like to see the young adult who was originally part of the study as a child. As before, completion of a mailed questionnaire will be required, followed by the conduct of a clinical examination, expected to take about 20 minutes, including measurement of height, weight, blood pressure and skin fold thickness and the taking of a blood sample. It will be necessary to fast overnight but breakfast will be provided.

The examinations will be carried out at the Adelaide Children's Hospital by Sister Margaret Logan, whom you met before. Clinics will be held on Monday, Tuesday and Thursday mornings, with some Saturday morning times available for those who cannot attend during the week.

What you need to do

Please fill out the enclosed form and return it in the reply paid envelope provided. This form is to let us know whether you would like to be involved in the follow up and when the most suitable time for an examination would be. Sister Logan will then contact you to confirm the appointment.

We do hope that you will decide to take part in this follow up. If you have any questions about the study or the examination, please do not hesitate to contact either myself or Sister Logan on 204-7359.

Yours sincerely,

RICHARD A COCKINGTON
Director
Ambulatory Paediatric Services

Adelaide Children's Hospital Family Heart Study

Please complete this form and return it in the reply-paid envelope.

Name ....

Please tick one of the boxes below to let us know whether or not you would like to be involved in the follow up.

I would like to be involved in the follow up   ❑

or

I do not wish to be involved in the follow up ❑

If you would like to be involved, please complete the section below.

The best day for my appointment at the Adelaide Children's Hospital would be:

Monday ❑   Tuesday ❑   Thursday ❑   Saturday ❑

The best time would be:

7:00 am ❑   7:30 am ❑   8:00 am ❑   8:30 am ❑

9:00 am ❑   9:30 am ❑   10:00 am ❑   10:30 am ❑

We will need to contact you to confirm the time for your appointment.

Please provide a telephone number where we can reach you, preferably during the daytime.

During the day I can be contacted on .... ☎

In the evening I can be contacted on .... ☎

Women's and Children's Hospital
ADELAIDE

Incorporating:
Adelaide Children's Hospital
Queen Victoria Hospital

ADELAIDE CHILDREN'S HOSPITAL

72 King William Road
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South Australia 5006

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AMBULATORY PAEDIATRIC SERVICES
DR. RICHARD A. COCKINGTON
MBBS,MSc,MPH,FRACP,FRACMA,FACEM,FAFPHM,DObstRCOG
DIRECTOR

Adelaide Children's Hospital Family Heart Study
Reminder that it's time to see you now!

Dear

A short time ago you should have received an invitation to take part in the next round of examinations for the Adelaide Children's Hospital Family Heart Study. This next stage of the study will further our understanding of heart disease, and is especially important as you have been involved before and have now reached adulthood. The valuable data we already have regarding you and your family will become more significant if we can obtain follow-up data now you are an adult.

If you have already returned the reply form, please accept our thanks and disregard this letter. We will be in touch. However, if you haven't done so, please fill in and post the reply form today.

Yours sincerely,

RICHARD A COCKINGTON

Appendix B

Questionnaire completed by subjects in the follow up at age 20

ADELAIDE CHILDREN'S HOSPITAL FAMILY HEART STUDY

QUESTIONNAIRE FOR 1995-96 FOLLOW-UP

PLEASE COMPLETE THIS QUESTIONNAIRE AND BRING IT WITH YOU TO THE FOLLOW-UP CLINIC.

Please indicate your answer by ticking the appropriate box or by writing your answer in the space provided.

Please use block letters.

If you are uncertain about the answer to any question, leave it blank and ask the nurse for help at the follow-up clinic.

Please <u>ask your parents</u> for the answers to the last five questions.

Please do not write in the far right hand column of each page.

Name _____

DOB □□□□□□

1. **Date of birth:** __ __ / __ __ / 19 __ __

2. **Sex:**

   Male □ 0

   Female □ 1

   SEX □

3. **Postcode of your usual place of residence:** __ __ __ __

   POSTCODE □□□□

4. **Please indicate the highest level of education you have attained.**

   Some high school □ 1

   Completed high school (Year 12 or equivalent) □ 2

   Some university, CAE or other tertiary institution □ 3

   Completed university, CAE or other tertiary qualification □ 4

   EDUC □

5. **Which of the following describes your current employment status?**
   Please tick more than one box where applicable.

   Working full-time □ 1

   Working part-time □ 1

   Unemployed □ 1

   Home duties □ 1

   Full-time student □ 1

   Part-time student □ 1

   Permanently unable to work / ill □ 1

   Other (please specify)

   .... □ 1

   WKFT □

   WKPT □

   UNEMP □

   HOME □

   STUDFT □

   STUDPT □

   UNABLE □

   OTHWK □

If you have a full-time or part-time job of any kind, please answer Questions 6 and 7; otherwise go to Question 8.

6. **In your main job, what is your occupation?**
    Give full title. (For example, civil engineering draftsman, accounts clerk, fast foods cook. Armed Services personnel state rank as well as occupation. Public Servants state official designation (e.g. ASO3) as well as occupation.)

    ....   JOB ☐☐☐☐☐☐

7. **What are the main tasks or duties that you usually perform in that occupation?**
    Describe as fully as possible. (For example, preparing drawings for dam construction, recording and paying accounts, cooking hamburgers and chips.)

    Tasks or duties ....

    ....

Concerning your FATHER:

8. **What is the usual occupation of your father?**
    (If your father is not working at present or has retired or died, please give the occupation he used to have.)

    ....   FJOB ☐☐☐☐☐☐

9. **What level of education has your father attained?**
    (If your father has died, please give the highest education level he had.)

Never attended school	☐	1
Primary school	☐	2
Some high school	☐	3
Completed high school (Year 12 or equivalent)	☐	4
Some university, CAE or other tertiary institution	☐	5
Completed university, CAE or other tertiary qualification	☐	6
Not known	☐	8

    FEDUC ☐

10. **What suburb or town does your father now live in?**

Not known ☐

Father is deceased ☐

Suburb or town: .... State: ....

FPCODE ☐☐☐☐

Concerning your MOTHER:

11. **What is the usual occupation of your mother?**
(If your mother is not working at present or has retired or died, please give the occupation she used to have.)

....

MJOB ☐☐☐☐☐☐

12. **What level of education has your mother attained?**
(If your mother has died, please give the highest education level she had.)

Never attended school ☐ 1

Primary school ☐ 2

Some high school ☐ 3

Completed high school (Year 12 or equivalent) ☐ 4

Some university, CAE or other tertiary institution ☐ 5

Completed university, CAE or other tertiary qualification ☐ 6

Not known ☐ 8

MEDUC ☐

13. **What suburb or town does your mother now live in?**

Not known ☐

Mother is deceased ☐

Suburb or town: .... State: ....

MPCODE ☐☐☐☐

14. **Have you ever been told that you have any of the following?**

	No	Yes
High blood pressure	☐ 0	☐ 1
High cholesterol	☐ 0	☐ 1
High triglycerides	☐ 0	☐ 1
Diabetes - if yes	☐ 0	☐ 1

when? 19 __ __ (year)

HIBP ☐

HICHOL ☐

HITRIG ☐

DIABETES ☐

YRDIABET ☐☐

15. **Are you on medication for blood pressure?**

No ☐ 0   Yes ☐ 1

TRTBP ☐

16. **Are you having treatment to lower your blood fat / cholesterol?**

No ☐ 0   Yes ☐ 1

TRTBFAT ☐

17. **Have you ever been given advice or treatment for diabetes?**

No ☐ 0   Yes ☐ 1

If yes, please state the year this advice or treatment was first given: 19 __ __ (year)

Was this: Diet advice   ☐ 1

Tablets   ☐ 2

Insulin injections   ☐ 3

Diet advice and tablets   ☐ 4

Diet advice and injections ☐ 5

TRTDIAB ☐

YRTRTD ☐☐

TYPTRTD ☐

18. **Concerning your FATHER:**

Is your father alive?

No ☐ 0   If no, at what age did he die? __ __ years

Cause of death: ....

Yes ☐ 1

FALIVE ☐
FAGEDTH ☐ ☐
FCDTH ☐ ☐ ☐

Has your father ever suffered from any of the following?
(If your father is no longer alive, please tick any conditions he had when he was alive.)

	No	Yes	Don't know	
Heart disease, heart attack or stroke	☐ 0	☐ 1	☐	FHTDIS ☐
High blood pressure	☐ 0	☐ 1	☐	FHIBP ☐
High cholesterol	☐ 0	☐ 1	☐	FHICHOL ☐
Diabetes	☐ 0	☐ 1	☐	FDIAB ☐

19. **Concerning your MOTHER:**

Is your mother alive?

No ☐ 0   If no, at what age did she die? __ __ years

Cause of death: ....

Yes ☐ 1

MALIVE ☐
MAGEDTH ☐ ☐
MCDTH ☐ ☐ ☐

Has your mother ever suffered from any of the following?
(If your mother is no longer alive, please tick any conditions she had when she was alive.)

	No	Yes	Don't know	
Heart disease, heart attack or stroke	☐ 0	☐ 1	☐	MHTDIS ☐
High blood pressure	☐ 0	☐ 1	☐	MHIBP ☐
High cholesterol	☐ 0	☐ 1	☐	MHICHOL ☐
Diabetes	☐ 0	☐ 1	☐	MDIAB ☐

20. **Concerning your FATHER'S FATHER**
(your grandfather on your father's side of the family):

Is your father's father alive?

No ☐0   If no, at what age did he die? __ __ years   FFALIVE ☐

          Cause of death: ....   FFAGEDTH ☐☐

Yes ☐1   FFCDTH ☐☐☐

Has your father's father ever suffered from any of the following?
(If he is no longer alive, please tick any conditions he had when alive.)

	No	Yes	Don't know		
Heart disease, heart attack or stroke	☐0	☐1	☐	FFHTDIS	☐
High blood pressure	☐0	☐1	☐	FFHIBP	☐
High cholesterol	☐0	☐1	☐	FFHICHOL	☐
Diabetes	☐0	☐1	☐	FFDIAB	☐

21. **Concerning your FATHER's MOTHER**
(your grandmother on your father's side of the family):

Is your father's mother alive?

No ☐0   If no, at what age did she die? __ __ years   FMALIVE ☐

          Cause of death: ....   FMAGEDTH ☐☐

Yes ☐1   FMCDTH ☐☐☐

Has your father's mother ever suffered from any of the following?
(If she is no longer alive, please tick any conditions she had when alive.)

	No	Yes	Don't know		
Heart disease, heart attack or stroke	☐0	☐1	☐	FMHTDIS	☐
High blood pressure	☐0	☐1	☐	FMHIBP	☐
High cholesterol	☐0	☐1	☐	FMHICHOL	☐
Diabetes	☐0	☐1	☐	FMDIAB	☐

22. **Concerning your MOTHER's FATHER**
(your grandfather on your mother's side of the family):

Is your mother's father alive?

No ☐ 0   If no, at what age did he die? __ __ years

Cause of death: ....

Yes ☐ 1

MFALIVE ☐
MFAGEDTH ☐ ☐
MFCDTH ☐ ☐ ☐

Has your mother's father ever suffered from any of the following?
(If he is no longer alive, please tick any conditions he had when alive.)

	No	Yes	Don't know	
Heart disease, heart attack or stroke	☐ 0	☐ 1	☐	MFHTDIS ☐
High blood pressure	☐ 0	☐ 1	☐	MFHIBP ☐
High cholesterol	☐ 0	☐ 1	☐	MFHICHOL ☐
Diabetes	☐ 0	☐ 1	☐	MFDIAB ☐

23. **Concerning your MOTHER's MOTHER**
(your grandmother on your mother's side of the family):

Is your mother's mother alive?

No ☐ 0   If no, at what age did she die? __ __ years

Cause of death: ....

Yes ☐ 1

MMALIVE ☐
MMAGEDTH ☐ ☐
MMCDTH ☐ ☐ ☐

Has your mother's mother ever suffered from any of the following?
(If she is no longer alive, please tick any conditions she had when alive.)

	No	Yes	Don't know	
Heart disease, heart attack or stroke	☐ 0	☐ 1	☐	MMHTDIS ☐
High blood pressure	☐ 0	☐ 1	☐	MMHIBP ☐
High cholesterol	☐ 0	☐ 1	☐	MMHICHOL ☐
Diabetes	☐ 0	☐ 1	☐	MMDIAB ☐

Questions 24 to 27 are for FEMALES ONLY.

24. **Have you ever taken the oral contraceptive pill?**

No ☐ 0 --- *Go to question 27.*

Yes ☐ 1

OCEVER ☐

25. **For how long altogether have you taken the oral contraceptive pill?**
(Please estimate the total of all periods of use.)

Less than 6 months ☐ 1

Between 6 months and 2 years ☐ 2

Between 2 and 5 years ☐ 3

Longer than 5 years ☐ 4

OCDURN ☐

26. **Are you now taking the oral contraceptive pill?**

No ☐ 0

Yes ☐ 1

OCNOW ☐

27. **Are you now pregnant?**

No ☐ 0

Yes ☐ 1

PREGNANT ☐

In the next three questions we want to find out about the EXERCISE you had during the PAST 2 WEEKS:
- for recreation, sport or health-fitness purposes;
- as part of your tasks at work and around the house.

Please distinguish between vigorous exercise which made you breathe harder or puff and pant, and less vigorous exercise.

28. In the PAST 2 WEEKS did you engage in vigorous exercise - exercise which made you breathe harder or puff and pant?
(e.g. vigorous sports such as football, netball, tennis, squash, athletics; jogging or running; keep-fit exercises; vigorous swimming; etc.)

No ☐0   Yes ☐1   EXERCISE ☐

If yes, how many sessions of vigorous exercise did you have

over the 2 week period ? ....   EXSESS ☐☐

Please estimate the total time spent exercising vigorously

during the past 2 weeks: .... hours .... minutes   EXTIME ☐☐☐☐

29. In the PAST 2 WEEKS, did you engage in less vigorous exercise for recreation, sport or health-fitness purposes which did not make you breathe harder or puff and pant?

No ☐0   Yes ☐1   LOEX ☐

If yes, how many sessions of less vigorous exercise did you have

over the 2 week period? ....   LOEXSESS ☐☐

30. In the PAST 2 WEEKS, did you engage in vigorous activity, apart from exercise, which made you breathe harder of puff and pant?
(e.g. carrying loads, heavy gardening, chopping wood, labouring - at home, during employment or anywhere else.)

No ☐0   Yes ☐1   ACTIVITY ☐

If yes, how many sessions of this type of exercise did you have

over the 2 week period ? ....   ACTSESS ☐☐

Please estimate the total time spent in these types of vigorous exercise

during the past 2 weeks: .... hours .... minutes   ACTTIME ☐☐☐☐

31. **Have you ever smoked cigarettes, cigars or a pipe regularly?**

    No   ☐0   --- *Go to Question 36.*

    Yes   ☐1

    SMOKER ☐

32. **At what age did you start smoking regularly?**

    I started smoking at __ __ years of age.

    AGESMOKE ☐☐

33. **Have you given up smoking?**

    No, I still smoke   ☐   --- *Go to Question 35.*

    YRGIVUP ☐☐

    Yes, I gave up smoking in __ __ (month) 19 __ __ (year)

    MTHGIVUP ☐☐

34. **Before you gave up smoking, how much did you smoke?**
    (Note: A 1³/₄ ounce pouch of cigarette tobacco equals 50 grams.)

    I used to smoke   .... manufactured cigarettes a day

    PASTCIG1 ☐☐

                  .... manufactured cigarettes a week (if cigarette smoking was not daily)

    PASTCIG2 ☐☐

                  .... grams 'hand-rolled' cigarette tobacco per week

    PASTROLD ☐☐☐

                  .... cigars per week

    PASTCIGR ☐☐

                  .... grams pipe tobacco per week

    PASTPIPE ☐☐☐

    --- *Go to Question 36.*

35. **How much do you usually smoke?**
    (Note: A 1³/₄ ounce pouch of cigarette tobacco equals 50 grams.)

    I currently smoke   .... manufactured cigarettes a day

    CIGSNOW1 ☐☐

                  .... manufactured cigarettes a week (if cigarette smoking is not daily)

    CIGSNOW2 ☐☐

                  .... grams 'hand-rolled' cigarette tobacco per week

    ROLDNOW ☐☐☐

                  .... cigars per week

    CIGRNOW ☐☐

                  .... grams pipe tobacco per week

    PIPENOW ☐☐☐

36. **How often do you usually drink alcohol?**

I don't drink alcohol	☐ 1	--- *Go to Question 38.*
Less than once a week	☐ 2	
On 1 or 2 days a week	☐ 3	
On 3 or 4 days a week	☐ 4	
On 5 or 6 days a week	☐ 5	
Every day	☐ 6	

ALCFRQ ☐

37. **On a day when you drink alcohol, how many drinks do you usually have?**

1 or 2 drinks	☐ 1
3 or 4 drinks	☐ 2
5 to 8 drinks	☐ 3
9 to 12 drinks	☐ 4
13 to 20 drinks	☐ 5
More than 20 drinks	☐ 6

ALCPRDAY ☐

38. **Do you add salt to your food after it is cooked?**

Rarely or never	☐ 1
Sometimes	☐ 2
Almost always or always	☐ 3

SALT ☐

39. **How often do you eat fried food with a batter or breadcrumb coating?**

6 or more times a week	☐ 4
3 to 5 times a week	☐ 3
Once or twice a week	☐ 2
Less than once a week	☐ 1
Never	☐ 0

BATTER ☐

40. **How often do you eat gravy, cream sauces or cheese sauces?**

6 or more times a week ☐ 4

3 to 5 times a week ☐ 3

Once or twice a week ☐ 2

Less than once a week ☐ 1

Never ☐ 0

GRAVY ☐

41. **How often do you add butter, margarine, oil or sour cream to vegetables, cooked rice or spaghetti?**

6 or more times a week ☐ 4

3 to 5 times a week ☐ 3

Once or twice a week ☐ 2

Less than once a week ☐ 1

Never ☐ 0

ADDTOVEG ☐

42. **How often do you eat vegetables that are fried or roasted with fat or oil?**

6 or more times a week ☐ 4

3 to 5 times a week ☐ 3

Once or twice a week ☐ 2

Less than once a week ☐ 1

Never ☐ 0

FRIEDVEG ☐

43. **How is your meat usually cooked?**

Fried ☐ 4

Stewed or goulash ☐ 3

Grilled or roasted with added oil or fat ☐ 2

Grilled or roasted without added oil or fat ☐ 1

Eat meat occasionally or never ☐ 0

MEAT ☐

44. **How many times a week do you eat sausages, fritz, salamis, meat pies, hamburgers or bacon?**

6 or more times a week	☐ 4
3 to 5 times a week	☐ 3
Once or twice a week	☐ 2
Less than once a week	☐ 1
Never	☐ 0

SAUSAGES ☐

45. **How do you spread butter / margarine on your bread?**

Thickly	☐ 3
Medium	☐ 2
Thinly	☐ 1
Don't use butter or margarine	☐ 0

SPREAD ☐

46. **How many times a week do you eat chips or french fries?**

6 or more times a week	☐ 4
3 to 5 times a week	☐ 3
Once or twice a week	☐ 2
Less than once a week	☐ 1
Never	☐ 0

FRIES ☐

47. **How often do you eat pastries, cakes, sweet biscuits or croissants?**

6 or more times a week	☐ 4
3 to 5 times a week	☐ 3
Once or twice a week	☐ 2
Less than once a week	☐ 1
Never	☐ 0

CAKES ☐

48. **How many times a week do you eat chocolate, chocolate biscuits or sweet snack bars?**

6 or more times a week	4
3 to 5 times a week	3
Once or twice a week	2
Less than once a week	1
Never	0

CHOCOLAT ☐

49. **How many times a week do you eat potato crisps, corn chips or nuts?**

6 or more times a week	4
3 to 5 times a week	3
Once or twice a week	2
Less than once a week	1
Never	0

CRISPS ☐

50. **How often do you eat cream?**

6 or more times a week	4
3 to 5 times a week	3
Once or twice a week	2
Less than once a week	1
Never	0

CREAM ☐

51. **How often do you eat icecream?**

6 or more times a week	4
3 to 5 times a week	3
Once or twice a week	2
Less than once a week	1
Never	0

ICECREAM ☐

52. **How many times a week do you eat cheddar, edam or other hard cheese, cream cheese or cheese like camembert?**

6 or more times a week ☐4

3 to 5 times a week ☐3

Once or twice a week ☐2

Less than once a week ☐1

Never ☐0

CHEESE ☐

53. **What type of milk do you drink or use in cooking or in tea and coffee?**

Condensed ☐4

Full-cream ☐3

Full-cream and reduced fat ☐2

Reduced fat ☐1

Skim milk or none ☐0

MILK ☐

54. **How much of the skin on your chicken do you eat?**

Most or all of the skin ☐2

Some of the skin ☐1

None ☐0

Don't eat chicken ☐0

CHICKEN ☐

55. **How much of the fat on your meat do you eat?**

Most or all of the fat ☐2

Some of the fat ☐1

None of the fat ☐0

Don't eat meat ☐0

MEATFAT ☐

Please ASK YOUR PARENTS for the answers to the following questions where necessary.

56. **Where in South Australia did your parents live when you were born?**

    Please specify:

    Suburb of Adelaide ....

    BTHPCODE ☐☐☐☐

    or

    Other place in South Australia ....

57. **When you were born, what was the highest level of education your FATHER had attained?**

    Never attended school ☐ 1

    Primary school ☐ 2

    Some high school ☐ 3

    Completed high school (Year 12 or equivalent) ☐ 4

    Some university, CAE or other tertiary institution ☐ 5

    Completed university, CAE or other tertiary qualification ☐ 6

    Not known ☐ 8

    FEDUCB ☐

58. **When you were born, what was the highest level of education your MOTHER had attained?**

    Never attended school ☐ 1

    Primary school ☐ 2

    Some high school ☐ 3

    Completed high school (Year 12 or equivalent) ☐ 4

    Some university, CAE or other tertiary institution ☐ 5

    Had university, CAE or other tertiary qualification ☐ 6

    Not known ☐ 8

    MEDUCB ☐

59. **What was your MOTHER'S own birth weight?**

Can't ask mother ☐

Mother does not know ☐

Mother's birth weight ....

(Please indicate whether in pounds and ounces, kilograms or grams.)

MOTHBWT ☐☐☐☐

60. **Were you breast fed as a baby?**

No ☐0

Yes ☐1 If yes, until what age? __ __ months

Don't know ☐9

BRFED ☐

AGEBRFED ☐☐

Thank you for your co-operation.
Please remember to bring the questionnaire to the follow-up clinic.

Adelaide Children's Hospital Family Heart Study 1995-96 Follow-up

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