

## The developmental origins of health and disease: an overview

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The concept of developmental origins of health and disease (DOHaD) grew from the earlier concept of fetal origins of adult disease (FOAD) (reviewed in Barker 1995, 1998). There are two important reasons for the change. The first results from the large amount of research (much of it reviewed in this book) showing that the early life events which determine in part the risk of later disease occur not only in the fetal period specifically, but throughout the plastic phase of development. In this respect the use of the word 'development' is helpful because it implies not only effects operating during early stages of embryonic life (usually the preserve of developmental biology) but also those in infancy. Secondly, the DOHaD terminology emphasises that this area of science has implications not only for disease, and its prevention, but also for health promotion. The latter is of great importance in public health and education programmes in many parts of the world. But the accent on 'developmental origins' is more than just a flag of convenience under which several disciplines may sail: it represents a fundamental shift in thinking about the way in which early life processes affect later health and disease in humans.

Previously, proponents of FOAD championed the view that prenatal events were of utmost importance. Adopting this position was tactically necessary in the battle (now won) to gain widespread recognition that the aetiology of many chronic diseases, such as coronary heart disease (Barker and Osmond 1986), type 2

diabetes (Ravelli *et al.* 1998) or osteoporosis (Cooper *et al.* 2002), lay not only in genetic predisposition or in adult lifestyle, but also in the ways in which early life events could affect subsequent biology. As a result, both epidemiologists and experimentalists have expanded the period of interest to that around conception (Cnattingius *et al.* 1998, Kwong *et al.* 2000, Inskip *et al.* 2001, Bloomfield *et al.* 2003, Robinson *et al.* 2004, Crozier *et al.* in press). In parallel, other clinical and basic scientists were stressing the importance of the postnatal environment during suckling, infancy and childhood in setting an individual on the path to health or disease (Eriksson *et al.* 1999, 2003, Singhal *et al.* 2002, 2003). At times, these two schools of thought appeared to be at loggerheads, and the resulting conflict did little to promote understanding of the importance of the field that they shared. Development is a continuum extending on either side of birth – consider the wide variation in maturation at birth in different species. More recently, the recognition that the field of evolutionary developmental biology ('evo-devo') has enabled the development of a broader understanding of the phenomenon and, in turn, studies of the DOHaD phenomenon have led to new concepts in evo-devo biology. Both these advances in theoretical thinking and new experimental observations allow recognition that both pre- and postnatal environmental factors play vitally important roles, and that what matters most is the degree of match/mismatch between

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them. This idea is more fully explained in Chapter 3. Suffice it to say here that the term 'development' helps to emphasise the importance of this continuity.

There are other ways in which the epidemiological work has continued to be controversial. The early concerns about confounding variables led to discussion on the relative importance of low birthweight versus other contributory factors. At times such discussions became rather sterile. Because the consensus in both animal and human research is now that phenotypes can be induced in offspring without necessarily being accompanied by low birthweight, it is clear that reduction of fetal growth per se does not lie on a causal pathway to later disease. Rather, low birthweight is a surrogate marker of the effects of the prenatal environment on the fetus, and one aspect of the fetal 'coping' responses to that environment. The problems in this area were compounded by an insufficient appreciation of the distinction between clinically manifest disease and other surrogate markers or risk factors for disease (Huxley *et al.* 2002). Examples included the use of elevated blood pressure as a marker for cardiovascular disease, or reduced insulin sensitivity as a marker of diabetes. With the wisdom of hindsight, it is not surprising that interpretation of the links between surrogates of fetal adaptation (birthweight) and later disease (blood pressure, insulin sensitivity) yielded different interpretations at the hands of different researchers. As the field has progressed, however, we have developed more sensitive markers of fetal adaptive responses and these can now directly relate to clinical disease. When this is done, the striking correlations that underpin the DOHaD hypothesis begin to emerge.

The work conducted by basic scientists, many of them using experimental animals, has not been without criticism either. Inevitably the use of a range of species to investigate the phenomenon, partly based on convenience, cost and suitability for experimental techniques, has produced a similarly sterile discussion about which provides the most suitable experimental model for the human (Symonds *et al.* 2000, Langley-Evans 2000, Bertram and Hanson 2001, Armitage *et al.* 2004). Ideas have become refined as

confirmation of similar aspects of the phenomenon across species has been made. Surprisingly, one of the features to emerge from the intense research activity in the area is how easy it is to manipulate the phenotype of offspring by changes in the early environment. This poses the problem of the relevance to humans of an observation made in animals. A key issue is to distinguish between factors that disrupt development and which are not regulated and those that are based on the processes of developmental plasticity and may have adaptive value – these ideas are expanded in Chapter 3. We have to accept that some environmental exposures, either clinical or experimental, simply disrupt the normal pattern of development. Such exposures do not necessarily lead to increased risk of disease (which cannot usually be ascertained in animals), nor have direct relevance to DOHaD in humans.

Notwithstanding these issues, studies in animals have revealed exciting insights into the mechanisms which underlie DOHaD. The first has been referred to above, and is the perception that changes in the developmental environment can induce phenotypic changes which are not necessarily accompanied by a reduction of birthweight or change in body proportions at birth (Hanson 2002). But perhaps the most exciting development relates to the area of gene–environment interactions, usually now referred to as epigenetics. As the reader will see (Chapter 5), it is now clear that graded changes in certain factors, such as histone acetylation and the degree of DNA methylation (Weaver *et al.* 2004), can produce subtle changes in the expression of genes. Coupled with our increasing knowledge about post-transcriptional and post-translational factors which influence gene expression, we are now beginning to see how developmental plasticity operates through environmental actions interceding between the genotype and the induction of the phenotype. Because such epigenetic processes depend on dietary availability of key nutrients and micronutrients, and because they can be affected by hormone levels (Waterland and Jirtle 2004), they are prime candidates for mechanisms underlying DOHaD, at least as regards the most commonly studied systems.

Moreover, whilst it was formerly thought that the methylation of DNA was established anew in the embryo at or before the blastocyst stage, it is now clear that levels of methylation can to a degree be transmitted from one generation to the next (Weaver *et al.* 2004). Research has revealed several ways in which transgenerational effects can be passed not only from the mother to her offspring but also to her grandchildren and possibly further down the lineage (Drake and Walker 2004).

In Chapter 3 we present a theoretical basis for the DOHaD phenomenon, in the context of previous theories that contribute substantially to it, such as metabolic teratogenesis, the thrifty genotype, thrifty phenotype and others. We believe that such an exercise is important for synthesising current ideas and allowing the incorporation of new experimental findings. It is surprising how easily current experimental findings fit into such a theory, but its real utility will probably be derived when a set of observations which do not fit is uncovered. In this sense using a theory makes the identification of such extraneous observations easier, and goes on to generate new experimental approaches, hypotheses and, ultimately, new theories. Even as it stands, however, the theory must ask questions about our tacit assumption that neo-Darwinian processes have contributed greatly to phenotypic diversity, including phenotypes susceptible to disease, in human populations. We think the implications of theoretical thinking regarding DOHaD for evolutionary biology will be substantial.

Most research in the field has been focused on metabolic disorders or on the cardiovascular system, reflecting the original epidemiological observations of Barker and his colleagues. Indeed, many of the chapters in this book reflect this emphasis. But now research in DOHaD is broadening to include other chronic diseases, such as osteoporosis (Cooper *et al.* 2002), cognitive decline (Richards *et al.* 2002, Gale *et al.* 2003), behavioural abnormalities (Thompson *et al.* 2001, Wahlbeck *et al.* 2001), obesity (Eriksson *et al.* 2001) and some forms of cancer (Dos Santos *et al.* 2004; see also Chapter 31). This does not mean that the phenomenon is so broad and all-

encompassing as to be meaningless. Rather it suggests that an entirely new way of viewing chronic disease will have to be developed in both developed and developing societies. The importance of this to public health policy makers is discussed in Chapter 34.

Many of the contributors to this volume make reference to the importance of the DOHaD concept to public health policy. Various estimates have been made of the impact of early-life factors in determining later risk of disease. A conservative estimate, based on the effects of low birthweight on later endothelial function in childhood, suggests that such early-life programming is equivalent in magnitude to the effect of smoking in later life (Leeson *et al.* 2001). More dramatic figures come from the retrospective studies of the Helsinki cohort (Chapters 3 and 15) which indicate that men who had a low ponderal index at birth and a high body mass index at age 12 had a five-fold greater risk of dying of coronary heart disease. In relation to the epidemic of obesity and associated diseases, data from India (Bhargava *et al.* 2004) suggest that the incidence of type 2 diabetes in adults who had an accelerated adiposity rebound as children will be about 25%. More work to define the magnitude of these effects is urgently needed.

Western societies are now characterised by increasing longevity, and this means that the number of those suffering from heart disease and related disorders will increase over the next few years, even though paradoxically those dying from such diseases will fall. There is no room for complacency in the latter statistic, as it may well be only temporary. Furthermore, there is increased interest in the effects of infection and inflammatory responses in early life in contributing to the increased longevity, but there are clearly many factors of equal importance. In earlier life the DOHaD concept is giving important insights into the epidemic of obesity developing in childhood and adolescence (see Chapter 18). The recognition that fat deposition (Vickers *et al.* 2000, Symonds *et al.* 2004), propensity to exercise (Vickers *et al.* 2003) and even dietary preference (Bellinger *et al.* 2003) may be programmed in early life now

makes it essential to think how to intervene. It is possible that 'lifestyle' interventions may be effective in developed societies, in a way that may be less so in developing societies (see Chapter 3). However, even if this is the case it is likely that there will have to be a shift away from public health messages aimed at targeting the population as a whole towards more individually 'customised' dietary and exercise plans for those at risk. This will not be easy; the perception that the risk of later disease may be less in the infant who is fat and becomes obese as a young adolescent, in contrast to the small baby who later becomes fat, raises important issues of interpretation. These two children in their teens may in the end have identical body mass indices, but have arrived at that point by different paths and, hence, in later life have very different prospects for disease risk.

Many other factors contribute to the importance of DOHaD in the social policy arena. In particular, family size is decreasing in both industrialised/developed and developing nations. In industrialised societies, this may reflect the tendency for women to pursue careers and to start families later, and reflect social policy as in China with a 'one child' policy to limit population size. Moreover, well-meaning programmes to promote contraception accessibility in many developing countries will serve to limit family size further. Because of the maternal-constraint issues raised in Chapter 3, these initiatives may make the mismatch between the pre- and postnatal environments greater.

Our overall conclusion, therefore, is that environmental factors acting during the phase of developmental plasticity interact with genotypic variation to change the capacity of the organism to cope with its environment in later life. Because the postnatal environment can change dramatically, whereas the intrauterine environment is relatively constant over generations, it may well be that much of humankind is now living in an environment beyond that for which we evolved. The DOHaD phenomenon can explain how this manifests in the ecological patterns of human disease. It is no longer possible for adult medicine to ignore the developmental phase of life.

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## The 'developmental origins' hypothesis: epidemiology

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### Introduction

Research worldwide has established that people who were small at birth and had poor growth in infancy have an increased risk of adult coronary heart disease and type 2 diabetes, particularly if this is followed by increased childhood weight gain. There is also evidence linking impaired early growth with other degenerative disorders in later life, including stroke, hypertension, obesity, osteoporosis, obstructive airways disease, reduced cognitive function and poor mental health. The relations between smaller infant size and an increased risk of ill health and adult disease extend across the normal range of infant size in a graded manner. Moreover, recent animal studies and epidemiological data have demonstrated that while maternal thinness and unbalanced diet during pregnancy may have modest effects on size at birth, they are nonetheless associated with raised blood pressure and altered glucose–insulin metabolism and stress responsiveness in the adult offspring. It is now clear that the associations do not simply reflect genetic influences; rather the findings indicate that interactions between the genetic influences and the early-life environment determine disease and susceptibility to adverse influences in the adult environment.

The observations have led to the hypothesis that cardiovascular disease, type 2 diabetes, osteoporosis

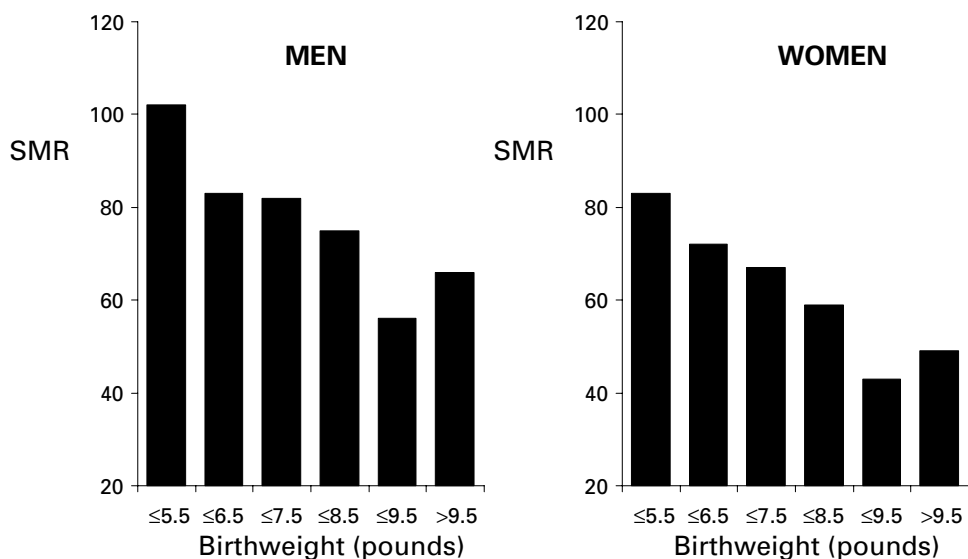
and obstructive airways disease originate through developmental plastic responses made by the fetus and infant as part of a prediction of the subsequent environment to which it anticipates that it will be exposed. Critical periods in development result in irreversible changes; if the environment in childhood and adult life differs from that predicted during fetal life and infancy, the developmental responses may increase the risk of adult disease. This chapter provides an overview of some of the epidemiological evidence underpinning the developmental origins of degenerative disease. Evidence is also accumulating indicating important developmental influences on cancer, described in Chapter 31.

### Fetal, infant and childhood growth in relation to health in later life

#### Ecological observations pointing to developmental influences on adult health

At the start of the twentieth century the incidence of coronary heart disease rose steeply in western countries so that it became the most common cause of death. In many of these countries the steep rise has been followed by a fall over recent decades that cannot be accounted for by changes in adult lifestyle. The incidence of coronary heart disease is now rising in other parts of the world to which western influences





**Figure 2.1** Coronary heart disease death rates, expressed as standardised mortality ratios (SMR), in 10 141 men and 5585 women born in Hertfordshire, UK, according to birthweight. Derived from Osmond *et al.* (1993).

are extending, including China, south Asia and eastern Europe.

A clue suggesting that coronary heart disease might originate during fetal development came from studies of death rates among babies in Britain during the early 1900s (Barker 1998). Perinatal mortality rates differed considerably between one part of the country and another, being highest in some of the northern industrial towns and the poorer rural areas in the north and west. This geographical pattern in death rates was shown to closely resemble today's large variations in death rates from coronary heart disease (Barker 1998). The usual certified cause of death in newborn babies during the early 1900s was low birthweight, and one possible conclusion suggested by the geographical association was that low rates of growth before birth are in some way linked to the development of coronary heart disease in adult life. Although it had previously been suggested that events in childhood influence the pathogenesis of coronary heart disease, the hypothesis that influences during fetal life and infancy play a critical role provided a new focus for research.

## Coronary heart disease

### Cohort studies of size at birth and coronary heart disease

The first direct evidence that an adverse intrauterine environment might have long-term consequences for the risk of coronary heart disease came from follow-up studies of men and women in middle and late life whose body measurements at birth had been recorded. A study of people born in Hertfordshire, UK, showed for the first time that those who had had low birthweights had increased death rates from coronary heart disease in adult life (Osmond *et al.* 1993, Barker 1998). Thus, among 15 726 people born during 1911 to 1930, death rates from coronary heart disease fell progressively with increasing birthweight in both men and women (Fig. 2.1). A small rise at the highest birthweights in men could relate to the macrosomic infants of women with gestational diabetes. Another study, of 1586 men born in Sheffield during 1907 to 1925, showed that it was particularly people who were small at birth as a result of growth

restriction who were at increased risk of the disease (Barker *et al.* 1993a).

Replication of the UK findings has led to wide acceptance that low rates of fetal growth are associated with coronary heart disease in later life. For example, confirmation of a link between low birthweight and adult coronary heart disease has come from studies of 1200 men in Caerphilly, south Wales (Frankel *et al.* 1996) and of 70 297 nurses in the United States (Rich-Edwards *et al.* 1997). The latter study found a two-fold fall in the relative risk of non-fatal coronary heart disease across the range of birthweight. Similarly, among 517 men and women in Mysore, south India the prevalence of coronary heart disease in men and women aged 45 years or older fell from 15% in those who weighed 2.5 kg or less at birth, to 4% in those who weighed 3.2 kg or more (Stein *et al.* 1996).

Follow-up studies of populations with more detailed birth measurements suggest that altered birth proportions are more strongly associated with late outcomes than is birthweight per se (Forsen *et al.* 1997). The Hertfordshire records and the nurses and Caerphilly studies did not include measurements of body size at birth other than weight, but in populations where birth length was recorded, derivation of ponderal index (birthweight/length<sup>3</sup>) allows a crude assessment of body composition and thinness at birth; ponderal index cannot, however, adequately distinguish variations in fat and lean mass. Where neonatal head circumference has also been recorded the baby whose body and trunk is small in relation to its head, as a result of 'brain sparing', can also be distinguished. Patterns of altered birth proportions and restricted fetal growth linked with later coronary heart disease may be summarised as a small head circumference, shortness or thinness (Barker *et al.* 1993a, Martyn *et al.* 1996a, Forsen *et al.* 1997, Barker 1998, Eriksson *et al.* 1999, 2001).

Although low placental weight (Forsen *et al.* 1997) and an altered ratio of placental weight to birthweight have also been linked with raised adult coronary heart disease death rates (Martyn *et al.* 1996a, Forsen *et al.* 1999), other studies have found no

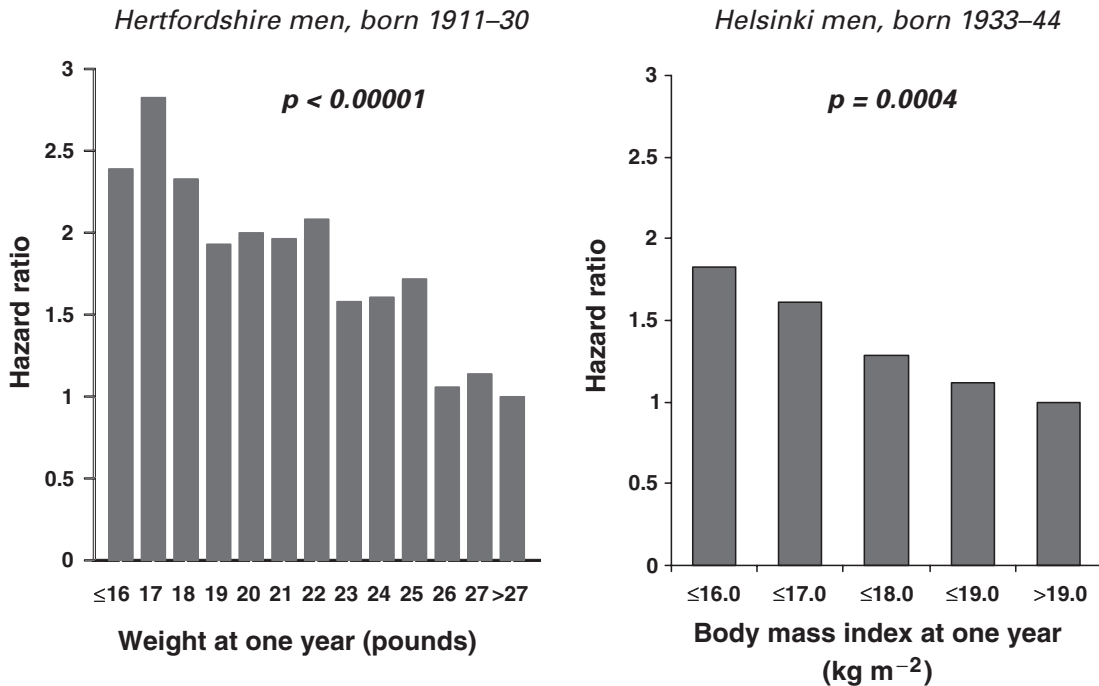
association with placental weight (Leon *et al.* 1998, Eriksson *et al.* 2001). Animal studies offer a possible explanation of this inconsistency. In sheep, the placenta enlarges in response to moderate undernutrition in mid pregnancy, presumably reflecting an adaptive response to extract more nutrients from the mother (Robinson *et al.* 1994); however, this effect is only seen in ewes that were well nourished before conception, and in ewes poorly nourished before conception undernutrition in mid pregnancy is associated with small placental size (Robinson *et al.* 1994).

### Infant and childhood growth and coronary heart disease

Evidence suggesting both additive and interactive effects of poor prenatal and infant growth on the risk of subsequent coronary heart disease is now emerging from epidemiological studies. Follow-up of men born in Hertfordshire, UK, between 1911 and 1930 found that lower weight at age 1 year was strongly associated with higher hazard ratios for coronary heart disease (Osmond *et al.* 1993; Fig. 2.2), and subsequent analyses of this cohort have suggested additive effects of poor fetal and infant growth (Barker 1998).

Confirmation that smaller and thinner infants at age one year have increased rates of coronary heart disease in adulthood has come from people born in the 1930s and 1940s in Helsinki, Finland (Eriksson *et al.* 2001; Fig. 2.2). These findings, described in detail in Chapter 15, point to the possibility that interactions between the pre- and postnatal environments have an important influence on the risk of coronary heart disease. In the Helsinki study, hazard ratios for coronary heart disease fell with increasing birthweight and, more strongly, with increasing ponderal index at birth. These trends were found in babies born at term or prematurely and therefore reflect slow intrauterine growth. Consistent with the findings in Hertfordshire and with the known association between coronary heart disease and short adult stature (Marmot *et al.* 1984), men in Helsinki who developed the disease also tended to have poor





**Figure 2.2** Hazard ratios for coronary heart disease according to weight at age 1 year in men born in Hertfordshire, UK, and according to body mass index at age 1 year in men born in Helsinki, Finland. Derived from Barker (1998) and Eriksson *et al.* (2001).

weight gain and low rates of height growth in infancy (Chapter 15). Although **infant** growth failure was deleterious in individuals that were both small and large at birth, **childhood** weight gain had very different effects in small and large neonates; in relation to the risk of adult coronary heart disease, there was a strong interaction between ponderal index at birth and body mass index in childhood. Among boys who were thin at birth with a below-average ponderal index, rapid weight gain and increasing body mass index during childhood was associated with higher rates of adult coronary heart disease; however, in boys who had an above-average ponderal index at birth, rapid childhood weight gain and increasing body mass index was unrelated to the risk of coronary heart disease (Eriksson *et al.* 2001). Findings among girls were similar, and again the risk of coronary heart disease was determined more by the tempo of weight gain than the body size attained (Forsen *et al.* 1999).

### Size of effects and potential confounding influences

The findings described above suggest that influences linked to pre- and postnatal growth have an important effect on the risk of coronary heart disease. Assessment of the relative importance of early and later-life exposures is difficult as there is a paucity of well-characterised cohorts with both perinatal data and health outcomes documented well into later life. Some commentators have argued that the magnitude of developmental effects on adult cardiovascular risk is small (Hattersley and Tooke 1999, Huxley *et al.* 2002), although the only published estimate based upon the Helsinki cohort suggests that it is considerable when clinical disease is used as the outcome measure (Barker *et al.* 2002). Analysis of the magnitude of developmental effects on health 50 or more years later in life is challenging because

concurrent risk factors can often be measured with greater precision and it is difficult to identify or attribute risk to distant, early-life factors. Moreover, the observed relationship between disease risk and birth size does not imply a causal role of being born small but reflects the sensitivity of fetal growth to adverse intrauterine influences. It is thought that it is the effect of environmental influences acting during early development that is the causal trigger. Indeed, much experimental and epidemiological evidence indicates that adverse developmental influences can affect disease risk without birth size being affected.

It has been argued that the associations between size at birth and later disease could primarily reflect genetic influences (Hattersley and Tooke 1999). Recent findings, however, indicate that it is interactions between the early-life environment and genetic influences that are likely to be the principal determinants of disease susceptibility (Eriksson *et al.* 2002; Chapter 15). Moreover, it is important to recognise that birth size has only a modest genetic component and primarily reflects the quality of the intrauterine environment (Morton 1955, Snow 1989, Brooks *et al.* 1995).

Other commentators have argued that people whose growth was impaired *in utero* may continue to be exposed to an adverse environment in childhood and adult life, and it is this later environment that produces the effects attributed to developmental influences. There is strong evidence that this argument cannot be sustained. In four of the studies which have replicated the association between birthweight and coronary heart disease, data on adult lifestyle factors including smoking, employment, diet, alcohol consumption and exercise were collected (Frankel *et al.* 1996, Rich-Edwards *et al.* 1997, Leon *et al.* 1997, Barker *et al.* 2001). Allowance for them had little effect on the association between birthweight and coronary heart disease. Influences in adult life, however, add to the effects of the intrauterine environment. For example, the prevalence of coronary heart disease is highest in people who had low birthweight but were obese as adults.

In studies exploring the mechanisms underlying the associations between early growth and later

coronary heart disease, there are similar trends between birthweight and major risk factors for cardiovascular disease, including hypertension and type 2 diabetes (Hales *et al.* 1991, Huxley *et al.* 2000). Studies of cardiovascular risk factors have been extended to children, and suggest that developmental influences on cardiovascular risk are still acting in today's children and not simply of historical importance (Hofman *et al.* 1997, Leeson *et al.* 1997). These prospective clinical studies of children have again shown that the associations with smaller size at birth are independent of social class, cigarette smoking and alcohol consumption.

A further aspect, suggested by data from the Helsinki cohort, is that the early life and adult environments may not simply have **additive** effects, but may **interact** to influence the risk of coronary heart disease. Poverty and low household income have long been linked with coronary heart disease, but recent analyses suggest that this effect occurs in those who are thinner than average at birth, but not in those who are fatter than average (Barker *et al.* 2001). If interactions between the early-life and adult environments are confirmed, this will have important implications for our understanding of the evolutionary implications of developmental responses (see Chapter 3).

### Stroke, hypertension and cardiovascular function

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As compared with coronary heart disease, epidemiological studies of developmental influences on the risk of stroke have been hampered by the lower population prevalence of the disorder and the paucity of cohorts including both early-life data and information distinguishing occlusive and haemorrhagic stroke. The information that is available suggests that stroke is associated with low birthweight, but not with stunting or thinness (Martyn *et al.* 1996a). In the Helsinki cohort, the association between small size at birth and haemorrhagic stroke was only significant after adjustment for head circumference, and there was no association with occlusive stroke