WHO/NHD/02.3
WHO/NPH/02.1
Distribution: General
English only

Programming of chronic disease by impaired fetal nutrition

Evidence and implications for policy and intervention strategies

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DEPARTMENT OF NONCOMMUNICABLE DISEASE PREVENTION AND HEALTH PROMOTION
WORLD HEALTH ORGANIZATION

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Designed by minimum graphics
Printed in Switzerland

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Acknowledgements

The author is grateful to WHO for identifying the fetal programming of impaired nutrition as a priority issue and supporting this extensive review. The author wishes to express her sincere gratitude to Dr Graeme Clugston, Director of the Department of Nutrition for Health and Development (NHD), Dr Bruno de Benoist, NHD, and Dr Pekka Puska, Director of the Department of Noncommunicable Disease Prevention and Health Promotion (NPH). The author is particularly indebted to Dr Chizuru Nishida, NHD, who took the responsibility for conducting the peer review of the draft report and facilitated the process of finalizing the report for publication.

Special thanks are also given to the peer reviewers for their valuable contributions and comments. They include Professor David Barker, University of Southampton, United Kingdom; Dr Terry Dwyer, University of Tasmania, Australia; Professor Alan Jackson, University of Southampton, United Kingdom; Professor Michael Kramer, McGill University, Canada; Dr Ruth Morley, University of Melbourne, Australia; Dr Marc Prentki, University of Montreal, Canada; Dr Srinath Reddy, All India Institute of Medical Science, India; and Dr Beat Schurch, Nestle Foundation, Switzerland.

Thanks are also given to Dr Judith Pojda for editing the manuscript and to Ms Patricia Robertson for her meticulous and thorough work in finalizing the document for publication.

A summary of this extensive review was presented at the WHO Symposium on Nutrition Transition and its Implications for Health (chaired by Dr Barry Popkin, University of North Carolina and Dr Chizuru Nishida, WHO), that was held at the occasion of the 17th International Congress of Nutrition in Vienna, Austria, from 27 to 31 August 2001.

Executive Summary

Undernutrition and micronutrient deficiency diseases continue to affect mothers and children of developing countries, and remain the major focus of nutrition intervention efforts. Low birth weight (LBW) associated with retarded fetal growth is at least twice as common in developing countries, and it reflects poor maternal nutrition, although maternal smoking may also emerge as an important factor in some societies. Concurrently, obesity and other diet-related chronic diseases, in particular cardiovascular disease (CVD) and diabetes mellitus (type-2: non-insulin-dependent), are increasing in most of the developing countries and in countries undergoing economic transition. Meanwhile, CVDs remain highly prevalent in most industrialized countries, although reductions in mortality from these diseases are now observed in Australia, Finland and the USA. Lifestyles are incriminated as a major determinant of diet-related chronic diseases, but poverty is also involved. Poverty (and marginalization) is not only a root cause of malnutrition and specific nutrient deficiencies; it is also associated with diet-related chronic diseases, an aspect all too often overlooked. Except perhaps in poorest countries, clustering of obesity and other chronic diseases is observed in the poorer segments of the population. Atherogenic lifestyle patterns, including tobacco smoking, lack of physical activity, and diets of high-fat, low-fibre, little fruits and vegetables were first developed in wealthier sectors of society but they spread to other groups experiencing urbanization and economic growth, while the more privileged are switching to healthier lifestyle practices. Therefore, the poorer come to bear a greater burden of diet-related chronic diseases, in addition to that of undernutrition and specific nutrient deficiencies.

Suboptimal fetal growth and nutrition may further contribute to increased risk of chronic disease, according to the Barker Early Origins Hypothesis. According to this theory, undernutrition *in utero* (and in early infancy) permanently changes the body's structure, physiology, and metabolism, thereby programming chronic diseases in later life, including coronary heart disease (CHD) and related disorders, such as stroke, diabetes and hypertension. Evidence of links between fetal growth and chronic disease in later life is accumulating, and even if fetal programming does not supplant the genetic and lifestyle theories of chronic disease, it may well represent an additional source of environmental risk which interacts with, and modulates, other determinants throughout the life course. This may have important policy and programme implications for the prevention of diet-related chronic diseases, particularly in populations with high rates of LBW, which reflect poor maternal nutrition.

The purpose of this paper is to review recent evidence of the link between fetal nutrition and CVD risk markers in later life, the mechanisms, and the causal pathways, based on epidemiological and experimental data, and to highlight some implications for policy and intervention strategies from developing country perspectives. The focus is on fetal programming, while acknowledging that the process may also extend to early postnatal life. The link between poor fetal growth and cardiovascular disease risk is given emphasis, rather than the determinants of impaired fetal growth per se. Consequently, while the importance of maternal smoking as a key factor of impaired fetal growth and lower birthweight is recognized, this issue is not addressed in any depth as it is beyond the scope of this review.

Epidemiological evidence linking small size or disproportions at birth and chronic disease

There is an increasing number of epidemiological studies reporting an inverse association between size at birth and chronic disease. Anthropometric indicators of impaired fetal growth other than LBW, for instance, thinness, shortness, low abdominal circumference, and a high placental ratio, have also been found to link with chronic disease. There appears to be a graded and inverse risk across the normal range of birth size or proportions, not only in LBW infants. Additionally, smaller size at birth (birth weight or body disproportions) appears to be more closely related to chronic disease when due to intrauterine growth impairment rather than premature birth. Further epidemiological evidence of the

link between fetal nutrition and chronic disease is provided by several studies in twins and observations in populations exposed to famines, although there are some conflicting findings.

Observational and historical cohort studies first showed an association between lower birth weights and later chronic disease rates in England and Scandinavia. Barker reported, for instance, that death rates from CHD fell by half from the lower to the upper end of the birth weight distribution in studies involving more than 16, 000 men and women in England. Many studies, including in the USA, Scandinavia, and India, have since confirmed the link between lower birth weight or measures of disproportions at birth and CVD in later life. Adjusting for several potential confounding factors, including socioeconomic status, family history, current body size, and behaviours, usually did not suppress this inverse association, which was strengthened by high current body mass index (BMI). In some studies, higher concentrations of serum fibrinogen and more adverse lipid profiles were observed in children or adults of small birth-size. Some twin studies, however, only showed that the shorter member of the pair was more likely to die of heart disease than the taller one, reporting no higher rate of ischaemic heart disease in twins than in the general population, in spite of lower birth weights.

Based on the findings of some 80 studies around the world, the inverse association of birth weight and systolic blood pressure was consistently observed, with only a few exceptions, in different age groups including children, and in developed as well as developing countries. Among adolescents, however, the inverse association is less consistent. Typically, the increase in blood pressure is of the order of a 2 mmHg per kg decrease of birth weight. The effect may appear small, but an increasing number of studies suggest that the inverse association is amplified over the life course, in particular among individuals with postnatal catch-up growth in weight, and in those who develop a high BMI. However, maternal blood pressure was not always controlled for, and according to some studies, it may confound the association. Furthermore, some twin studies did not observe higher blood pressure in twins. Nevertheless, supportive evidence for the link between fetal growth restriction and hypertension risk comes from monozygotic twin studies showing that lighter members of pairs tended to have higher blood pressure, in childhood and as adults. The protein deficiency model in pregnant rats also resulted in significantly increased blood pressure compared to offspring of normally fed dams, in spite of normal size litters.

Not only CHD and hypertension, but also insulin resistance and type-2 diabetes have been found to be independently related to small size at birth, which strongly suggests that fetal growth is connected with many components of syndrome X (or metabolic syndrome). In the British cohorts, for instance, impaired glucose tolerance and type-2 diabetes in 64 year-old men showed a progressive three-fold decline with increasing birth weight (after adjustment for current size). These observations were confirmed in many other studies, including in Sweden and India. Among subjects with a family history of diabetes, small size at birth was found to further enhance the risk. Even in Pima, Indians in the USA, who exhibit the highest rates of type-2 diabetes worldwide, an inverse relationship with birth weight was observed, although there was a U-shape relationship, with highest birth rates associated with macrosomia due to gestational diabetes. The findings of the large Nurses' Health Study in the USA provide strong support for an inverse association over the whole range of the birth weights, in all current BMI categories, and independently from infant feeding and later lifestyle patterns (ie. smoking and physical activity).

In Beijing, a recent study among 45 year-old men and women reported an inverse association of birth weight (at term) with several syndrome X components, after adjusting for current size and other confounding factors. Insulin resistance associated with smallness at birth (lower birth weight, shortness, or thinness) was shown to be already present at a young age in several studies, even in children, as observed in India. As suggested, impaired glucose tolerance may only appear with increasing age, once the observed compensatory mechanisms of increased insulin secretion and glucose effectiveness would progressively fail. Twin studies also revealed that in pairs discordant for diabetes, birth weight was significantly lower in the diabetic members of pairs.

Insulin resistance is known to be strongly and positively associated with current obesity and abdominal fat. It was observed in many studies that the association of lower birth weight with syndrome X was either confined to, or strengthened in subjects with high BMI. Small size at birth was also found to be associated with more central obesity and a higher percentage of body fat for a given body mass in a few studies.

The large body of data on people exposed to the Dutch Famine (1944–45) while *in utero* support the hypothesis of chronic disease programming by intrauterine undernutrition, and highlight differences in long-term effects according to the timing of the insult. Those exposed in early gestation were at increased risk of CHD, had more atherogenic blood lipid profiles, and

were more likely to become obese as adults, compared to those only exposed in late gestation, or not exposed at all, although birth weights were little affected. In contrast, those who were exposed through their mother in late pregnancy had lower birth weights, and a lower risk of obesity in adulthood, but they showed a higher rate of impaired glucose tolerance and type-2 diabetes. Cautious interpretation is warranted, however, because survivors of the severe food deprivation may not be representative. Furthermore, these effects were not observed in people exposed to another war famine, the Leningrad Siege, although in the latter case, the population was chronically undernourished before and after the famine, which is at variance with the Amsterdam population.

Fetal programming of chronic disease: The concept, experimental evidence, and proposed mechanisms

The notion of fetal programming implies that during critical periods of prenatal growth, changes in the nutritional and hormonal milieu of the conceptus may alter the full expression of the fetal genome, leading to permanent effects on a range of physiological functions and structures. Some also use the term of fetal "imprinting". Programmed changes in structure and function may include a reduction in the number of cells, or changes in the distribution of cell types and in organ structure, or else, resetting of hormonal feedback. What makes the early origins hypothesis difficult to prove in spite of its biological plausibility, is the long stretch of time separating the insult and the adverse effects, the numerous factors that may modulate this relationship throughout life, and the possibility that small size or disproportions at birth and chronic disease are not causally linked, but share a common origin.

Experimental data, particularly from animal models, support the theory and help explain the mechanisms of chronic disease programming *in utero*. The effects of maternal undernutrition throughout gestation or at specific periods of fetal growth and metabolism have been extensively studied in animals. It was shown, for instance, that undernutrition in early gestation in rats resulted in fatter offspring in spite of little birth weight effect, whereas acute malnutrition in late pregnancy significantly impaired fetal growth and glucose tolerance of the offspring. These effects mimic those observed in people exposed to the Dutch Famine.

Protein deficiency in pregnant rats, in particular, has provided a model for studying the metabolic and endocrine adaptations of the fetus to poor nutrition, their molecular basis, and their long-term impact. A protein-restricted, isocaloric diet throughout gestation induced a permanent reduction in size of the offspring. The effect could be reversed by having the rats breastfed by dams on a normal diet, but this resulted in reduced life-span. The reduced longevity was found to be associated with shorter kidney (and liver) telomeres. Systolic blood pressure was also permanently increased in the offspring of dams fed on the low-protein diet; kidney weight and the number of glomeruli were shown to be reduced. Glucose tolerance was impaired, although diabetes was not observed. Selective hepatic alterations were induced by the low protein maternal diet, with an altered response to insulin and to glucagon, and marked changes in expression of key enzymes of gluconeogenesis and glycolysis (increased phosphoenol pyrivate kinase, and reduced glucokinase activity). Pancreatic insulin content and β-cell mass were reduced. All these effects were observed with a moderate protein deficiency, and rather modest effects on birth weights. Rats exposed to the low-protein diet throughout gestation and lactation, and weaned on a "cafeteria" diet, not only had high blood pressure, but they became obese, had high concentrations of triacylglycerol, and were glucose intolerant. These are typical components of the metabolic syndrome. It has been postulated that the nutritional programming of the cardiovascular system is steroid-dependent. Increased blood pressure was associated with a reduction of the enzyme 11-β-hydroxysteroid dehydrogenase (11-β-OHSD), and could be prevented with suppression of maternal and fetal glucocorticoid synthesis. Glucocorticoid-inducible enzymes were also found to be elevated in the brain and liver of protein-deficient offspring, and these rats exhibited hypersensitivity to glucocorticoids.

Thus, nutritional programming of chronic disease has been demonstrated in animals. Given species differences, extrapolations to humans have to be cautious, however. Alterations in set-points of major hormonal axes are the most likely dominant mechanisms of fetal programming, in addition to some structural changes. Resetting of the hypothalamus-pituitary-adrenal (HPA) axis and of the IGF-1 and insulin axis are likely to be implicated.

Overexposure of the fetus to glucocorticoids as a result of activation of the HPA axis in stressful intrauterine conditions including undernutrition is likely to be involved in the programming of chronic disease. Excess glucocorticoid may also be due to a deficiency of 11-β-OHSD, which normally acts as a placental barrier protecting the fetus from maternal glucocorticoids, even without activation of the HPA axis. This enzyme is likely attenuated in impaired fetal

growth. This is consistent with the inverse relationship between plasma cortisol concentrations and weight or length at birth in different adult populations, and with the positive correlation of cortisol and blood pressure. High fetal glucocorticoid levels have the short-term benefit of increasing glucose and other fuels, but they may have various permanent effects on the cardiovascular system, including altered sensitivity of the HPA axis to feedback hormones, and altered renal morphogenesis and renin-angiotensin system. It may also operate a permanent up-regulation of gluconeogenesis by programming key hepatic enzymes. As glucocorticoids regulate the fetal expression of insulin-like growth factors, their receptors and many binding proteins, they may affect fetal growth through this pathway as well.

Resetting of the glucose-insulin-IGF-1 (insulin-like growth factor) system, which is the primary axis regulating fetal growth, has been implicated in fetal programming. IGFs are the primary growth promoters *in utero*, whereas the role of growth hormone is largely confined to the postnatal period. IGF-1 and IGF-2 both promote growth during early embryonic development, and only IGF-1 appears to have a role in later fetal growth. Down-regulation of fetal growth is mediated by reduced concentrations of IGF-1, which controls fetal growth in late pregnancy and is under acute nutrition control. Fetal IGF-1 is secreted in response to fetal insulin, itself determined by placental glucose transfer. Fetal insulin acts primarily as an adipogenic factor, while its effect on lean body mass is probably mediated through IGF-1. Low substrate availability to the fetus shuts the IGF-1 system off with resulting lower fetal levels of IGF-1 and insulin, and indeed, low IGF-1 appears to be an indicator of fetal malnutrition in humans as well as in animals. This is connected with the "thrifty phenotype" theory proposed by Hales and Barker in the early '90s as an alternative to the "thrifty genotype" theory of Neel to account for the associations observed between fetal growth retardation and the subsequent development of chronic diseases, notably diabetes. The metabolism would become "thrifty" when the fetal nutrient supply is limited, in order to salvage vital organs, particularly the brain, at the expense of growth. This is where insulin resistance appears beneficial, particularly if it is selective, as suggested by some findings; that is, resistance to glucose transport action of insulin without resistance to its anabolic effect. However, this metabolic resetting as an adaptation for survival in a poor nutritional environment, becomes a liability in nutritional abundance. After birth, tissues that were chronically deprived of insulin and IGF-1 during fetal life are suddenly exposed to high levels of both hormones because of a supposedly adequate nutrient supply. It is speculated that insulin resistance helps to counteract their additive insulin-like effects to avoid hypoglycemia while growth catch-up takes place. It is not known, however, how insulin resistance develops. Leptin has been shown to interact with insulin, IGF-1 and cortisol, and it is known to play a role in the regulation of body weight and fat mass. It was proposed that intrauterine undernutrition induces impaired neuroendocrine regulation leading to hyperphagia, insulin and leptin resistance, obesity, and hypertension in adult life.

Restricted fetal growth and programming of chronic disease: the role of maternal nutrition

The link between smallness or body disproportions at birth and chronic disease is now strongly implicated and widely accepted. Underlying mechanisms are only beginning to be understood, based on experimental data. Genes and nutrition interact in utero, but short nutrient and oxygen supply, combined or not with maternal constraints, appear to be predominant factors of impaired fetal growth. Fetal malnutrition is not synonymous with maternal malnutrition, however. An inadequate supply of nutrients (or oxygen) to the fetus may also be due to maternal disease, abnormal utero-placental blood supply, or to placental insufficiency. Tobacco smoking during pregnancy is another well-known cause of fetal hypoxemia.

While the role of maternal nutrition may appear modest in affluent populations, poor nutritional status and poor food intake of mothers is recognized as a major factor of fetal growth impairment in developing countries and poorer population groups. Maternal nutritional status before and during pregnancy has to be distinguished from maternal energy and protein intake during pregnancy. Maternal nutritional status at the onset of pregnancy appears to be more critical than her nutritional adequacy during pregnancy for fetal growth, but it is not known whether this is also the case for chronic disease programming. Maternal height and pelvic dimensions, which reflect the mother's own nutritional past, already impose a constraint to fetal growth, and this provides one explanation for intergenerational effects of malnutrition. It is known that maternal height and BMI at the onset of pregnancy, and weight gain in pregnancy, are major determinants of size at birth.

There are different patterns and long-term consequences of fetal growth restriction, depending on the timing, nature and extent of the insult, as suggested by famine studies and animal models. Early or chronic

fetal undernutrition appears to be linked with a higher risk of hypertension, obesity, and CHD. In contrast, impaired fetal nutrition in late pregnancy exposes to insulin resistance and type-2 diabetes. A lower growth trajectory set early in uterine life in response to the intrauterine nutritional and hormonal environment represents an adaptation to reduce the risk that could be associated with short substrate supply in late gestation. Placental size alone, or in combination with birth weight, may be another important anthropometric indicator, as placentas that are either too small or too large seem to be associated with higher chronic disease risk, but further research is needed.

Body size and proportions at birth are only surrogate markers for the influences that programme the fetus, however, and fetal programming may occur without much effect on anthropometric measurements at birth. For instance, protein deficiency in early pregnancy may not only affect size at birth, but it may also be associated with high blood pressure in later life, possibly through a glucocorticoid effect. Evidence based on food supplementation data shows that dietary protein balance is critical, and that too much dietary protein may be as detrimental for fetal growth as not enough dietary protein. High protein and fat intakes of mothers during pregnancy were found to be associated with disturbances of glucose and insulin metabolism in 50 year-old adults, independently from maternal BMI or weight gain. This again suggests a role for dietary macronutrient imbalances during pregnancy. Maternal status or intake of specific micronutrients may also limit fetal (and placental) growth, and be implicated in programming of chronic diseases. Interestingly, maternal diet quality, more than quantity, was found to be related to the neonatal phenotype in India. Micronutrients presently suspected of having a programming role include iron, folate, zinc, magnesium, calcium, and vitamin C. Whether or not a high placental ratio, as reportedly associated with maternal iron deficiency anaemia, results in more hypertension in the offspring remains to be elucidated. Aside from its impact on neural tube defects, a contribution of folate deficiency to impaired fetal growth and fetal programming for CHD through elevated blood homocysteine is not unlikely, and it is an interesting research avenue. Dietary folate deficiency is compounded in a small proportion of the population by a genetic defect in an enzyme required for folate metabolism (5,10-methylenetetrahydrofolate reductase). In such people, dietary folate requirements to prevent homocysteinemia are much increased. It is hypothesized that folate deficiency in pregnancy may be associated with LBW, and that it may explain the link of LBW with cardiovascular risk in later life via the accumulation of homocysteine, as a result of the genetic defect, aggravated in certain instances by inadequate intake. Zinc supplementation has been associated with higher birth weights, but whether it is involved in fetal programming is not known. Some findings suggest that magnesium, essential fatty acids, and even vitamin C, would have growth and programming effects on the fetus. A calcium supplementation trial in pregnant women provided the first piece of experimental evidence of fetal programming by maternal nutrition in humans. Lower blood pressure was observed at the age of 7 years in children of supplemented mothers in spite of no significant differences in birth weight from controls. It is speculated that some micronutrients could have an important fetal programming role independent from an effect on birth-size, and future research will hopefully elucidate these effects.

If fetal nutrition is the major regulator of fetal growth, then one would expect nutritional supplementation of mothers to benefit fetal growth. However, the effects on birth weights have been found to be mitigated, perhaps with the exception of balanced energy-protein supplements. It may well be that nutrition helps prevent, but not reverse, impaired fetal growth. Research findings suggest that dietary imbalances may play as important a role as absolute deficits of energy or specific macro- or micronutrients. Inadequate study designs are another possible factor. Furthermore, partitioning of energy and nutrients between the mother and the fetus according to maternal status is not clear, and studies suggest that it may be in favour of mothers when they are depleted or still growing. Nevertheless, significant increases in birth weights have been observed when malnourished women were targeted for supplementation before, and during pregnancy. Similarly, multiple micronutrient supplements have been shown to improve pregnancy outcomes, including birth weights among poorer women.

Maternal nutrition programming effects may not be totally mediated by its effects on size at birth, as suggested by independent associations of maternal nutritional status with chronic disease markers in the progeny. For instance, low maternal BMI early in pregnancy was found to be independently associated with elevated blood pressure in Jamaican children, and with high rates of CHD in Indian men and women. In China, adults born small whose mothers were thin early in pregnancy, were more likely to show insulin resistance. In contrast, there are indications from Scandinavian studies that high maternal BMIs combined with shortness enhance CHD risk among individuals who were thin at birth. It was speculated that a high maternal

BMI increases fetal demand for nutrients, which cannot be met because of the constraint on placental growth owing to short stature. Intergenerational influences of maternal undernutrition that are not mediated by effects on birth-size of the first generation were also observed in famine studies, animal models, and a few prospective intergenerational studies. It now appears that maternal birth weight is positively and independently associated with offsprings' birth weight and length, as well as negatively with blood pressure in adults independently from the association between mother and child birth weights. Thus, promoting fetal growth will benefit not only this generation of infants, but also the subsequent ones. However, the benefit to be gained with regard to putative reduction of chronic disease risk cannot merely be inferred from the impact on average birth weights, given that fetal programming by nutritional influences may occur without altering size at birth.

Catch-up growth and propensity to obesity further enhance chronic disease risk associated with impaired fetal growth

There are obviously cumulative influences on chronic disease risk throughout the life cycle, and links between fetal growth and chronic diseases have to take this into account. Growth in postnatal life is only considered in the present paper for its interrelationships with prenatal growth. There appears to be a window for programming in early infancy, and this would deserve a comprehensive review in its own right. Catch-up growth and obesity in later life are discussed, as these appear to modulate the risk associated with impaired fetal growth.

Genes set the potential body size, metabolic competence, and functional capacity of individuals. To what extent this potential is achieved is determined by environmental experiences, including the intrauterine environment, and is expressed in the physical, hormonal, and metabolic phenotype. Throughout the course of life, the interactions of genes and phenotype factors determine the response of the body to environmental challenges, for instance stress, diet and other lifestyle patterns, or obesity. Impaired fetal growth conceivably modifies postnatal risk in three ways: small size at birth may increase vulnerability through "catch-up growth" in infancy; it may increase the propensity to obesity; and it may increase the risk generally associated with obesity. In order to elucidate the independent association of birth size with chronic disease factors in later life, it is customary to adjust for potential confounding factors, including current body size. However, this may not be entirely justified on the basis of concept, as current BMI may have been partly programmed in fetal life. It was observed that impaired fetal growth could predispose to obesity, and to a higher percentage of body fat irrespective of body mass. Children born growth retarded were also shown to have a tendency to put on more weight during the puberty growth spurt than those of normal size at birth. Furthermore, many studies indeed show an interaction between small size at birth and large body mass in later life with respect to CHD risk, high blood pressure, and metabolic syndrome. Hence, it was suggested to present adjusted and non-adjusted findings, and to assess the interactions between small birth size and current body size.

An increasing number of studies suggest that catch-up growth in children born light and thin is associated with higher risk. It seems that more than smallness at birth *per se*, it is the failure to achieve one's own growth potential *in utero* that is associated with higher risk of chronic disease. Catch-up growth refers to accelerated gain in height and weight, or both in postnatal life, to compensate for intrauterine growth impairment. It is not known whether its association with disease risk is mediated by the increased fat mass, the catch-up growth process itself, or the endocrine resetting of endocrine axes. Catch-up in weight and height does not imply full recovery at organ level, and it may shorten lifespan, as suggested in animal studies. It has been postulated that hormone-mediated increased food intake is responsible for postnatal catch-up growth leading to increased risk of obesity, but statistical evidence is still lacking. Similarly, catch-up growth has been found to be associated with an exaggerated insulin response in children, although this requires confirmation. Overcompensation for prenatal growth impairment may be common, as suggested by the tendency of children born small to put on more weight at pre-puberty and puberty.

Much epidemiological data on the impact of catch-up growth comes for prospective studies in Scandinavia. In a cohort of men born in Helsinki in the '20s and '30s, the highest death rates from CHD were observed in men who were thin (low ponderal index) at birth, and who had caught-up for weight by the age of 7. In this study, the increased risk associated with poor growth in terms of weight, height and BMI at the age of one year, irrespective of birth weight, is noteworthy. In the corresponding female cohort, shortness at birth was more of a risk for CHD than LBW, and catch-up for height further increased the risk. In both men and women, those who later developed hypertension or type-2 diabetes showed accelerated growth from birth to 7 years of age compared to normals, whereas only

those who developed diabetes had accelerated growth in height and weight between the age of 7 and 15 years. These data strongly suggest that fetal growth restriction increases the vulnerability to weight (and sometimes height) gain in childhood and pre-adolescence, in addition to a suspected propensity to obesity.

Several studies suggest that the effects of smallness at birth on chronic disease markers is amplified with age, and that it is an interaction with current BMI, so that the effects are enhanced in heavier individuals. In certain studies, the adverse effect of small size at birth is only apparent among the more obese individuals. Notwithstanding the described evidence of strengthening of the inverse association of birth size with markers of cardiovascular risk in later life, the relative contribution of impaired fetal growth, independently from, and in interaction with, other risk factors, whether genetic or environmental, is little known.

Controversial issues and related hypotheses

Epidemiological associations between birth size and proportions and later chronic disease, even if they are robust considering the delay between exposure and outcome, do not prove a cause-and-effect relationship. A major objection to the fetal programming theory is that rather than being causally related, lower birth weights and higher rates of chronic diseases are both related to a common cause. Poverty is seen as a common determinant, and according to some researchers, socioeconomic status can hardly be fully accounted for, leaving much unexplained residual variation. It is widely known that higher rates of CVD (and in general poorer health) are observed in lower socioeconomic groups. A similar social stratification is observed with regard to rates of LBW. In only a few studies, including that on CHD in South India, the inverse association of size at birth and chronic disease was no longer significant when adjusting for socioeconomic status. This association was little affected in most studies, and it was even strengthened in some when correcting for socioeconomic status. Nonetheless, low socioeconomic status may predispose to both suboptimal fetal growth, and to lifestyles in later life that increase chronic disease risk, such as tobacco smoking, lack of physical activity, and "atherogenic" diets (high-fat, low-fibre, little fruits and vegetables). These behavioural factors would have to be simultaneously and adequately controlled for in studies linking prenatal growth and later chronic disease, which has seldom been done. The association observed between birth weights and maternal mortality from all causes and from CVD also suggests a common cause, and intergenerational genomic and epigenetic processes underlying the link between mothers' and children's birth weights were postulated to influence cardiovascular risk rather than mere behavioural factors, in view of the magnitude of the association.

Genetic factors are also suspected of being responsible for both impaired fetal growth and chronic disease, be it CHD, hypertension, or diabetes. As described above, folate deficiency due to a genetic enzymatic defect aggravated by low intake could be related to both lower birth weights and higher CHD risk, but this would only explain a small fraction of the variance of CVD. Regarding type-2 diabetes, the "thrifty" phenotype theory is challenged by the "thrifty" genotype and the fetal insulin hypotheses, which postulate that the same genetic factors that impair insulin secretion or sensitivity may alter fetal growth and glucose tolerance in later life. The main difference between the thrifty phenotype and genotype theories is that the latter ascribes to genetic factors the predisposition to obesity and diabetes, while the former ascribes it to fetal programming; insulin resistance could be the common denominator. The end result might be the same, since whether individuals are born with the thrifty genotype or phenotype, they are likely to be vulnerable to overnutrition and physical inactivity as amplifiers of the initial risk. According to the fetal insulin hypothesis, insulin resistance would be genetically determined, and would be responsible for impairment of fetal growth. Abnormal vascular development in early life and adverse body fat distribution would increase hypertension and vascular disease risk. It is plausible that both fetal programming and genetic insulin resistance have a role in explaining the links between fetal growth and adult disease. Future studies should assess the respective role of genetics and fetal malnutrition in children born with impaired fetal growth.

Conclusions and recommendations

Although there are still controversial areas and information gaps, there is accumulating evidence for an inverse association between size at birth and chronic diseases such as CHD, hypertension, and insulin resistance syndrome deriving from experimental models of fetal programming by nutrition as well as from an increasing number of retrospective and longitudinal studies from developing countries. It is noteworthy that the early observational studies leading to the theory came from European cohorts born in the '20s and '30s, when maternal and child health and nutrition was not up to the standards of today. The same sequence of events is likely occurring now with nutri-

tion transition in developing countries. In intrauterine growth impairment, whether or not it is due to maternal malnutrition or to other factors such as maternal smoking, fetal programming of chronic diseases appears to be mediated through resetting of major hormonal axes of fetal growth regulation; there may also be some structural changes.

Thus, fetal programming likely represents one more risk factor for chronic diseases, in addition to genetic and environmental factors. The implications may be dramatic for populations which currently have (or recently had) high rates of LBW, as this additional risk factor would be compounded with increasing obesity and sedentary lifestyles typical of urbanization and rapid economic growth.

The development of chronic disease should be conceived as resulting from cumulative risks throughout the course of life, an approach that may easily reconcile apparently conflicting theories based on genetic susceptibility, fetal (and early postnatal) programming, or lifestyle risk factors. Whether the predisposition to chronic diseases related to nutrition is genetic or the result of fetal programming, or both, it remains that this predisposition will be expressed when diets and lifestyles are conducive to it. However, fetal programming of common adult diseases, unlike the genetic theories, provides additional justification, if needed, for emphasis on optimal fetal growth and development. Prevention of impaired fetal growth through improved nutrition of girls and women not only contributes to lower maternal mortality, and better child survival and development, it may also help to prevent chronic disease, and in particular, the obesity, diabetes, and CVD epidemic in developing countries. Although the portion of chronic disease that can be explained by fetal programming (and prevented by optimal fetal growth) may appear small, intrauterine growth impairment affects 30 million children annually, of whom 75% are in Asia and 20% in Africa. Furthermore, the benefit of improving maternal (and fetal) nutrition may go beyond what may be projected based on birth weights since intrauterine programming may occur without verifiable effect on size or proportions at birth. However, in view of available evidence, new interventions directed at women for the specific purpose of reducing the risk of chronic disease in the offspring do not appear relevant as yet, beyond early action to ensure that women enter pregnancy with an adequate nutritional status, and have appropriate nutrition monitoring and promotion throughout pregnancy. The importance of stimulating non-smoking behaviours at society level is also stressed, as active as well as passive smoking during pregnancy is a recognized factor of impaired fetal growth.

With rapid nutrition (and economic) transition, an initial increase in CVDs in many population groups is to be feared because of atherogenic lifestyles. This initial increase may be even higher because of fetal programming associated with malnutrition and poverty early in life, and/or because of genetic susceptibility.

The fact that children who showed impaired fetal growth are at enhanced risk of chronic disease by virtue of catch-up growth, and particularly so if they become obese, may have practical implications for policy. Better data bases on birth weights (with information on gestational age) should be developed and maintained. Furthermore, children born small should be targeted by nutrition promotion and obesity prevention activities, especially those administered through the school system.

The issue of fetal nutritional programming of chronic diseases is progressively attracting more attention in health and development circles. It has to be set in the overall framework of nutrition transition, and it triggers challenging strategies of simultaneously addressing undernutrition and overnutrition throughout life course. Therefore, stronger collaboration is required between academic institutions, national governments, and international, bilateral and nongovernmental organizations. In addition, a consultation is urgently needed among concerned experts to further examine the evidence for developing effective intervention strategies and policies and to identify research gaps.

Many lines of research require development in order for the mechanisms of fetal programming to be better understood, to clarify the role of maternal nutrition, and more importantly, to determine whether the potentially adverse effects of impaired fetal growth on chronic disease may be delayed or prevented by an adequate and prudent postnatal diet. The following appear as particularly pressing research needs:

- Conjunct analysis of available population data on birth weights, the prevalence of obesity, and the prevalence and death rates from CVD and type-2 diabetes;
- Respective role of fetal and placental growth in predisposing to adult diseases;
- Effect of suboptimal maternal nutrient intake, and its timing, on fetal and placental growth, in adolescent and adult mothers, with a clear definition and measure of prenatal "exposure";

- Effects of deficiencies in specific micronutrients, and of their timing, on fetal growth and chronic disease markers, in particular, iron, folate, magnesium, zinc and vitamin C;
- Extent of spontaneous and controlled catch-up growth in infancy according to type of fetal growth impairment, including that due to maternal smoking, and parental size;
- Potential for "reprogramming" of growth-restricted newborns through nutrition-controlled catch-up growth in the first years;
- Effectiveness of pilot interventions promoting simultaneous improved nutrition for the prevention of undernutrition/impaired fetal growth, and for the prevention of obesity/chronic diseases.
- Effects of maternal smoking on infant body composition, postnatal growth, and chronic disease risk later in life

1. Introduction

Rates of obesity and other diet-related chronic diseases, particularly cardiovascular disease (CVD),[1] are increasing in most of the developing world and in countries undergoing economic transition. While rates remain elevated in most of the industrialized world, CVD shows a declining trend in Australia, Finland and the USA (WHO, 1998). Paradoxically, obesity continues to increase—at least in the USA. Meanwhile, undernutrition and micronutrient deficiency diseases still affect large numbers of mothers and children in developing countries. Low birth weight (LBW) associated with retarded fetal growth, which partly reflects poor maternal nutrition, is widespread in developing countries, and rates may reach 40% in vulnerable population groups. Maternal smoking, either active or passive, is also considered an important factor of impaired fetal growth and lower birth weight in an increasing number of developing countries. Lifestyle and genetic predisposition in certain population groups are incriminated as major determinants of chronic diseases, while poverty is recognised as a common denominator in undernutrition and specific nutrient deficiencies. Poverty is also associated with a higher risk of chronic disease, although it is all too often overlooked. Thus, developing countries face a double burden—malnutrition (general and micronutrient deficiencies) and diet-related chronic diseases (Popkin, 1994, 1998).

Undernutrition is implicated in more than half of the 12 million annual deaths of children under five-years-old (WHO, 2000). Early undernutrition may also contribute to increased risk of chronic disease, in particular CVD and associated conditions. This is the crux of Barker's (1992) "early origins" hypothesis, which is based on ecological data in England more than a decade ago, and for which evidence is accumulating. This environmental hypothesis is regarded by many health professionals and scientists as a major revolution from the predominantly genetic and lifestyle approach to chronic disease. It may have major implications for public health policy and development in developing countries. The theory helps explain the sometimes galloping increase of CVD when populations shift from chronic undernutrition to affluence; a phenomenon described as the "nutrition transition" (Popkin 1998). It may also explain why chronic diseases are more widespread in poorer groups of industrialized countries; and why obesity has less of a deleterious effect in population groups who have been exposed to food abundance for many generations. According to Barker, coronary heart disease (CHD), type-2 diabetes, and syndrome X are the postnatal price to pay for fetal adaptation to suboptimum nutrition. In spite of the enthusiasm raised by the hypothesis, other scientists are more skeptical (Paneth & Susser, 1995; Joseph & Kramer, 1996; Anon., 2001). If causal links between preventable prenatal (or early infancy) factors and adult CVD and related chronic diseases are demonstrated, the public health community can address more than lifestyle changes associated with risk factors operating through adulthood. Fetal programming may represent an additional source of environmental risk which interacts with other determinants throughout the life course.

Presently, CVD mortality rates are highest in eastern and northern Europe; however, there is a burgeoning epidemic of CVD in the former socialist economies and in some developing countries. The CVD epidemic is still relatively less significant in sub-Saharan Africa. In India, the high rates of CVD cannot be explained solely on the basis of known risk factors. They are associated with the insulin resistance syndrome[2] (McKeigue, Shah & Marmot, 1991), and they are more

[1] Cardiovascular disease refers primarily to coronary heart disease (CHD) and stroke.

[2] Insulin resistance syndrome, or syndrome X, or metabolic syndrome is characterized by clustering of insulin resistance (or type-2 diabetes or impaired glucose tolerance) with other biological markers of CVD risk, in particular high blood pressure and high triglyceride concentrations. Impaired glucose tolerance is defined by elevated blood glucose (≥7.8 mmol/L plasma) 2 hours following an oral glucose load although fasting blood glucose is normal. Diabetes is defined by elevated fasting glucose (≥7.0 mmol/L plasma) (WHO 1999a).

common in urban areas and among lower socioeconomic groups (Fall & Barker, 1997). In urban Madras, the rate of diabetes had risen to 11.6% in 1994, a 40% increase in five years, while impaired glucose tolerance remained stable (Yajnik 1998). India suffers a major problem in that postnatal nutrition has improved, but prenatal nutrition has not: mean birth weight is still 2.9 kg. When Indians move to other countries, CVD rates rise still higher (Yajnik, 1998). American Indians were thought to be inherently protected from CVD, but recent data indicate that rates are rising and may exceed those of the general population in the USA (Howard et al., 1999). The high and increasing prevalence of type-2 diabetes is the most likely explanation for rising CVD rates among American Indians, who also show a high prevalence of insulin resistance syndrome. Latest projections predict that the total number of people who are affected by diabetes will double over the next 25 years, reaching 300 million by 2025 (King, Aubert & Herman, 1998).

As rates of obesity and diabetes increase in several populations, there may be a world upsurge of CVD. Since the mid-'90s, CVD has been at the top of the list of major diseases in industrialized countries as well as in developing countries. As a cause for disability, it will be the world leader by 2020, by which time CVD will exceed parasitic and infectious disease rates everywhere except sub-Saharan Africa (Bulatao & Stephen, undated; Chockalingam & Balaguer-Vintro, 1999). Cardiovascular disease accounts for nearly one third of all deaths worldwide, and the most frequent causes are CHD and stroke. Out of the 15 million deaths due to CVD each year, 9 million are in developing countries and 2 million in countries with economies in transition. Unless there is a better understanding of its origins, a prediction of its magnitude, and the organization of preventive and case-management strategies early enough to control it, a global epidemic of CVD in developing countries may be inevitable (Pearson, 1999). The increasing magnitude of the obesity problem in developing countries has been stressed by WHO (2000). Even in China, where undernutrition still affects a sizeable proportion of the population, obesity, hypertension, and CVD are becoming more highly prevalent in urban population groups ,which is typical of "nutrition transition" (Popkin et al., 1993; Popkin, 1998).

It is known that early malnutrition may permanently affect the expression of genetic potential in terms of growth, metabolic processes, and even cognitive performance. The "early origins" hypothesis traces common chronic diseases in adulthood back to disturbances during fetal or early development which "programme" for these diseases. This theory may offer an alternative—or better, a complement—to genetic and lifestyle hypotheses to explain the dramatic rise of chronic diseases, such as CHD and diabetes, in several groups, particularly indigenous peoples and developing country populations. Genetic predisposition and lifestyle changes cannot fully account for this chronic disease surge. Obviously, there are several influences on health and development throughout the life cycle. Attempts at elucidating the links between fetal (or early infancy) growth and nutrition and chronic diseases have to take into account the interaction with, and modulation by, events occurring during childhood, adolescence, and adulthood, which makes the demonstration even more difficult.

Although the portion of chronic disease, especially diabetes and CHD, that could be explained by impaired fetal growth may be small in some settings, it is worth underlining that intrauterine growth retardation (IUGR) affects approximately 30 million newborns annually, of whom around 75% are in Asia, 20% in Africa, and 5% in Latin America (de Onis, Blössner & Villar, 1998). The incidence of LBW due to IUGR is six times higher in developing than in industrialized countries. The nutrition transition may further contribute to an increase in chronic disease with the emerging role of catch-up growth as an additional risk factor (see Section 7.1.). In countries undergoing a shift from chronic undernutrition to adequate nutrition, postnatal nutrition improves faster than prenatal nutrition, making (over)compensatory weight and height gain more likely. In such circumstances, the prevalence of insulin resistance syndrome and type-2 diabetes appears to increase (Fall et al., 1998).

The "early origins" hypothesis has evolved over the last 15 years or so based on accruing evidence. It is still controversial, and many areas of uncertainty remain. The purpose of this paper[3] is to review recent epidemiological and experimental evidence of intrauterine programming of chronic disease by impaired fetal nutrition. Although the vulnerable period for programming may extend into infancy, and perhaps even later into childhood, the focus of this paper is on prenatal

[3] The first draft of this paper was prepared in 1999. In the meantime, a considerable number of new research and conference reports, reviews (Cox, 2000; Godfrey & Barker, 2000; Holness, Langdown & Sugden, 2000; Huxley, Shiell & Law, 2000; Harding, 2001; Rasmussen, 2001), and books (Barker, 2001; Nathanielsz, 1999) have been published. The wealth of these new data is indicative of the interest in (and debate around) the early origins hypothesis.

origins of chronic diseases. Postnatal factors are only considered when they interact with (modulate, amplify) prenatal influences. Cardiovascular disease, hypertension, type-2 diabetes, and factors of insulin resistance syndrome are primarily considered; other chronic diseases are only briefly alluded to inasmuch as fetal programming may potentially be involved. Based on the review, lines of intervention strategies and needs for further research are identified, with particular focus on developing countries.

2. The concept of fetal programming of chronic diseases

According to the fetal origins hypothesis, alterations in fetal growth result in developmental adaptations that "programme" vulnerability to cardiovascular, metabolic and endocrine disease in later life (Barker, 1995). "Programming" is a phenomenon whereby a long-term and irreversible alteration in structure or metabolism is induced by a relatively brief stimulus (Martyn, 1994). During fetal growth, changes in the nutrient and hormonal milieu of the conceptus at critical periods may alter expression of the fetal genome, leading to permanent effects on a range of physiological functions and structures (Lucas, 1991). The important point of this definition is that the programming event can only occur during a specific window of sensitivity (Lucas, 2000). Programming reflects a general principle of developmental biology, and a wide range of organs and systems may be programmed by the intrauterine environment (Godfrey, 1998).

Other than through direct damage, there are two ways in which a stimulus or insult at a critical period in early life may influence long-term outcomes (Lucas, 1998):

1. induction, deletion or impaired development of a somatic structure
2. physiological "setting", such as resetting of hormonal feedback, with long-term consequences for function.

In Scrimshaw's terms (1997), interaction between nutritional factors and gene regulators may "programme" the fetus, leaving it with a spectrum of metabolic or tissue properties that have significant impact on the individual's proneness to disease later in life. It is in fact re-programming, which reflects the metabolic, physiological, and endocrine adaptations that the fetus undertakes when substrates or oxygen are in short supply for one reason or another.

Other principles of fetal programming as described by Nathanielsz (1999) for a non-specialized readership include: a role for the placenta; postnatal interventions to compensate for intrauterine deficiencies, which may carry a price later in life; the potential effects of programming across generations; and the frequently observed differences in programming effects in males and females.

The concept of programming goes far beyond the widespread recognition that conditions during gestation shape the health of the newborn. Permanent effects of early malnutrition that are the result of programming include neural tube defects linked with folate deficiency, and altered mental development in iodine deficiency. What makes the fetal programming hypothesis more difficult to confirm or accept is the long stretch of time separating the insult and the adverse effects, the numerous factors that may modulate this relationship throughout life, and the possibility that impaired fetal growth (often reflected in smaller size or altered body proportions at birth) and chronic disease are not causally linked, but share a common origin, such as poor socioeconomic conditions, or genetic predisposition (see Section 8.1.). The fetal programming hypothesis is nevertheless gaining grounds as evidence accumulates from observational studies and particularly from experimental models.

Biological mechanisms may "memorize" the metabolic effects of early nutritional environments (Waterland & Garza, 1999). Paneth (1994) refers to "fetal impression". As noted by Hay (1999), fetal metabolism is led by nutrient supply, and hormonal regulation becomes important only in neonatal life. The short supply of nutrients to the fetus during critical periods may impair fetal growth and permanently affect the development and function of systems, leading to metabolic changes in later life such as reduced insulin sensitivity (Ravelli et al., 1998; see 3.4. and 3.5.). According to Hales (1997a,b), the residual function of organs may be affected by fetal conditions and therefore, such effects would only appear in mid-life.

The term "metabolic imprinting" rather than "programming" is used by Waterland and Garza (1999) in order to encompass adaptive responses to specific early nutritional conditions which have the following features:

1. susceptibility limited to a critical period early in development (narrowly defined period)

2. persistent effect through adulthood
3. specific and measurable outcome
4. dose-response or threshold relation between specific exposure and outcome.

Lucas (2000) objects, however, that fetal programming goes beyond resetting metabolism and therefore, considers that "programming" is more appropriate than "metabolic imprinting". Furthermore, he views this substitution as introducing unnecessary confusion with imprinting of genes, although Signorello & Trichopoulos (1998) suggest that genomic imprinting may be a form of programming that could explain some observed links. This type of imprinting has a strong biologic foundation, and it involves non-permanent DNA modifications that may extend their influence over several generations. Intergenerational effects, as observed in the progeny of individuals exposed to famine while *in utero* (see Section 6.6.), are regarded as supporting the theory of genomic imprinting.

3. Fetal programming of chronic diseases: supportive evidence from epidemiological data

High infant mortality was found to be associated with higher death rates from CHD first in Nor way. Several studies had identified a link between birth weight and blood pressure, and Barker and his team in England were able to find an inverse association between birth weight and CHD, in historical cohorts of adults born in the '20s and '30s and for whom well-documented birth records were available. Inverse associations of size at birth (birth weight, length, or ponderal index) with coronary artery disease, hypertension, type-2 diabetes, and insulin resistance syndrome have now been reported in all continents. Potential confounding factors include age, sex, current body size, and socioeconomic status, but they have generally been adjusted for in studies. The inverse relationship between fetal growth and markers of cardiovascular risk and insulin resistance has also been observed in children and adolescents. Further epidemiological evidence for the hypothesis of fetal programming is provided by observations in twins and in populations exposed to famines, although there are conflicting reports. These and other associations between fetal growth and risk of degenerative disease have been extensively reviewed by Barker (1998; 2000).

3.1 Historical overview

The relationship between infant mortality and subsequent ischaemic heart disease in survivors from the same generation was first demonstrated in Norway (Forsdahl, 1977). Neonatal mortality was found to be more strongly associated with CHD than post-neonatal mortality, which pointed to the importance of prenatal life. The same type of ecological correlation was reported in 1986 by Barker & Osmond in England and Wales. It was observed that CHD was most common in the poorest parts of the UK (Martyn, 1994). Areas of the country that had high rates of infant mortality in the past, now have high rates of heart disease. In contrast, those with low infant mortality now have relatively lower rates of CHD. High infant mortality occurs in places with high rates of LBW, reduced infant growth, and poor nutrition and health of pregnant women. As LBW and reduced infant growth reflect adverse environmental influences during pregnancy or infancy, it was hypothesized that these influences initiated patho-physiological mechanisms that ultimately lead to CHD.

A major difficulty has been the availability of data on birth weight and other relevant obstetric and neonatal information in order to substantiate the hypothesis. Barker began by documenting CHD events in population groups where he could find well-kept records on births. This is how he studied the relationship of early events (birth weight and status at birth, weight gain, feeding in infancy, etc.) and disease patterns in large cohorts of adults born in the '20s and '30s in Hertfordshire, Preston and Sheffield. He developed his "early origins" hypothesis based on these retrospective studies showing an inverse association of birth weights and CHD mortality and morbidity rates. He also proposed that poor nutrition during fetal (and early postnatal) life was the factor responsible for increased vulnerability to chronic disease. Epidemiological data from Britain and other parts of Europe, Australia, Asia, the Caribbean and Latin America, the USA, and even Africa, have since corroborated and extended the initial observations of increased risk of CHD, type-2 diabetes, and other components of the insulin resistance (or metabolic) syndrome with decreasing birth weights. Reviews on various aspects of the "early origins" hypothesis are available (Leon, 1998; Phillips, 1998; Whincup, 1998; Lucas, Fewtrell & Cole, 1999; Waterland & Garza, 1999; Cox, 2000; Godfrey & Barker, 2000; Holness, Langdown & Sugden, 2000; Huxley, Shiell & Law, 2000; Harding, 2001; Rasmussen, 2001), in addition to Barker's research reports and reviews (1992–99). Consensus was reached in an international nutrition coordinating body regarding the existence of associations between fetal growth as evidenced by anthropometric indicators and adult disease, in particular high blood pressure, ischaemic heart disease, and type-2 diabetes, although areas of uncertainty were underlined (Grivetti et al., 1998). The First World Congress on the Fetal Origins of Adult Disease held in Mumbai (India) in February 2001 confirmed

that there is a link between fetal growth and later diseases, although the exact mechanisms remain to be elucidated (Robinson, 2001).

Many of the conditions which have been diversely linked to size or proportions at birth as a reflection of fetal growth often coexist as part of syndrome X or metabolic syndrome (Reaven 1988), that is, hypertension, dyslipoproteinemia, and other CVD risk markers such as obesity, in addition to insulin resistance or impaired glucose tolerance or type-2 diabetes. Barker et al. (1993b) even coined the name "small baby syndrome" for syndrome X. Yet, chronic disease risk markers associated with suboptimum fetal growth have been usually considered individually, particularly in earlier studies. This is the reason for separately reviewing epidemiological findings on CHD, high blood pressure, and insulin resistance/diabetes. The main epidemiological studies of the last decade on the fetal origins of CVD are summarized in Appendix A.

3.2 Size or proportions at birth and cardiovascular disease

The inverse relationship of birth weight with CHD death rates was first demonstrated in England by Barker and coworkers. In a large study in Hertfordshire on 16, 000 men and women born in the '20s, the death rates fell by half from the lower to the higher end of the birth weight distribution (Barker et al., 1989b; Osmond et al., 1993). There was a small rise in the highest birth weights, which could relate to the macrosomic infants of women with gestational diabetes. In another historical cohort of men in Sheffield, Barker et al. (1993c) confirmed the increased CHD risk associated with fetal growth restriction, and the inverse association of ponderal index(PI)[4] at birth with CHD mortality. In these cohorts, death from stroke was also found to be associated with lower birth weight, and with low infant weight in men (Martyn, Barker & Osmond, 1996). Differences noted in the patterns of fetal growth restriction were associated with high mortality rates from CHD and from stroke. Stroke was associated with low placental weight and birth weight relative to head circumference, with the highest rates associated with a high ratio of head circumference to placental weight. An association was found between flat pelvis in the mothers, lower birth weight, and stroke in the offspring. The authors suggested that this association was indicative of the link of the disease with poor nutrition of the mother in her childhood, which adversely affected her subsequent ability to sustain fetal growth. In contrast, mortality from CHD showed a U-shaped association with the ratio of placental to birth-weight, and a direct relationship with thinness, shortness, or small head circumference. This reflects various types of fetal adaptation to undernutrition.

In Finnish men born in Helsinki in the '20s and '30s, Forsén et al. (1997) observed a strong inverse association between PI at birth and mortality from CHD, while there was a non-significant negative trend with birth weight. For each unit decrease in PI, there was a 14% increase of hazard ratio. Among women of the same cohort, Forsén et al. (1999) found that the rate of fatal and nonfatal CHD was associated with lower birth weight after adjusting for placental weight, and even more strongly with short length at birth. The risk ratio increased by 10.2% per cm decrease in birth length. There were also interactions with postnatal growth. In men, higher weight at age 7 increased the CHD risk associated with small size at birth, while in women, there was an interaction between shortness at birth and tallness at age 7, particularly among those with tall mothers. The authors speculated that there is a sex difference in the response of the fetus to growth constraint because the female fetus grows more slowly; this could be related to the lower rate of CHD among women.

Also in Scandinavia (Uppsala, Sweden), Koupilova, Leon & Vagero (1997) showed that in men born about the same period of time birth weight was inversely related to mortality from circulatory diseases: the rate ratio was 0.67 per kg increase in birth weight. This relationship was not mediated through increased blood pressure, nor was it affected by adjusting for socioeconomic status and smoking. It was slightly strengthened, however, when adjusting for body mass index (BMI) at age 50. In a male cohort also born in the '20s and '30s, Frankel et al. (1996a,b) did not observe an inverse association of birth weight with fatal and nonfatal CHD during a 14-year follow-up period of men initially aged 45–60 years, except in the upper tertile of current BMI. Interactions of size at birth and size at later times are discussed in Section 7.

A study in southern India also showed that LBW and CHD were linked (Stein et al., 1996). The prevalence of CHD in men and women aged 45 or older reached 18% in those weighing ≤2.5 kg at birth, to 4% in those weighing ≥3.2kg. Short birth length and low head circumference at birth were also associated with raised prevalence of the disease. Furthermore, CHD was related to low maternal weight in pregnancy thus the highest rates were found in persons with LBW and thin mothers. Coronary heart disease was associated with the conventional risk factors including age,

[4] Ponderal index (PI)=[weight(g)/length(cm)^3]x100.

diabetes, high blood pressure, adverse serum lipid profiles, short stature, and smoking, but not with raised fibrinogen concentrations or obesity. Simultaneous regression analyses suggested that the associations between reduced fetal growth and conventional coronary risk factors did not suppress the association between birth length and CHD. Lack of birth weight information resulted in a very low participation rate, which highlights the difficulty of such studies in developing countries.

In a subset of the Hertforshire cohort of men born in the '20s and '30s and still living there in the '90s, Vijayakumar et al. (1995) observed that left ventricular mass was not related to birth weight, but it was highest in men with the lowest weight at the age of one year, after controlling for current age, body size, and systolic blood pressure. The enlargement was concentric, which is a known risk factor for CHD. Similarly, in French subjects aged 8–24 years (Zureik et al., 1996), a concentric increase of left ventricular mass was found to be inversely related to weight at the ages of 9 months and at 2 years, but not to birth weight. These data suggest that poor postnatal growth may be an independent risk factor.

In the Nurses Health study involving 80, 000 women in the USA, there was a twofold fall in the relative risk of nonfatal CHD across the range of birth weight (Rich-Edwards et al., 1995a,b). Height was also found to be inversely related to coronary disease risk in these women, even after adjusting for age, birth weight, and current BMI. Adjustment for several potentially confounding variables did not alter the inverse association. Furthermore, short stature was associated with many cardiovascular risk factors (including high BMI, high cholesterol, diabetes, and parental history of myocardial infarction). As suggested by the authors, height may be a marker for coronary artery lumen. It is also in part an indicator of early childhood nutritional status, and of socioeconomic circumstances. An inverse association between height and myocardial infarction was observed in various cohorts of men, and in the prospective Framingham Heart Study (Kannam et al., 1994). Height was inversely associated with all-cause mortality, respiratory disease, stroke, and CHD mortality in a prospective observational study of more than 15, 000 men and women recruited since 1972 in Scotland (Davey-Smith et al., 2000). Short bones were found to be a marker of short life (Gunnell, Rogers & Dieppe, 2001). Both genetic potential and the magnitude of fetal growth determine final height, as verified in a population-based longitudinal cohort study of term babies in Sweden (Karlberg & Luo, 2000).

Conversely, birth weight of offspring was found to be associated with CVD mortality risk among parents. In a retrospective observational study in England, Davey-Smith et al. (1997) found that each kilogram decrease in birth weight of the infant was associated with a doubling in the risk of parental mortality from CVD between the ages of 45–64 years. The relationship was stronger with mothers, and adjusting for several confounding variables did not alter it. As expected, mothers of larger babies were also taller, had higher BMI, and were less likely to smoke than mothers of smaller babies. The finding was replicated in a large longitudinal study of infants born between 1976 and 1997 to over 44, 000 women aged 15–45 years in England and Wales (Davey-Smith, Harding & Rosato, 2000). This suggests that mortality is influenced by social, health or nutritional factors that are related to birth weight and that are transmissible across generations, although the association cannot solely be explained by non-genetic factors, given its strength (see Sections 6.6. and 8.1.).

3.3 Blood lipid profile and blood coagulation

Blood markers of cardiovascular risk and their association with size at birth have been examined in a few studies, including Barker's in England (Barker et al., 1992; 1993b,c; 1995), which showed that raised total and low density lipoprotein (LDL) cholesterol was associated with impaired fetal growth (in addition to the type of infant feeding). Babies with a small abdominal circumference had higher serum cholesterol. Small abdominal circumference suggests failure of growth of abdominal viscera, including the liver, in late gestation. Programming of adult serum cholesterol may occur during a phase of rapid growth of the liver in the last trimester of pregnancy. Even if birth weight was within the normal range, men who were disproportionally short for head size at birth had persistent disturbances of cholesterol metabolism and blood coagulation. There was a strong inverse relationship between fibrinogen levels, the strongest determinant of CVD also synthesized in the liver, and abdominal circumference at birth (Barker et al., 1992). These fetal (and infancy) effects were independent of lifestyle effects, such as smoking, which is known to be positively associated with fibrinogen level (Martyn, 1994). This is in contrast with the positive association of birth weight with fibrinogen levels in the cohort study of South Wales men (Frankel et al., 1996a,b) born in the '20s and '30s. In this study, triacylglycerol levels were also positively related to birth weight.

Findings on plasma lipids in children are conflicting. In a large retrospective cohort study on Jamaican

schoolchildren (Forrester et al., 1996), serum cholesterol was found to be inversely related to length at birth and current height but not birth weight, in addition to being directly related to current triceps skinfold. Cook et al. (1999), however, found that fibrinogen and factor VII were related to adiposity in British children aged 10–11 years, but not to fetal growth. In UK children aged 11–14 years, Morley et al (2000) found a significant inverse association between birth weight and serum triglycerides, but not with other lipids. Social deprivation was associated with higher fibrinogen, but not lipid levels.

Increased apo-lipoprotein B and elevated ratio of apo-B to A-1 are predictors of atherogenesis. Based on fetal umbilical plasma samples from 18 IUGR and 23 normal fetuses, Radunovic et al. (2000) found significantly higher levels of apo-B and higher ratios of apo-B to A-1 in growth retarded fetuses than in normal ones, while triacylglycerol levels were not different. The samples came from an ethnically homogeneous, non-smoking population. According to the authors, previous results had been inconsistent perhaps because of ethnic and behaviour variations. Decsi et al. (1999), however, did not find that impaired fetal growth was associated with a higher risk of disturbed lipid homeostasis than prematurity in a study of 10 year-old children who were LBW. As stressed by Barker (1999c), further research is required on the linkages between abdominal circumference at birth, fetal liver development, and blood lipid profile in later life, as well as on the underlying mechanisms of altered lipid homeostasis that may originate *in utero*.

A study compared migrants from the Punjab region who were living in London, with their siblings who remained in India. The migrant men and women had higher serum cholesterol and glucose, and lower high density lipoprotein (HDL) cholesterol. Serum Lp(a) concentrations, which are believed to be determined genetically, were similar in both groups (Bhatnagar et al., 1995). Possible explanations (Fall & Barker, 1997) which are not necessarily mutually exclusive, are that this reflects the link between higher chronic disease risk and lower size at birth according to the "early origins" hypothesis; or that the genetic predisposition to CHD is expressed when there is exposure to sedentary lifestyles, obesity and other aspects of westernisation, in keeping with the "thrifty gene" hypothesis of Neel (1962; 1982) (see Section 8.3.).

Hence, lower birth size has been found to be associated with higher CHD risk in widely different settings, although its relationship with blood lipid profile appears inconsistent. Additional supportive evidence for an association of small size at birth with high blood pressure and metabolic syndrome (or syndrome X) also exists.

3.4 High blood pressure

Law & Shiell (1996) reviewed 34 studies describing the relationship of blood pressure with birth weight in quantitative terms and in non-pathological groups, representing 66,000 individuals. Nearly all reported an inverse association, with a few exceptions in adolescents and newborns. There were 25 cohort studies, 4 case-control or comparative studies and 5 longitudinal studies. Nearly half the studies were from UK, and only 4 included nonwhite subjects. Roughly half of the studies reported multiple regression analyses, controlling for current size which was the most important potential confounder. Blood pressure was typically 2–3 mmHg lower per kg increase in birth weight. In only one study in adolescents in Israel, and only in girls, there was a positive correlation between birth weight and blood pressure (Seidman et al., 1991a). When blood pressure was measured during the first four days of life, the relationship with birth weight was consistently positive. The longitudinal studies with repeated measures during infancy and childhood (none was done in adults) suggested that after being positive in the first few months of life, systolic blood pressure is negatively associated with birth weight. One study described a U-shaped relationship in 4-year olds, with higher blood pressure both in children who were smaller and those who were bigger at birth (Launer, Hofman & Grobbee, 1993). In a systematic review update (Huxley, Shiell & Law, 2000), 46 studies on birth weight and blood pressure were examined, representing with the previous review more than 444,000 male and female subjects of all races and ages. Other measures at birth and the role of postnatal catch-up growth were also considered in the later review of 37 cohort studies and 9 longitudinal studies. The inverse association of birth weight and systolic blood pressure was described in the majority of studies, with a decrease of around 2 mmHg per kg increase in birth weight. The relationship was present but attenuated at adolescence, compared to other periods of life. Of other birth measures, head circumference was the most consistently (and inversely) related to blood pressure.

The inverse relationship between birth weight and blood pressure, particularly systolic blood pressure, has been observed in white and non-white populations, in all age groups, in cohort, retrospective and longitudinal studies, and in industrialized and developing countries, although there are some divergent findings. There is less consistency in the reported associations between

blood pressure and other measurements at birth.

In industrialized countries, for instance, birth weight was inversely related to blood pressure in adults in Sweden (Koupilova et al., 1997), USA (Curhan et al., 1996a,b), and Finland (Forsén et al., 1997). No such association, however, was found in another study in Sweden (Siewert-Delle & Ljungman, 1998), and in South Wales (Frankel et al., 1996a,b). In the Netherlands, blood pressure was inversely related to birth weight throughout a follow-up period of 14 years, in a longitudinal study on subjects initially aged 5–21 years (Uiterwall et al., 1997). This is in contrast with a study in adolescents in Israel showing a positive relationship between blood pressure and current BMI, but no association with birth weight (Laor et al., 1997), much like a previous study by Seidman et al. (1991a). Matthes et al. (1994) did not observe an association among adolescents either. Although it was weak, a negative association of birth weight and blood pressure was reported in Italian adolescents (Rabbia et al., 1999), and in New Zealand adolescents as well (Williams, St George & Silva, 1992). In France, an inverse association was observed by Zureik et al. (1996) in the age range of 8–24 years. Similarly, among 3–4-year-old children in France, Said et al. (1998) found that blood pressure was inversely associated with PI at birth after adjusting for current body size. In the longitudinal cohorts of the large Bogalusa Study in Louisiana, there was some evidence of a greater risk of high blood pressure at age 7–11 years in LBW children, but primarily in the young black males; results in other age and sex groups were inconsistent (Donker et al., 1997). When the analysis was restricted to full-term births, BMI was a much stronger determinant than birth weight in this longitudinal study. In a 3-year-old child cohort from Avon Country (England), Whincup et al. (1999) reported an inverse and graded relationship of birth weight with both systolic and diastolic blood pressure after adjusting for current height and weight. It was found in this study that other measures of size at birth (PI, length and head circumference) did not have an independent effect on blood pressure, although they did in other studies. In Australian youth, for instance, Moore et al. (1999) observed that not only lower birth weight, but also thinness or shortness at birth, and high placental ratio were associated with higher blood pressure. In a large record linkage study in Sweden on more than 165,000 male conscripts aged 18 years and born after 35 to 44 weeks of gestation (Leon, Johansson & Rasmussen, 2000), systolic was found to be inversely and independently associated with birth weight for gestational age; the effect was -1.47 mmHg per kg increase in birth weight. There was also a small but independent inverse relationship with gestational age, but not with birth length. The authors suggested that the rate of accretion of fetal soft tissue mass, rather than bone growth, is the component of fetal growth that is independently and inversely associated with later blood pressure. This is at variance with a previous population-based study in Sweden which reported that gestational age was inversely related to adult blood pressure while birth weight was not independently so (Siewert-Delle & Ljungman, 1998).

In developing countries, an increasing number of researchers report an inverse association of size at birth and blood pressure, both in children and adults, since it was first reported from southern India (Stein et al., 1996). In China, for instance, both systolic and diastolic blood pressure were strongly and inversely related to birth weight in adults in their mid-forties (Mi et al., 2000), and this association was independent of maternal blood pressure and of length of gestation. For every kilogram increase in birth weight, there was a 3 mmHg drop in systolic blood pressure, which represents a strong effect. In African children from Zimbabwe (Woelk et al., 1998), birth weights were significantly and inversely associated with systolic blood pressure after adjustment for current weight, but not with diastolic blood pressure. There was also an inverse association of head circumference at birth and systolic blood pressure, and birth weight and birth length were also inversely associated with pulse rate. These findings corroborate those in Jamaican children (Forrester et al., 1996). In the Democratic Republic of the Congo (Longo-Mbenza et al., 1999), in a large random sample of poor urban schoolchildren (age range 5–18), it was found that the likelihood of high systolic and diastolic blood pressure was twice as high in LBW children compared with those weighing more than 2500 g at birth. There was no adjustment, however, for current weight or for length of gestation, and the reliability of retrospective information on birth weight is questionable, as the resulting rate of LBW among participants would have reached 63%. In disadvantaged urban children of Soweto (South Africa), Levitt et al. (1999) observed an inverse association of birth weight and systolic blood pressure, in 5-year-old children belonging to a prospective cohort. Current size-adjusted blood pressure fell by 3.4 mmHg per kg increase of birth weight. Gestational and maternal age, and socioeconomic status were not independently associated with systolic blood pressure. Although cohort studies in the Gambia did not reveal an inverse relationship of birth weight and blood pressure in children from age 1–9 years, the observed negative and significant association of blood pressure at age 8–9 years with mater-

nal weight gain in the last trimester of pregnancy was interpreted as reflecting the link between maternal nutrition and offspring's blood pressure (Margetts et al., 1991). In the British birth cohort of 1946, Barker et al. (1989a) had found that the tallest mothers had children with the lowest blood pressure, and the effect was even more pronounced when adjusting for concurrent body weight. This was similarly observed among children born in 1984–85 (Law et al., 1991). In a longitudinal study of 122 subjects born in 1967 and followed up until age 30 in Hong Kong, it was found that PI and length standard deviation score at birth, as well as postnatal changes in PI from age 6 to 18 months were significantly and inversely associated with systolic blood pressure at age 30 (Cheung et al, 2000). Postnatal changes in length standard deviation score were not associated with systolic blood pressure. Regarding diastolic blood pressure, of all the birth anthropometric parameters studied, only birth length standard deviation score was inversely associated with it. It is estimated that normalization of birth length would mean a decrease of diastolic blood pressure by approximately 2.1 mmHg, which would bear public health significance.It was observed in some studies that babies with a large placenta were later more likely to have high blood pressure than if the placenta was small. Highest blood pressures were in adults with LBW and high placental weights (Barker et al., 1990). Large placental size may be a consequence of maternal undernutrition, (see Section 6). In Aberdeen, Campbell et al. (1996) observed an association between blood pressure of middle-aged men and women and their mothers' intake of protein and energy during pregnancy. An inverse relationship between maternal protein intake and blood pressure has also been observed in animal experiments (Langley-Evans & Jackson, 1994; 1996) (see Section 4.1.).

Major potential confounding (or mediating) factors of the inverse association of size at birth and systolic blood pressure later in life are current size and socioeconomic status, as in most chronic diseases, and gestational age at birth, and maternal blood pressure during, or outside of, pregnancy. Current size, which is positively associated with blood pressure, has generally been controlled for, and the negative association of birth weight either becomes apparent after the adjustment, or more commonly, it is strengthened. Small birth size and later large body size seem to potentiate each other (Leon, 1998; see Section 7). Confounding effects of parental socioeconomic status appeared minimal, as described in a few studies. For instance, adjusting for socioeconomic circumstances at birth and at age 50, and for behaviours at age 50 (smoking and drinking) led to only a small reduction in the inverse relationship of birth weight and blood pressure in Sweden (Koupilova, Leon & Vagero, 1997).

Maternal blood pressure is inversely related to birth weight (Churchill, Perry & Beev(?)ers 1997), and it may therefore be confounded with the inverse association of birth weight and blood pressure later on in life as suggested in some studies (Perry, 1997; Martyn et al., 1995; Himmelmann, Svensson & Hansson, 1994). Walker et al. (1998) reported an inverse association of birth weight and blood pressure in young adults aged 16–26 years. After correction for maternal blood pressure 9–19 years after delivery (which was positively correlated with offspring blood pressure and negatively correlated with birth weight), however, the inverse association of birth weight and blood pressure was weaker, suggesting that inherited predisposition to hypertension confounds the effect of LBW (Walker & Watt, 1999). In a study among adolescents in Italy, the inverse association was strengthened when all the confounders were included, in particular maternal and environmental factors of severe placental hypoperfusion (Rabbia et al., 1999). The authors tentatively concluded that the observed association was explained in large part by fetal placental unit dysfunction. Similarly, in Japanese children aged 3 years, systolic blood pressure was positively correlated with maternal systolic blood pressure during pregnancy, in addition to showing an inverse association with birth weight (Hashimoto et al., 1996). In Argentina, Bergel et al. (2000) found, in a prospective cohort of first-borns and their mothers, that blood pressure at 5–9 years was not independently associated with birth weight or other body measurement at birth, nor with any maternal characteristic during pregnancy except haemoglobin level (positive association with blood pressure). This is in contrast with significant and positive associations of blood pressure at that age with current height and BMI of the child, and with maternal systolic and diastolic blood pressure at that time. LBW was a predictor of higher blood pressure in the upper quartile of current BMI of children, as evidenced by the significant interaction of birth weight and BMI, but this effect was no longer significant when adjusting for maternal blood pressure at follow-up. Therefore, this study found weak support for an association of adverse fetal environment with subsequent high blood pressure, except perhaps among children who exhibit rapid postnatal growth. It suggests that genetic and environmental factors shared by mother and child may link LBW with maternal hypertension, and it highlights the need to control for both current size and maternal high blood pressure outside of pregnancy.

Departing from the above findings, Taylor et al. (1997; 1998) found in a large population-based study that the inverse relationship between birth weight and blood pressure (apparent after correction for current body size) of British children was independent of maternal blood pressure. Maternal blood pressure also did not explain the inverse association of birth weight and blood pressure in Chinese children (Mi et al., 2000). Taylor et al. (1997) also found that the negative association was stronger in British girls than boys (age 8–11), although current body size was a much more important determinant.

Adult blood pressure was not related to weight at one year independently of birthweight in the Brompton Cohort Study (de Swiet, Fayers & Shinebourne 1992) as reviewed by Law & Shiell (1996). High blood pressure appears to be more strongly associated with reduced growth *in utero* than events in postnatal life, although postnatal catch-up growth, whether skeletal or non-skeletal, was found to be positively associated with blood pressure in later life in a majority of studies that examined this relation ship (Huxley, Shiell & Law, 2000) (see Section 7.1.).

This is also suggested by Levine, Hennekens & Jesse (1994), who observed, in a cohort of twins, a positive correlation between blood pressure and weight at birth, but also a more rapid rate of rise in blood pressure during the first year in lower birth weight twins, above that being explained by catch-up growth (see Section 3.5.1.).

In a county of England, Pharoah, Stevenson & West (1998) were able to follow-up all the very LBW babies (<1.5 kg) and they reported on their blood pressure at age 15 compared with age-sex matched controls from the same schools selected when the children were 8 years old. While diastolic blood pressure was not different, systolic blood pressure was significantly higher in LBW adolescents, and controlling for anthropometric indices (all lower in cases than controls) further increased the differences. The difference was 4–5 mmHg, which is important, considering that systolic, and not diastolic blood pressure, is considered to be the important determinant of CVD risk and life curtailment (Stamler, Stamler & Neaton, 1993). It was also observed, however, that a higher proportion of mothers and adolescents in the case group than in controls were smokers, which suggested that adverse social influences initiate their cardiovascular effects during fetal development and are compounded during childhood, adolescence, and adulthood. Thus, the fetal programming effects would be added to those of "social patterning".

In spite of the numerous reports showing an inverse association of birth weight and blood pressure, the relationship is quite complex, and the relative influence of maternal, intrauterine, and postnatal factors is still obscure. While there is considerable evidence for a negative effect of small size at birth, high body mass or rapid postnatal growth may be more strongly associated with high blood pressure; and maternal high blood pressure may contribute to both LBW and high blood pressure in offspring. Poor maternal nutrition may also be a contributing factor as suggested by several studies (see Section 6).

3.5 Insulin resistance syndrome and type-2 diabetes

The strongest association between birth weight and chronic diseases is probably seen with the features of the insulin resistance syndrome (or syndrome X, or metabolic disease), which combines high blood pressure, hypertriglyceridemia, and often obesity, with insulin resistance or diabetes (Hales et al., 1991). However, there are conflicting results, such as the absence of association between birth weight and any marker of metabolic risk around age 30 in a longitudinal study of 137 African Americans (Hulman et al., 1998).

In Beijing (Mi et al., 2000), birth weight of term offspring was negatively associated not only with blood pressure, but also with 2-h serum glucose and insulin, and with triacylglycerol concentrations, in a cross-sectional sample of over 600 men and women aged 45. Current weight and sex were controlled for. There was also a positive association of birth weight with HDL-cholesterol levels, but not LDL-cholesterol.

Although the relationship of birth weight with obesity in later life is inconsistent (Martorell et al., 2001), a higher risk of abdominal obesity, and a higher percentage of body fat, have been found to be associated with small size at birth (Law et al. 1992; Hediger et al. 1998; 1999) (see Section 7.2.). It was shown by Jaquet et al. (2000) in 25-year-old men and women that IUGR-born subjects had decreased insulin-stimulated glucose uptake associated with a lesser degree of free fatty acid suppression in adipose tissue. This suggests that adipose tissue plays a role in insulin resistance of IUGR subjects, in addition to impaired fetal growth possibly leading to a higher level of body fat in later life without major change in body mass.

Insulin resistance in children and adults has been found to be associated with thinness (low PI) at birth. Persons who are insulin resistant have a markedly increased susceptibility to insulin resistance syndrome (Phillips et al., 1994; Law et al., 1995; Barker et al., 1993b). In a study of more than 300 young Danish

adults, insulin sensitivity index was significantly, but only weakly, related to birth weight and there was no significant association with PI (Clausen, Borch-Johnsen & Pedersen, 1997). Concurrent BMI and waist-hip ratio were much more strongly related to insulin sensitivity than birth parameters. In Finland, longitudinal studies of subjects born after World War II only showed an association of lower birth weight with higher risk of metabolic syndrome among those who were in the upper BMI quarter in early school years (Vanhala et al., 1999). In Australia, Flanagan et al. (2000) observed that shortness at birth, and not thinness, was associated with reduced insulin resistance, but only in males. They examined insulin sensitivity and insulin secretion in relationship with birth size in men and women aged 20 years, and born at term, using an intravenous glucose tolerance test with minimal model analysis of glucose disappearance. This model provides a measure of glucose sensitivity to insulin (reverse of insulin resistance), as well as of glucose effectiveness, which depends on inhibiting glucose output from the liver, and insulin-independent peripheral glucose uptake. It was found that small size at birth was associated, but only in male subjects, with increased insulin resistance and hyperinsulinemia independently from body mass or percent body fat. While obesity added to the effects of shortness at birth in men, obesity appeared to be the major determinant of insulin sensitivity in women. Glucose tolerance, however, was not affected because of compensatory increased insulin secretion and glucose effectiveness. These observations are in keeping with reported hyperinsulinemic trends, but no impaired glucose tolerance (IGT) was found in a case-control study of adults born small for gestational age (SGA) compared to those appropriate for gestational age in France (Léger et al., 1997). It was suggested by Flanagan et al. (2000) that with increasing age, declining glucose tolerance in people with impaired fetal growth may be due to failure of these compensatory mechanisms.

In Pune, India, cohort studies showed that components of the insulin resistance syndrome that are "programmed" *in utero* may already be apparent in childhood. In a group of almost 400 children aged 4 years, those with birth weights >2.5 kg had significantly higher plasma insulin concentrations 30 minutes after a glucose load, independent from their current size (Yajnik et al., 1995). Plasma glucose and insulin were independently and inversely related to birth weight, although current weight and skinfold thicknesses were positively related to glucose and insulin (Yajnik, 1998). At the age of 8 years, LBW was associated in these children with clustering of insulin resistance syndrome factors, although current weight had a stronger effect (Bavdekar et al., 1999). In Jamaican schoolchildren, Forrester et al. (1996) observed that the level of glycated hemoglobin, which reflects poor control of glucose metabolism, was related to shortness at birth, as well as to current triceps skinfold. Similarly, in South African Black children aged 7 years, an inverse association of birth weight with insulin secretion or blood glucose was observed following an oral glucose tolerance test (Crowther et al., 1998). Height at birth was inversely related to insulin resistance as well. Those children born small, and showing a high growth velocity at age 7, showed more insulin resistance than those remaining in the lower range.

In the Hertfordshire cohort, it was found that the rate of type-2 diabetes and impaired glucose tolerance fell progressively with increasing birth weight and weight at one year. The difference was threefold between birth weights >4.3 kg and those <2.5 kg (Hales et al., 1991). This association was confirmed in Sweden (Lithell et al., 1996) and in the USA (Valdez et al., 1994; McCance et al., 1994; Curhan et al., 1996a,b). Also in Sweden, Carlsson et al. (1999) found that men, who had a birth weight lower than 3 kg and who had a family history of diabetes, were 10 times more at risk of diabetes than those with a higher birth weight, for whom the odds ratio is 5.4 with a positive family history, and 2.3 without. The effect of increasing body mass was highest in those whose birth weight or weight at one year had been low (Hales et al., 1991). Even among the Pimas, who have one of the highest rates of type-2 diabetes, an association between LBW and subsequent diabetes has been reported (McCance et al., 1994). The relationship between birth weight and subsequent diabetes, however, is U-shaped, as very high birth weights (macrosomia) also increase the risk of subsequent diabetes, and are frequently associated with gestational diabetes. Maternal diabetes was shown to be an independent risk factor for high blood pressure, insulin resistance, IGT, and obesity in the offspring at adolescence (Cho et al., 2000). Nevertheless, Pimas with low (<2, 500 g) and high (>4, 500 g) birth weight represented only roughly 10% of adult Pimas with glucose intolerance, meaning that 90% had a normal birth weight (McCance et al., 1994). Thus, factors other than birth weight have to be major contributors of risk. The findings of the Nurses' Health Study support the inverse association of birth weight with increased risk of type-2 diabetes over the whole range of birth weights, not only LBW, with a J-shaped age-adjusted reverse association (Rich-Edwards et al., 1999). In this large cohort of 69,526 women born between 1921 and 1946 in the USA, and followed-up until 1992, there

were 2023 cases of confirmed type 2 diabetes. Further adjustments, including socioeconomic status, history of breast feeding, physical activity, smoking and other lifestyle did not change the relationship, but adjusting for waist circumference strengthened the association. The association held within all BMI strata, and within 3 age groups. The inverse association was stronger among subjects with no parental history of diabetes. Yet in this cohort, women who had a higher birth weight tended to have a higher BMI, not the reverse.

Additional evidence, although indirect, of a likely relationship of less than optimal fetal nutrition with diabetes in later life comes from three sources: Ethiopian Jews moving to Israel (Cohen et al., 1988); the Nauruans from the atoll Nauru in the West Pacific (Dowse et al., 1991), known to have the highest rate of type-2 diabetes in the world; and Indians (Yajnik, 1998). In the first instance, the migrants moved to Israel after surviving famine conditions in Ethiopia. Studies in famine-exposed populations (see Section 3.5.2.) contribute to a better understanding of the long-term impact of fetal nutrition. In the second case, Nauruans became very affluent, but only after having suffered great nutritional hardship during World War II. Interestingly, a decline in the incidence of diabetes has been observed in Nauru, and this could reflect improved fetal and infant nutrition following the end of the war in 1945. In a study of more than 300 Indian adults (85% of eligible subjects) aged more than 40 years and residing in a village near Pune (India), the rate of diabetes and IGT in this short and thin population was 4% each. Post-glucose load plasma glucose was positively related to BMI and waist-hip ratio, and inversely related to height in men and head circumference in women, two anthropometric indicators of restricted growth *in utero* or during childhood. Furthermore, glucose, insulin, and other cardiovascular risk markers (low HDL-cholesterol, high triglycerides and high blood pressure) were interrelated, suggesting an association with insulin resistance syndrome (Yajnik, 1998).

Further evidence for the influence of fetal environment on the development of syndrome X is provided by studies in twins, which show that lighter members are more prone to insulin resistance and higher blood pressure, and by the protein deficiency model in pregnant rats, with associated enzyme changes related to carbohydrate metabolism in offspring.

3.6 Evidence for fetal programming of cardiovascular disease and metabolic syndrome from studies in twins, and in populations exposed to famine

Studies in twins, in populations exposed to famines, and animal experimental data, allow researchers to examine the biological plausibility of environmental programming in utero. Such studies tend to support the fetal origins hypothesis. However, there are discordant views (Kramer, 2000).

3.6.1 Studies in twins

Twins provide an opportunity to test the fetal origins hypothesis, as the association between fetal growth, as determined by differential placentation and fetal supply line, and chronic disease risk is largely independently from genes and other maternal factors, which are by definition similar for members of a twin pair (Leon, 1999). Furthermore, twins have lower than average birth weight owing to restricted fetal growth in the third trimester of pregnancy and not because of social disadvantage and therefore, studies in twins eliminate the potential of socioeconomic confounding.

In Sweden, Vagero & Leon (1994) tested the hypothesis of an inverse association between birth weight and ischaemic heart disease by comparing ischaemic heart disease mortality of nearly 15, 000 twins with that of the general population. Ischaemic heart disease mortality was not higher among twins, and the authors suggested that the type of growth retardation experienced by twins is not the type that programmes for heart disease. However, the shorter twin of a pair was more likely to die of heart disease than the taller one (OR: 1.15; CI: 1.03–1.25). As the association between height differences and ischaemic heart disease risk differences was observed in monozygotic twins and in dizygotic twins, the authors concluded that the relationship between height and IHT does not have a genetic basis. Similarly, in a smaller study of 132 same-sexed twin pairs discordant for acute myocardial infarction, Hübinette et al. (2001b) did not find significant differences in birth measurements between cases and healthy co-twins, although cases had lower birth weight, birth length, and head circumference than external matched control twins. The findings did not support a direct causal effect, and according to the authors, factors operating during infancy, childhood or adolescence, and influenced by fetal growth, may underlie the reported associated between birth weight and CHD. This does not appear to exclude, however, the interaction between intrauterine and postnatal factors, even in the absence of differences in birth phenotype.

Studies on monozygotic twins discordant for type-

2 diabetes in Denmark showed that the twin with diabetes had a significantly lower birth weight, which shows the importance of non-genetic factors (Vaag et al., 1996; Poulsen et al., 1997; Poulsen, Vaag & Beck-Nielsen, 1999). It was also observed that in twins aged 55–64, monozygotic pairs had higher insulin concentrations than dizygotic ones 30 minutes after a glucose load, although the prevalence of diabetes and IGT was the same in both groups of twins. Excluding pairs with diabetes or IGT, and those with diabetes among first degree relatives, it was found that among twins with normal glucose tolerance, monozygotic ones had higher glucose and insulin concentrations at 30-min past the glucose load, but weights and waist-hip ratios were similar. This suggested to the authors that because of a shared placenta, the uterine environment may be less optimal in monozygotic than in dizygotic pairs, which could explain the higher risk of developing insulin resistance in the former than in the latter. Thus, zygosity would appear to affect glucose homeostasis and insulin resistance, while having no effect on body weight or fat distribution.

Consistent with the fetal programming hypothesis, a tendency for lighter members of monozygotic twin pairs to have higher blood pressure was reported by Dwyer et al. (1999) in 8-year-old Australian twins, and by Poulter et al. (1999) in 50-year-old British female twins. The associations, however, were not statistically significant. When all monozygotic and dizygotic twins were examined, the association of the difference in birth weight with a difference in blood pressure was significant in the study of Poulter et al. (492 twin pairs), but not in that of Dwyer et al. (55 pairs). The effect observed by Poulter et al. (1999) was even larger than the inverse association shown in singletons, with a decrease of over 5 mmHg for every kilogram increase in birth weight. In a cohort study of 800 subjects including 22 twins in New Zealand, Williams & Poulton (1999) reported that twins had lower blood pressure at age 9 and 18 years than singletons whether or not adjustments are made for birth weight and current size. This finding challenges the fetal origins hypothesis, according to the authors. However, the number of subjects was small, and there was no distinction between monozygotic and dizygotic twins.

If intrauterine factors that influence birth weight have an enduring impact on adult BMI, then a correlation between within-pair difference in birth weight and the within-pair difference in adult BMI should be observed in twins. However, this was not observed by Allison et al. (1995) in a study of 2, 880 monozygotic twins. Within-pair weight differential at birth was correlated separately with weight and height differentials at age 40, although this was not so for BMI. Nevertheless, the significant correlation between birth weight differential and adult height and weight differentials suggests that intrauterine non-genetic influences on both birth weight affect final height, but not adiposity in adulthood.

3.6.2 *Observations in populations exposed to famines*

Studies conducted among people who were exposed to famine while in utero have provided much insight into the differential programming effects according to timing of deprivation, and the lag effects, even in the absence of obvious impact on size at birth. Three major famine situations provided for natural experiments: Holland (1944–45), Leningrad during the German siege (between 1941–44), and an earlier famine due to severe crop failure in Finland (1866–68). The Dutch Famine (1944–45), in particular, has provided a "natural laboratory".

In Finland, the famine affected 200, 000 people, but subsequently there was no evidence of significant excess cardiovascular mortality that could have been attributed to impaired fetal growth (Kannisto, Christensen & Vaupel, 1997). The authors analysed survival of the cohorts born in Finland during the famine years, and during the 5 years prior to it or following it. Survival from birth to 17 years of age was significantly reduced for people born before and during the famine, but there were no after-effects on survival in later life. However, there was no birth data nor information on cause-specific mortality of these cohorts. Had child survival been higher because of better health care as seen more recently, associations between exposure to famine *in utero* and adult mortality might have emerged.

In the Netherlands, birth information was available for people born during the famine, as well as before or after. Cohorts of people exposed to famine at various times of gestation, or not exposed, have been extensively studied. Infants born at the time of the war-induced Dutch Famine of 1944–45 (Ravelli, Stein & Susser, 1976; Lumey, 1992; 1998), and whose mother's nutrition was compromised at the time of conception or during the first trimester of pregnancy, exhibited an increase in placental weight but birth weights were not significantly affected. The increase in placental weight was interpreted as compensatory for the reduction of maternal intake. *In utero* exposure to undernutrition early in pregnancy, while not affecting birth size, was associated with higher obesity in adulthood (twofold increase). The mechanisms need to be explored, but it is possible that the weight increase results from

greater metabolic efficiency, increased dietary intake, or decreased physical activity; it is also possible that changes in the fetal brain have permanent effects, through changes in appetite or weight control, as speculated by Ravelli, Stein & Susser (1976). In 300,000 Dutch male draftees aged 19 years, those exposed to famine *in utero* during the first 2 trimesters indeed experienced a significantly much higher prevalence (+80%) of overweight than those from nonfamine areas (Ravelli, Stein & Susser, 1976). Those exposed during the last trimester or in postnatal life had a 40% lower prevalence and a lower birth weight, while those exposed early in pregnancy had normal birth weight (Stein et al., 1975). The mean reduction of birth weight at the time of the Dutch Famine, however, was only 300 g, and maternal caloric intake had to fall below 800 kcal/day to affect fetal size (Kusin, Kardjati & Renqvist, 1994). Similarly, women aged 50 who had been exposed to famine early in uterine life, and whose mothers were adequately nourished for the remainder of their pregnancy had a higher BMI and waist-hip ratio than those exposed in late pregnancy or not exposed, in spite of no differences in birth weight (Ravelli et al., 1999). This effect was only observed in women, and not in men, which led the authors to suggest that increased obesity after exposure to famine in early gestation is due to altered function of central endocrine regulatory mechanisms rather than to abnormalities of adipocytes. Among men and women aged 50 years, exposure to the Dutch Famine late in gestation was also associated with greater risk of impaired glucose tolerance and type-2 diabetes than non-exposed people or those exposed early in gestation (Ravelli et al., 1998).

Further studies on these cohorts revealed that people exposed to famine early in gestation (first 16 weeks) had a more atherogenic profile than those exposed later, or not at all (Roseboom et al., 2000a). Total cholesterol, LDL cholesterol, and the ratio of LDL:HDL cholesterol were significantly higher, while HDL-cholesterol tended to be lower. Similarly, factor VII concentrations (but not plasma fibrinogen) were found to be significantly lower in people exposed early compared to those who were not exposed, and this was not related to birth weight (Roseboom et al., 2000b). This suggests that liver function may be affected by undernutrition in early pregnancy. Furthermore, the prevalence of CHD was only increased with early exposure to famine. There was a tendency for people with CHD to have a lower birth weight and head circumference at birth (Roseboom et al., 2000c). Systolic or diastolic blood pressure at age 50 was unaffected by early or late prenatal exposure to the Dutch Famine, but birth weight was inversely associated with systolic blood pressure (Roseboom et al., 1999). The effect was -2.7 mmHg per kg increase in birth weight. Looking more closely at the link between maternal diet during pregnancy in these famine cohorts and blood pressure of offspring in later life, Roseboom et al. (2001) found that the balance of macronutrients had more effect than their absolute amounts. The protein:carbohydrate ratio of maternal diet towards the end of pregnancy (32–36 weeks) was shown to be inversely related with systolic blood pressure, in exposed as well as nonexposed people, showing that the association was independent from starvation. The effect may be related to the impact of dietary protein restriction on glucocorticoids, as animal studies show (see Section 4.1.).

Stanner et al. (1997) reported that maternal starvation in pregnancy during the siege of Leningrad was not associated with higher risk of CHD at age 50–55. The siege had resulted in very severe starvation, particularly during the winter of 1942, and one million deaths occurred. Birth weights for children born during the siege were 16% and 18% lower for girls and boys, respectively. Three groups were studied: adults exposed to the siege *in utero* (and in early infancy); adults exposed as infants; and adults not exposed because they were born just outside the siege area. There were no major differences among the three groups in anthropometry, glucose tolerance, blood pressure, blood lipids, and fibrinogen levels. The food shortage may have been too short to affect fetal growth. Furthermore, there was no distinction of the moment in pregnancy when the growing fetuses were likely exposed to maternal food deprivation, which the Dutch Famine studies showed to be critical. Birth weights were also not available. Yet, it was found that the positive relationship between current BMI and systolic (and diastolic) blood pressure was stronger in the subjects exposed during fetal life than during infancy.

The Dutch Famine is very distinct from other famines, and this may explain the differences in the findings. In Holland, there was a sudden famine in a previously well-nourished population. It only lasted 5 months, and adequate nutrition was restored at once after the famine. In contrast, the Leningrad Famine during the German Siege of 1941–44 lasted 28 months and most people were exposed during the entire period of gestation as well as in infancy. The population was chronically malnourished before being taken to near starvation for two years, and Living conditions remained poor in Leningrad after the siege. Nonetheless, the food deprivation was severe in Holland, and the survivors may not be considered to be representative of the whole population owing to selection

(Jackson, Langley-Evans & McCarthy, 1996). More modest dietary inadequacies or imbalances of the type frequently encountered during pregnancy in poor populations may have similar effects.

3.7 Other systems or functions putatively programmed in utero

Several systems or functions are believed to be programmed in utero (Barker, 1998; 2001). These are only briefly reviewed here, as our focus is CVD and risk markers.

3.7.1 Infection, immunity and autoimmune diseases

Presently, only a few studies link adult immune function to birth size. One report links disproportionate fetal growth (acute IUGR) with altered IgE concentrations in adults (Godfrey, Barker & Osmond, 1994). A few studies have observed an association between birth weight and autoimmune diseases. LBW at term was found to be inversely related to autoimmune thyroid disease (Phillips et al., 1993; Barker, 1998). It has also been suggested that type-1 diabetes might be programmed in utero, based on the observed association of risk in children with birth weight in Sweden, after controlling for maternal age, parity, diabetes, and smoking (Dahlquist, Bennich & Källen, 1996). The observed association, however, was positive, while it is negative for type-2 diabetes. The case-control study of children under 14 years of age and diagnosed for diabetes showed that children born large for gestational age (z-score of ≥ 2) were at significantly higher risk, while those born small (z-score <2) were at lower risk.

Based on cohort studies in the Gambia and in view of animal evidence, fetal programming of immunity was hypothesized (Moore et al., 1997; Prentice et al., 1999). In this country with yearly seasonal patterns of food shortage, birth weights were found to be 200–300 g lower in the hungry season. Impaired fetal growth causing high rates of LBW in the hungry season is nutritionally mediated, since the incidence of LBW was reduced by supplementary feeding of mothers (Ceesay et al., 1997). Three villages have kept accurate vital statistics since 1949, which made it possible to study survival and causes of death, using season of birth as a proxy for early environmental insults. The cohort consisted of more than 3,000 individuals. Similar mortality patterns were observed up to puberty irrespective of season of birth. There was a marked increase thereafter, with a risk ratio of 3.7 for deaths after 14.5 years, and of 10.3 for deaths after 25 years, in people born during the hungry season. Causes of death were primarily infection or infection-related, not chronic diseases. It was therefore suggested that early life events caused permanent damage to the immune system. In support of this hypothesis, a longitudinal study in the Philippines by McDade et al. (2001) found that impaired fetal growth as reflected in small-for-gestational-age (SGA) at birth was associated with reduced plasma thymopoietin concentration at adolescence (103 subjects), after controlling for potential confounding variables. It is known that thymic hormones play an important role in T-cell development and function, and therefore, altered thymus development during fetal life could programme impaired immunity in later life as well as affecting survival in early years. In addition to seasonal undernutrition, other potential initial insults in the Gambian study include exposure to aflatoxin, prenatal malaria, or postnatal viral infection. As reviewed by Prentice (1998), there is abundant evidence of sustained effects of fetal undernutrition on immunological function in animals. Zinc depletion during gestation, in particular, has a profound effect on the development of lymphoid organs, especially the thymus and spleen, and later repletion is ineffective. Intergenerational effects of maternal zinc deficiency have even been reported in the '70s. Similar effects may result from protein-energy or other micronutrient deficiencies, but zinc is known to play a prominent role in the modulation of immune function.

The reported inverse association of birth weight with asthma is not unrelated to possible early programming of immunity. As reviewed by Shaheen et al. (1999), some studies have found a relation between birth weight and asthma in children, although most have not. Two large studies of male conscripts have found an association (Seidman et al., 1991b; Braback & Hedberg, 1998). Using a British cohort born in 1970, Shaheen et al. (1999) investigated the relationship between birth weight and childhood (age 10) and adult anthropometry (age 26) and adult asthma/wheezing in adults. Many confounding factors were controlled for, including maternal age, smoking history in pregnancy, duration of breastfeeding, socioeconomic status of the father, and number of children in the household. It was found that among respondents (age 26), asthma and wheezing fell with increasing birth weight, and this effect was even stronger when gestational age was controlled for. The odds ratio was 3.3 (CI: 1.31–7.46) for those with birth weights lower than 2 kg compared with birth weights between 3–3.5 kg. Asthma and wheezing also increased as BMI increased, particularly so in the last quintile. Controlling for birth weight increased the estimated effect of BMI. The relationship was also stronger for women, who were more affected by asthma

than men. Impaired fetal growth of airways, leading to small airway size, could be responsible for the association, as described by Harding et al. (2000).

3.7.2 *Breast cancer*

It has been postulated that breast cancer may originate in utero. Available evidence, however, is in the opposite direction of that of CVD, with higher birth weights associated with higher odds ratio for breast cancer (Signorello & Trichopoulos, 1998). However, current evidence for perinatal influences on breast cancer risk is less consistent than the evidence for perinatal influences on CVD.

The hypothesis of early life modulation of breast cancer risk is supported by immigrant studies. The rate of breast cancer in Japanese migrants rises to the level observed in white Americans only after two or more generations, whereas colorectal cancer becomes similar to the host population within a few decades of migration. This suggests that the latter is influenced more by lifestyle factors than the former (Ekbom et al., 1992; Ziegler et al., 1993).

An intrauterine origin could be linked to estrogens or other hormones, or to other pregnancy-related processes. Fetal growth is associated with estrogens, but primarily at the extreme ends of the range. Whether the fetus is exposed to any of the estrogens in the mother's circulation is unclear, however. Studies have either found no association of birth weight with breast cancer, or a positive trend. Sanderson et al. (1996) found a positive association, but only in premenopausal women, which lends support to the hypothesis linking breast cancer with pregnancy estrogens. In the large prospective cohort studies on American nurses, a nested case-control study (Michels et al., 1996) revealed that for women with a birth weight of ≥4 kg, there was a graded reduction of risk which reached 45% in those weighing 2.5–2.9 kg at birth. In Sweden, Hübinette et al. (2001a) reported in a case-control study on breast cancer in sister twins (96 pairs). Case pairs were compared with external age-matched twin pairs. Healthy sister twins were the internal control group. Gestational age >40 weeks considerably increased the risk compared to twins of gestational age <32 weeks (OR: 8.4; CI: 1.3–54.4). It was also found that cases had significantly higher birth weight and PI at birth. The risk increased with increasing birth weight, but the trend was not significant. Another study in Swedish women (Andersson et al., 2001) revealed that the risk of all site cancer and non-hormonal type of cancer was also increased with increasing birth weight and birth length, even after controlling for potentially confounding variables. This suggests that size at birth may influence cancer sites other than hormone-related sites like the breast. However, more research is required to elucidate this relationship.

3.7.3 *Polycystic ovary syndrome*

Polycystic ovaries in adult life have also been linked with fetal growth and length of gestation (Cresswell et al., 1997). Placental failure associated with postmaturity may expose the hypothalamus to increased concentrations of androgens and estrogens, and reset its responses to them. There could be an altered hypothalamic-pituitary "set point" for luteinizing hormone (LH) release, and this may programme one type of polycystic ovaries (Cresswell et al., 1997). Another form may also be programmed in utero, and is associated with high birth weight, high maternal weight, and high current BMI. It is interesting to note that women with polycystic ovaries are at higher risk of diabetes and CVD after menopause, and that in such women, hyperinsulinemia and insulin resistance tend to worsen spontaneously (Pasquali et al., 1999).

3.7.4 *Other diseases suspected of fetal programming*

Among the several conditions that are postulated as being programmed in utero, renal disease among Amerindians (Hoy et al., 1999), and osteoporosis markers in Caucasian populations (Cooper et al., 1997; Jones, Riley & Dwyer, 1999) have been studied. However, as seen in Appendix A, very limited evidence exists to date. Reports of psychological and mental repercussions of early life experience in the literature are dated (Stein et al., 1975), but there has been a recent upsurge of interest, with data suggesting that behavioural development and mental disorders may have a link with prenatal growth. In a population-based UK cohort study of people born in 1946, birthweight was significantly and positively associated with cognitive ability at age 8 and older, although the association was less strong than at age 8 (Richards et al., 2001). The association was strengthened when controlling for socioeconomic status. It was suggested that insulin deprivation, or altered action in the growing brain may be involved (Wickelgren, 1998).

4. Experimental models of fetal programming, and possible mechanisms

Beyond rather consistent epidemiological associations, experimental models provide strong support to Barker's hypothesis. Animal models that are particularly relevant to fetal programming mechanisms are the genetically obese, hypertensive, or diabetic rats, as well as dietary manipulations during gestation in rats and other species. Furthermore, there are two sets of experimental data on early nutritional programming in humans. One is the randomized calcium supplementation trial in pregnancy (Belizan et al., 1997). The other one is the preterm infant trial (Lucas, 1998).

4.1 Animal models

More emphasis is given to dietary manipulation models, which may mimic nutritional inadequacies in human pregnancy.

4.1.1 Genetic and surgical models

Genetic models of hypertension, for instance, appear to be associated with IUGR in rats (Iwase et al., in Langley-Evans et al., 1996). Another model is the glucokinase-deficient mouse which provides putative explanations for the link of LBW to hyperglycemia. Mice lacking glucokinase, which catalyses the rate-limiting step of glucose breakdown, have significantly lower birth weights than heterozygous or wild mice, according to Japanese researchers (Terauchi et al., 2000). This appears to be associated with insufficient insulin effect during embryogenesis. The homozygous mice had the lowest insulin levels at birth, and became diabetic shortly after birth. Maternal environment also had an effect, since heterozygous neonates from hyperglycemic heterozygous mothers had higher birth weights than those from wild mothers.

4.1.2 Maternal dietary manipulations in animals

Long term effects of maternal undernutrition have been studied extensively in animals since the early work of McCance & Widdowson (1966). Recent reviews on the topic are available (Hoet & Hanson, 1999; Waterland & Garza, 1999). The effects of overall dietary restriction throughout pregnancy or at specific moments, and of iso-energetic low-protein diets, on fetal growth and metabolism have been studied (Langley-Evans et al., 1999). Similarly, the metabolic and endocrine effects of overfeeding and underfeeding at various periods of gestation have been documented in animal models. As Hoet & Hanson (1999) underscore, nutritional or metabolic disturbances in the intrauterine environment in rats can affect homeostatic mechanisms in a subtle manner, even without overtly impairing fetal growth.

- *Effects of energy restriction and its timing*

Several groups observed that energy restriction during the first two-thirds of gestation followed by *ad libitum* feeding of rat dams resulted in 10–20% heavier and fatter offspring. The increased adiposity, owing to hypertrophied adipocytes rather than hyperplasia, is ascribed to compensatory hyperphagia of the dams during gestation, or lactation, or both following a period of restriction, rather than because of the restriction *per se*. Smaller rats born to underfed dams (30% of *ad libitum* intake), were shown to have significantly increased food intake early in the postnatal period (Vickers et al., 2000). It was also observed that food intake of these rats from undernourished mothers continued to increase with age, and to be further amplified by a high fat diet. These rats had higher body weights and retroperitoneal fat pads, and they showed elevated systolic blood pressure and markedly increased fasting insulin and leptin in plasma. The authors propose that fetal undernutrition induces impaired neuroendocrine regulation in which hyperleptinemia, hyperinsulinism, and insulin and leptin resistance may lead to hyperphagia, obesity, and hypertension in adult life. Further evidence of these effects, in particular, leptin resistance and hyperphagia, is an area for future research. In sheep, feeding pregnant ewes half of their energy requirements over the gestation period associated with rapid placental growth (roughly the first

half), followed with normal diet for the remainder of pregnancy, resulted in higher placental weight and a higher ratio of placental to fetal weight, although there was no demonstrable effect on birth weight (Heasman et al., 1998; 1999). Length was also increased. Additionally, maternal nutrition restriction was associated with lower brain weight, and increased levels of triiodothyronine in umbilical cord plasma (Clarke et al., 1998). It was suggested, however, that in response to moderate undernutrition, the growth of the placenta depended on the nutrient stores of the mother at the beginning of pregnancy (McCrabb, Egan & Hosking, 1991). In cows, early protein restriction followed by increased protein in the second trimester gave a similar pattern of increased placental development, and increased fetal growth as well (Perry et al., 1999).

The effects of maternal undernutrition on insulin-like growth factors (IGFs) were studied in sheep (Gallaher et al., 1998). IGFs play a key role in fetal growth, and the IGFs-IGF binding protein axis has been implicated in the association of impaired fetal growth with chronic disease in later life (Barker et al., 1993b). It was observed that early maternal undernutrition did not change fetal concentrations of IGF-1 in late gestation. However, a short exposure of pregnant ewes to undernutrition in late gestation resulted in reduced concentrations of IGF-1 and IGFBP-3 (IGF binding protein), and the reduction was significantly greater in fetuses whose mothers had also been exposed to undernutrition in early gestation. These results suggest that early maternal exposure to undernutrition "reprogrammes" fetal IGF-1 and IGFBP-3.

In adolescent ewes, a high level of complete diet during gestation resulted in lower placenta and lamb birth weight compared with pregnant adolescents offered a normal level of complete diet (Wallace et al., 1997). Maternal insulin level was higher throughout gestation with the high nutrient intake, and it was inversely related to birth weight. Maternal IGF-1 and thyroid hormones were also elevated with the high ration, while growth hormone concentrations were lower. Growth hormone levels were inversely related to food intake and positively to placental and birth weight. This suggests that early in gestation, high insulin and IGF-1 in adolescent ewes ensure that the anabolic drive to maternal tissue synthesis is established, and this is at the expense of placental growth. Restriction of placental growth results in limitation of fetal growth. It was also shown that reducing maternal dietary intake from a high to a moderate level at the end of the first third of gestation stimulates placental and fetal growth, whereas increasing maternal intake from a normal to a high nutrient diet at that time reduces placental development and fetal growth (Wallace et al., 1999). Thus, rapid maternal growth throughout pregnancy in adolescent sheep restricts placental growth and leads to a significant decrease in birth weight relative to normally growing adolescents. Insulin and IGF-1, which do not cross the placenta to an appreciable extent, are responsible for the partitioning of nutrients in favour of the mother. It may be that down-regulation of placental IGF-1 receptor expression results from exposure to high levels of maternal IGF-1, thereby reducing placental growth. The balance between maternal and fetal IGF-1 level appears to play a major role in the partitioning of nutrients between the mother, the placenta and the fetus (Wallace, Aitken & Cheyne, 1996).

Pennington et al. (1999) developed an acutely malnourished pregnant rat model to investigate the offsprings' response to oral glucose. Acute maternal fasting in late pregnancy caused significant fetal growth suppression that was associated with hyperglycemia following an oral glucose load. The rats were not insulin resistant, unlike the protein deficiency model (see the section on *low-protein diets* below); on the contrary, they tended to be hypoinsulinemic after the glucose challenge. The observed glucose intolerance was reversed by the age of one year, but more so in males than in females, whose insulin levels remained lower than controls. It may be speculated, based on these results, that a higher rate of impaired glucose tolerance (without insulin resistance) would be observed in women than in men in population groups with a high rate of fetal malnutrition.

Kind et al. (1999) studied the effect of maternal dietary restriction (15%) in guinea pigs on the response of the offspring to cholesterol feeding. Unlike in rats and like in humans, guinea pigs have a higher plasma level of LDL than HDL-cholesterol, and they respond to dietary fat and cholesterol in a manner quite similar to humans. It was observed, as expected, that maternal dietary restriction reduced weight gain in gestation and resulted in lower birth weights (-13%), length, and abdominal circumference of offspring. Plasma total cholesterol was higher prior to and following 6 weeks of cholesterol feeding in offspring of undernourished mothers. While plasma cholesterol levels prior to cholesterol feeding did not differ according to birth weight, total and LDL-cholesterol was roughly 30% higher in low birth weight males than in higher birth weight animals following cholesterol feeding. However, this response was only observed in male offspring: female offspring did not respond differently to cholesterol feeding according to maternal nutrition and birth weight. Adult offspring weight and length were also

reduced by maternal undernutrition, but only in males. Plasma cholesterol tended to inversely relate to abdominal circumference at birth, as observed by Barker et al. (1993c) in humans. HDL-cholesterol was also positively related to abdominal circumference at birth and adult liver size in cholesterol-fed guinea pigs. Thus, maternal undernutrition and small size at birth alter postnatal cholesterol homeostasis in the male guinea pig. Further studies are required to explain the impaired ability of males to control cholesterol levels.

- *Low-protein diets*

As underlined by Desai et al. (1996), chronic diseases associated with poor fetal growth as observed in epidemiological studies can be reproduced in experimental animals by subjecting them to general protein-energy malnutrition or to protein deficiency alone. Studies in animal models show that maternal malnutrition may affect birth weight, selective organ weight, and organ function. Feeding the rat with a low-protein diet (5–8% by weight) during pregnancy and lactation resulted in permanently small offspring. If the small offspring were breastfed by lactating rats on a normal diet (20% protein), complete catch-up growth was observed, but these rats that caught up had a 20% reduction in lifespan (Desai et al., 1996). This gives an indication that catch-up growth may not fully reverse the intrauterine alterations, and actually, that it can be deleterious. At birth, it was observed in the offspring of protein restricted dams that organ weight reduction was proportionally greater than body weight reduction in the case of pancreas, spleen, muscle and liver; the reduction was in proportion to body weight in the heart, kidney and thymus, while the lung and the brain were spared. At 11 months, rats exposed prenatally to protein deficiency still had lower muscle weight (in grams and in %). In female rats only, lower relative weight of the pancreas was observed after exposure to protein deficiency throughout gestation and lactation, or during lactation only, but not during gestation only (Desai et al., 1996). Protein deficiency in pregnant rats also provided a model of fetal programming of CVD and impaired glucose and insulin metabolism.

- *Association with cardiovascular disease*

The low-protein diet model extensively studied in rats may help explain the molecular basis of the association of maternal malnutrition with later CVD. Rats exposed to a low-protein diet (50% reduction) throughout gestation have significantly higher systolic blood pressure than control animals at weaning, (Langley-Evans, Gardner & Jackson, 1996). The rat diet is isoenergetic and protein restriction is moderate, as the 8% protein level still provides 75% of the requirement. The effect on blood pressure of the offspring is independent from maternal blood pressure changes during gestation. The largest increases are observed when the protein restriction occurs in late pregnancy, but even brief exposures to the deficient diet at any time in pregnancy will increase blood pressure in the offspring (Langley-Evans et al., 1999). The isocaloric protein-deficient diet resulted in lower kidney weight and a reduced number of glomeruli in rat offspring, and these changes were not reversible. In addition to smaller kidneys, Nwagwu, Cook & Langley-Evans (2000) observed changes suggestive of progressive renal deterioration in 4-week-old rats exposed in utero to protein deficiency: reduced creatinine clearance, increased blood urea nitrogen, urinary output, and urinary albumin excretion. This may be related to the effect on blood pressure, as suggested in their review by Hoet & Hanson (1999). Furthermore, this diet induced changes in distribution and level of biogenic amines in the brain and modifications of tryptophan metabolism. These alterations became more severe when the dietary restriction was maintained in subsequent generations. Many of the effects observed in rats given a protein deficient, isocaloric diet during gestation occurred without major changes in birthweight. Severe dietary restriction only in late gestation did not produce hypertensive offspring (Holemans et al., 1999), which suggests that early fetal insults have greater effects on the cardiovascular system of the offspring.

In rats exposed to a low-protein diet throughout gestation, lactation and weaning, and then fed normal rat chow, Petry et al. (1997) reported that blood pressure was increased over that of controls by the age of one year, while their weight remained lower. Rats similarly exposed to low-protein diet, but refed on a "cafeteria" diet rather than normal chow also had high blood pressure, and in addition, they had become obese and had high triglyceride levels and poor glucose tolerance. This suggests that early protein deficiency and later obesity are independent risk factors for hypertension, and may be additive.

Nutrients other than protein may be implicated in programming of cardiovascular system. Langley-Evans (2000) showed, for instance, that two isocaloric low-protein rat diets with a different make-up in fatty acids, some amino acids, and source of carbohydrate similarly reduced weight gain during gestation and birth weights, but did not have the same effect on systolic blood pressure. This is in line with previous observations (Langley-Evans, 1996) suggesting that

high intake of saturated fats, or low intake of linoleic acid by pregnant dams programme high blood pressure in the offspring through a different mechanism from protein restriction. Using iron deficiency anaemia as a model, Crowe et al. (1995) showed that birth weights and neonatal blood pressure were reduced in rats, but that the offspring became hypertensive relative to controls upon catch-up growth.

Langley-Evans et al. (1999) observed that placental 11-β-hydroxysteroid dehydrogenase activity (11-β-OHSD), which normally protects the fetus from overexposure to corticosteroids, is lowered by maternal protein deficiency in rats. Protein-deficiency induced hypertension was prevented by suppressing maternal and fetal corticosteroid synthesis in rats, which provides evidence for the programming *in utero* of the hypothalamic-pituitary-adrenal (HPA) axis function (Langley-Evans, Gardner & Jackson, 1996). HPA axis resetting may in turn be responsible for altering the homeostatic controls over cardiovascular function. It was observed that glucocorticoid-inducible enzymes were all elevated in brain and liver of protein deficiency exposed rats at weaning, which suggests a role of glucocorticoids on gene expression. Hypersensitivity to glucocorticoids was also observed in rats exposed to protein deficiency *in utero*, at birth and in postnatal life (Langly-Evans, Gardner & Jackson, 1996). It appears that type II glucocorticoid receptors are inappropriately regulated in rats exposed to maternal low-protein diets. Thus, it is speculated that nutritional programming of the cardiovascular system is a steroid-dependent phenomenon.

In keeping with these observations, Benediktsson et al. (1993) found that rat placental 11-β-OHSD activity correlated positively with term fetal weight, and negatively with placental weight. Fetuses with low birth weight and high placental weight had the lowest level of 11-β-OHSD and presumably the highest exposure to cortisol and corticosterone. These observations support the role of overexposure of the fetus to glucocorticoids because of attenuated 11 β-OHSD in explaining the link between low birth weight and high placental weight with hypertension. Lesage et al. (2001) recently reported that 50% maternal food restriction in late gestation in rats also depressed placental 11-β-OHSD expression and induced overexposure of fetuses to maternal corticosteroids IUGR. Treatment with dexamethasone during gestation, which leads to impaired fetal growth, provides an experimental model of early programming of adult onset disease which is quite similar to the protein deficiency model. Dexamethasone is not metabolized by placental 11-β-OHSD which normally prevents overexposure of the fetus to glucocorticoid by converting these to inactive forms. Along with causing hypertension, hyperinsulinaemia and elevated corticosterone in adult offspring, dexamethasone was found to selectively up-regulate cardiac glucose transporter 1 (GLUT1) protein expression and markedly activated Akt/Protein Kinase B in adulthood (Langdown et al., 2001). In sheep, only two days of dexamethasone treatment early in pregnancy increased blood pressure of the lambs without any effect on birth weight; dexamethasone was without effect when administered later on in gestation (Dodic et al., 1998). Furthermore, the mean arterial pressure effect of dexamethasone treatment seemed to be enhanced with age in the offspring (Dodic et al. 1999). Impaired expression of placental glucose transporters was also observed following glucocorticoid administration in cultured human placental trophoblast cells, and in pregnant rats (Hahn et al., 1999). The glucocorticoid-induced down-regulation of placental glucose transport may help to explain fetal growth restriction following glucocorticoid treatment or as a result of elevated glucocorticoid levels during pregnancy.

In lamb fetuses exposed to early intrauterine undernutrition, HPA axis response to adrenocorticotrophin hormone (ACTH) challenge in late gestation is suppressed, as well as basal cortisol concentration (Hawkins et al., 2000), which could be related to prior exposure to elevated corticosteroids. In contrast, after birth, these lambs exposed to periconceptual undernutrition have a higher arterial blood pressure and an exaggerated blood pressure response to a HPA axis challenge. The mechanisms for this switching from blunted response *in utero* to enhanced response postnatally are not known.

Corticosteroids can directly promote increases in blood pressure through their action on vascular smooth muscle, as well as indirectly through stimulation of central control centers. Glucocorticoids may modulate the renin-angiotension system function through inducing the expression of angiotensinogen, renin-angiotensin converting enzyme, and angiotensin II receptors, with resulting hypersensitivity of the system to glucocorticoids in later life, as suggested by Langley-Evans et al. (1999). Prenatal undernutrition may further have an impact on chronic renal function and cardiovascular control through impaired nephrogenesis.

● *Association with impaired glucose tolerance and insulin resistance*

Much of the research effort undertaken to understand the molecular basis of the relationship between early

growth retardation and later risk of type-2 diabetes has focused on the rat model of protein deficiency during gestation. Whether exposed to protein deficiency only during uterine life or also during lactation, offspring have worse glucose tolerance than controls by 15 months (Langley-Evans & Jackson, 1994), and this can be worsened by a high fat diet (Wilson & Hughes, 1997). Although frank diabetes has not been produced, many features of insulin resistance syndrome have, providing much information on potential mechanisms for these effects.

It was also observed in rats that pancreatic insulin content and β-cell mass were significantly decreased at adulthood among those whose mothers had received a low-protein diet, whether isocaloric or energy-restricted, during gestation. This effect was not observed with energy restriction only (Bertin et al., 1999). In rat fetuses of low protein mothers, it was found that the islets, while showing no difference in basal insulin secretion, had a reduced secretory response to both leucine and arginine (Dahri et al., 1995). Similarly, glucose-induced insulin secretion was impaired (Reis et al., 1997). As reviewed by Ozanne (1999), livers of protein-deprived offspring are resistant to glucagon in that they show an altered ability to stimulate hepatic glucose output, and they also have an altered response to insulin, somewhat similar to what is observed in subjects with type-2 diabetes, and in young Aborigenes, a population highly exposed to developing diabetes.

Protein deficiency during pregnancy was shown to selectively induce in offspring rats profound hepatic alterations, with markedly increased phosphoenol pyruvate kinase and reduced glucokinase activity (Burns et al., 1997; Desai et al., 1997). This represents a fourfold shift in hepatic carbohydrate metabolism in a direction opposite to what would be induced by insulin (Lucas, 1998). These effects could not be attributed to glucagon or insulin, although there is insulin and glucagon resistance in reduced protein offspring (Ozanne & Hales, 1999). The underlying mechanisms for the change of expression of these enzymes remain to be elucidated. Furthermore, these effects were only observed in offspring of rat dams exposed to low-protein diets during gestation, not in those exclusively exposed to maternal protein deficiency during lactation. The expression of these key hepatic enzymes of gluconeogenesis and glycolysis therefore appear to be permanently altered by inadequate maternal diet in a direction expected to result in an insulin-resistant liver.

Jennings et al. (1999; 2000) reported that in rats with impaired growth in prenatal life, postnatal catch-up growth was associated with a shorter life span and shorter kidney telomeres. In contrast, growth impairment in postnatal life was associated with significantly longer kidney telomeres. Telomere shortening (in liver and kidneys but not brain) was found to be associated with reduced longevity, and to be accelerated by oxidative damage. This may provide a mechanistic basis for the observed epidemiologic association of fetal undernutrition and adult degenerative diseases.

4.2 Experimental evidence in humans

Belizan et al. (1997) observed that calcium supplementation during pregnancy resulted in lower systolic blood pressure in the offspring by the age of 7 years, compared to offspring of placebo-treated mothers. This is considered the first evidence from a randomized controlled trial of intrauterine programming of childhood blood pressure through a nutritional intervention during pregnancy. Most of the calcium effect was concentrated in children with a BMI above the group median at assessment. Blood pressure was reduced >3 mmHg in these children with high BMI, which may bear physiological significance. This effect was independent from birth weight, which only showed a non-significant negative trend with children's blood pressure. The incidence of gestational hypertension had been lower in the calcium-treated group of mothers. At assessment 7 years later, maternal systolic blood pressure was not different, but diastolic blood pressure was significantly lower in the calcium-supplemented group. The mechanism of action is still speculative, and the authors propose that the effect is either mediated by lower maternal blood pressure or resulting directly from increased calcium transport to fetal circulation.

It is feasible and ethical to use preterm infants to test the importance of the perinatal period as a window for nutritional programming (Lucas & Morley, 1994; Lucas, 1998). Impaired fetal growth, rather than prematurity, seems to be associated with chronic diseases such as CVD and metabolic syndrome. Preterm infants, however, may be particularly sensitive to programming stimuli since they were born during a period of rapid development. Nevertheless, the preterm infant model is incomplete. Certain fetal adaptations such as diversion of blood to protect the brain are no longer possible after birth. Furthermore, the role of the placenta in programming ceases at birth (Barker, personal communication).

The longest standing trial undertaken in 1982 and involving over 900 preterm infants showed that by a short postnatal period of dietary manipulation, permanent effects could be programmed, as suggested by follow-up in children aged up to 12 years (Lucas, 1998), and then at 13–16 years (Singhal, Cole & Lucas, 2001).

For example, it was found at 5-year follow-up that bone mineral content was higher in children assigned randomly to human milk versus formula in the first 4 weeks of life. Follow-up at 9–12 years showed that osteocalcin level (marker of bone formation) was higher in children with suboptimum feeding postnatally . These observations are in line with early programming. Investigation continues on the propensity to bone disease and to CVD in later life in those children born preterm and assigned to various early feeding regimens. At follow-up at age 13–16 years, it was observed that mean arterial blood pressure of the 66 children assigned bank breastmilk was significantly lower (-4.4 mmHg, CI: -6.6 to -1.6 mmHg) than that of children who had been assigned preterm formula for a mean of 30 days. Within the breastmilk group, there was a graded negative response between total milk consumption and later blood pressure. This is at least partly consistent with the hypothesis that high blood pressure in later life has early nutritional origins. A decrease of 3 mmHg in blood pressure, as observed in this and in previous studies, is important for public health policy in light of the Framingham study projections which show that a decrease of only 2 mmHg has a substantial impact on reducing blood pressure. In these adolescents, blood pressure was unrelated to birth weight for gestational age, nor was it related to weight change from birth to adolescence. Sodium and fat were not he mediators of the effect. Then, it may be the unique trophic factors, or the fatty-acid profile of human milk (which contains long chain polyunsaturated fatty acids not found in formula) that explain the effect (Roberts, 2001).

5. Underlying mechanisms of fetal programming of chronic diseases

From experimental data, there is clear evidence that transient events in early life have permanent and profound effects on physiology and metabolism. Impaired structure or function, or metabolic adaptations, may link unfavourable intrauterine exposure and chronic disease. For instance, in the case of type-2 diabetes, pancreatic β-cell function (Hales et al., 1991; 1996), or insulin action (Phillips et al., 1994) may be impaired. Fetal programming by nutritional and hormonal factors has been demonstrated in animals, and there is growing evidence from experimental, clinical, and epidemiological data, that it also operates in humans. The underlying mechanisms are not clear, although animal models provide more than hints on the molecular basis of programming itself and of its metabolic consequences (Holness, Langdown & Sugden, 2000). Lucas (1998) speculated that nutrients may be critical signals acting on receptors in sensitive tissues. When programming, or resetting of a later function is involved, a key question is: how is the memory of these early events stored throughout life in spite of continuous cell replication and renewal? Proposed mechanisms include adaptive effects on gene expression, or on differential cell proliferation for which there is indirect evidence from animal studies. Intergenerational effects of programming may be explained by epigenetic inheritance, based on DNA methylation (Holliday, 1993).

Alterations in set-points of major hormonal axes are now gathering support as the most likely dominant mechanisms of fetal programming. In particular, the IGF-1 and insulin axis, and the HPA axis are suspected of important modifications in fetal malnutrition, which could explain increased CVD and insulin resistance syndrome in adulthood.

5.1 Fetal glucocorticoids and resetting of the hypothalamus-pituitary-adrenal axis

From animal studies, it is inferred that maternal nutritional deprivation or imbalances, (particularly protein) and fetal exposure to excess glucocorticoids, may result in higher blood pressure and hyperglycemia (Benediktsson et al., 1993; Lindsay et al., 1996). Protein deprivation and glucocorticoid excess are likely related. In utero, excess cortisol may occur either from fetoplacental stress (and undernutrition is one type of stress), or from deficiency in the normal placental enzyme barrier that protects the fetus from its mother's glucocorticoids.

The fetus normally has much lower levels of physiologic glucocorticoids than the mother, owing to their rapid conversion by placental 11-β-OHSD to inert forms. This placental barrier is effective in protecting the fetus against overexposure to corticosteroids. The enzyme is normally maintained in humans until the end of gestation, but it may be attenuated in IUGR, which would explain higher cortisol levels observed in growth retarded human fetuses (Goland et al., 1993; Seckl, 1998a,b). An inverse association of plasma cortisol concentrations and birth weight was observed in adults aged from 20 to 65 years from three different populations (Phillips et al., 2000). Birth length (but not PI) was also inversely correlated with cortisol. This association was independent of age, sex, smoking, current body weight, and socioeconomic status. Plasma cortisol was positively correlated with blood pressure, and this relationship was stronger in obese people, supporting an amplification role of the programming effects by obesity.

Permanent alterations in the expressions of glucocorticoid receptors in specific tissues of the offspring and hyperactivity of the HPA axis (Levitt et al., 1996) may contribute to the observed rise in blood pressure and glucose. Chronic activation of the HPA axis with high fetal cortisol levels could permanently alter gene expression through chromatin remodeling, as suggested by Radunovic et al. (2000). In the protein restricted rat model, the offspring had glucocorticoid-dependent raised systolic blood pressure throughout life, there was a marked decline of expression of 11-β-OHSD, and the expression of glucocorticoid (but not mineralocorticoid) receptor protein and mRNA was reduced (Bertram et al., 2001). Observations of an inverse association of birth weight with plasma cortisol concentrations in human adults (Phillips et al., 2000),

and of a positive association of cortisol with insulin resistance, blood pressure triacylglycerol level, fasting and 2-h glucose (Phillips et al., 1998; 2000) are consistent with programming of the HPA axis *in utero*.

The role of intrauterine glucocorticoids and the long-term consequences of high fetal exposure was reviewed (Fowden, Li & Forhead, 1998; Dodic et al., 1999). Prenatal glucocorticoids stimulate tissue differentiation and hence organ maturation rate, including the lung, heart, kidney, and immune system. They coordinate the various adaptations needed to survive the transition from intra- to extra-uterine life. While in normal conditions glucocorticoid concentrations only rise before term as a signal for tissue maturation, fetal cortisol levels become elevated earlier, possibly as a consequence of HPA axis activation, in stressful intrauterine conditions such as placental insufficiency, undernutrition, or restricted blood flow. Elevated cortisol induces an early shift from cell proliferation to cell differentiation, with an inappropriate pattern of growth for the stage of development, and possibly adverse consequences much later in life. Fetal glucocorticoid excess may achieve a short term benefit by increasing the availability of glucose and other fuels, but adverse effects may result in the longer term. Glucocorticoids may well have a pivotal role in the prenatal programming of adult disease. According to Langley-Evans et al. (1999), the chain of events leading from glucocorticoid action in the fetus to hypertension in the adult involves the development of hypersensitivity to glucocorticoids in adult life, with activation of the renin-angiotensin system, and increased sensitivity of the vessels to angiotensin II. Glucocorticoids can also impair the development of blood vasculature and programme the renin-angiotensin system of the kidney, as suggested by animal studies (Langley-Evans & Jackson, 1994; Langley-Evans et al., 1999; Martyn, Barker & Osmond, 1996). Impaired fetal nephrogenesis is also likely involved, with lifelong impact on renal function and cardiovascular control. Low birth weight babies have fewer nephrons, and this may be related to the renin-angiotensin involvement in explaining higher blood pressure in such individuals. Additional evidence for programming of the sympatho-adrenal function comes from the observation that resting pulse rate, an indicator of increased sympathetic nervous system activity, is raised in subjects with LBW (Phillips & Barker, 1997; Pharoah, Stevenson & West, 1998).

The hypercorticoidism of the fetus exposed to excessive maternal cortisol could not only enhance susceptibility to hypertension but also reset, in the long term, the HPA axis controlling cortisol metabolism (James, 1997; Lesage et al., 2001). While severe maternal undernutrition was shown in rats to activate maternal HPA and affect the development of fetal HPA axis secondary to transplacental corticosterone transfer (Lesage et al., 2001), Gluckman (2001) suggests that less severe undernutrition may cause more subtle elevations in fetal glucocorticoid exposure which may impair fetal growth, but without impacting on fetal HPA axis development. Such resetting of the HPA axis controlling cortisol metabolism has been observed in adults who have abdominal obesity (Björntorp, 1993). While stress-related cortisol secretion is likely an inducer of the HPA axis, a depressed function of the HPA axis may be present in a small proportion of adults, and associated with low secretion of sex steroid and growth hormones (Björntorp, 1999). The resetting of corticosteroid responses may be established *in utero*, leading to exaggerated cortisol responses that, in turn, promote both accumulation of abdominal fat and insulin resistance.

Overexposure to glucocorticoids *in utero* may lead to adult glucose intolerance and insulin resistance through several mechanisms: glucose production may be permanently enhanced by the cortisol-induced upregulation of gluconeogenesis in the liver and kidney; although little evidence exists, there may be changes in pancreatic β-cell function; and glucocorticoids may also alter the expression of glucoregulatory genes in tissues, such as skeletal muscle, which make a major contribution to insulin-sensitive glucose disposal. It is noteworthy that the major systems affected by early life programming also appear to be glucocorticoid sensitive (Seckl, 1998b). Glucocorticoids regulate insulin growth factors, their receptors and several binding proteins, and they may consequently affect fetal growth and programming through this route.

5.2 The "thrifty phenotype" hypothesis

This represents the second part of the fetal origins hypothesis (Hales & Barker, 1992), and the environmental pendant of the thrifty genotype hypothesis of Neel (1962; 1982). It was proposed by Barker and his co-workers to account for the associations observed between fetal or early growth restriction and the subsequent development of chronic disease, in particular insulin resistance and impaired glucose tolerance.

According to more recent updates, the theory postulates that changes in fetal growth evolve to aid fetal and postnatal survival ("fetal salvage" according to Hofman et al., 1997) by selective changes in growth rates of specific organs, or more likely, by adaptations in fetal metabolism. Studies in rats, as discussed earlier, show that during periods of inadequate nutri-

tion, growth of the brain and lungs is protected, while that of the kidneys is reduced. Growth of pancreas is impaired in females, not in males. More subtle changes in organ structure and function are imposed during periods of inadequate nutrition, and these may not be obvious on the basis of organ weight. Resetting of metabolism may be involved, with changes intended for the metabolism to become "thrifty" when the nutrient supply is reduced (Hales, 1997a). These metabolic changes would serve to adapt the offspring for survival in the poor nutritional environment experienced by the mother. While these adaptations may be beneficial in times of short nutrient supply, they would become a liability in nutritional abundance, with risk of obesity and type-2 diabetes. These adaptive processes are as yet unclear, although animal data provide partial explanation.

The endocrine alterations could be intended for survival, through redirecting limited nutrient supply for development of vital organs such as the brain, at the expense of growth. This is where insulin resistance could be beneficial, in gaining more growth stimulation from hyperinsulinaemia through redirecting glucose away from the skeletal muscle and towards vital organs like the brain and placenta. As discussed by Ozanne & Hales (1998), there is evidence that resistance to glucose transport action of insulin is not necessarily accompanied by resistance to its anabolic effect. There could be selective resistance to insulin, and this would be coherent with Neel's (1962; 1982) and Reaven's (1988; 1998) postulated survival advantage associated with insulin resistance, but also associated increased risk of diabetes. Reduced peripheral insulin sensitivity would stimulate β-cells to produce larger amounts of insulin to maintain normal glycaemia, contributing to pancreas exhaustion. This is supported by animal studies showing reduced glucose transporter protein concentration in skeletal muscle in IUGR fetuses but normal concentration in the brain (Simmons, Flozak & Ogata, 1993).

5.2.1 *Resetting of the insulin-like growth factor system*

Insulin-like growth factors (IGFs) are major mediators of pre- and postnatal growth in humans as well as in rodents, and their production in utero appears largely independent of GH (Rosenfeld, 1997). The growth-promoting role of GH appears to be largely confined to the postnatal period, while IGFs have a primary role in the prenatal period. IGF-1 and IGF-2 bind to the type 1 receptor, which appears to mediate the major mitogenic actions of both peptides. Both IGFs also bind to the insulin receptor, but with lower affinity than does insulin. The role of the insulin receptor as an alternative growth promoting receptor requires further evaluation. The type 2 receptor binds IGF-2 with high affinity, but has little affinity for IGF-1 or insulin. Its primary role appears to be to degrade IGF-2. In plasma and other biological fluids, IGFs are complexed to a large family of binding proteins (IGFBPs) exhibiting various levels of affinity and capable of regulating the access of IGFs to their receptors, or by direct effects upon the cells. The regulation of IGFs and IGFBPs is very complex. It is not clear why both IGFs have a role in early embryonic development while IGF-1, but not IGF-2, has a role in later fetal (and perinatal) growth. According to Gluckman (1997), IGF-2 is dominant early in gestation, when placenta is not limiting for substrate availability. Later in gestation, when the fetus must compete with the placenta and mother for substrate, and when placenta function is limiting, it is important that the IGF system be regulated by nutrition. The system would then switch to IGF-1, which is under acute nutritional regulation, explaining that IGF dominates later in pregnancy, while the expression of IGF-2 is then reduced (Gluckman, 1997).

Based on animal studies, it was proposed that the primary axis regulating fetal IGF-1, and therefore fetal growth, is the glucose-insulin-IGF-1 axis (Gluckman, 1997). Fetal IGF-1 is secreted in response to fetal insulin, which is itself determined by placental glucose transfer. Fetal insulin acts primarily as an adipogenic factor, while its effect on lean body mass is probably mediated through IGF-1. GH has a small but demonstrable effect on fetal growth, also through regulation of IGF-1.

The increase in plasma IGF-1 in childhood has implicated this factor in fetal programming through intricate mechanisms (Fall et al., 1995b). Different studies suggest that IGF-1 bioavailability or action may be altered whenever fetal growth is threatened (Langford et al., 1995; Cianfarani et al., 1998). Low IGF-1 (and low IGFBP-3) at birth appears to be an indicator of fetal malnutrition in humans (Léger et al., 1996; Cance-Rouzaud et al., 1998), as well as in animals (Gallaher et al., 1998). Evidence of the link between IUGR and low IGF-1 comes from the severe IUGR observed in animals and humans with IGF-1 gene mutagenesis or deletion, as reviewed by Cianfarani et al. (1998) . It addition, low levels of IGF-1 and IGFBP-3 were observed in children born SGA but who did not show catch-up growth and had remained short, compared to normal or short stature children but with adequate size for gestational age at birth (Boguszewski et al., 1997). A reduced rate and abnormal pattern of

GH secretion was also present, suggesting that a persistent defect of the GH-IGF-1 axis may occur in those SGA children who do not experience postnatal catch-up.

According to the catch-up growth hypothesis of Cianfarani, Germani & Branca (1999), tissues are depleted of insulin and of IGF-1 during fetal life when there is a shortage of nutrient substrates, as the IGF-1 system is then switched off. After birth, faced with ample supply of both hormones (IGF-1 and insulin) because of adequate nutrient supply, it is speculated that insulin resistance develops as a defense mechanism against hypoglycemia. The overactivation of the IGF system determines early postnatal catch-up growth, but also induces insulin resistance as metabolic adaptation with potentially detrimental effects in the long term. Catch-up growth and its relation with chronic disease risk is further discussed with postnatal factors modulating the effect of impaired fetal growth, in Section 7.

5.2.2 *A role for leptin?*

Leptin, a peptide hormone involved in growth and metabolism, likely plays a role in the regulation of body weight and fat mass. Interactions with other hormones, including insulin, IGF-1, and cortisol have been reported in vivo and in vitro (Kolazynski et al., 1996). In newborns, serum leptin concentrations are higher in females than males, and they are particularly strongly correlated with birth weight and insulin level. There is also a significant relationship with IGF-1 and cortisol. However, cortisol is apparently the only hormone having an independent effect on serum leptin (Maffeis et al., 1999). Concentrations are low in growth retarded or premature babies and appear to predict weight gain and catch-up growth in early infancy (Jaquet et al., 1998; Ong, Ahmed & Dunger, 1999). The association of birth weight with adult leptin was examined (Phillips et al., 1999). In adults aged 61–73 years, leptin levels were higher in women than in men. In both sexes, fasting leptin correlated positively with BMI, fasting insulin, and 2-hour insulin and glucose levels. Leptin was also positively correlated with waist-hip ratio in men. At given obesity levels, those who had lower birth weight had higher leptin levels than those of higher birth weight. The highest leptin levels were found in those who were small at birth and obese as adults. Jaquet et al. (1999) examined the role of leptin in catch-up growth in a longitudinal study of children born with IUGR, compared to children without IUGR. It was found that at the age of one year, children born with IUGR had significantly higher leptin levels than normal children, independent of BMI (Jaquet et al., 1999).

The lack of correlation of BMI and leptin in IUGR children, as well as the absence of sex-related difference in leptin concentrations, suggest that IUGR children develop leptin resistance, as also speculated in rats born to underfed mothers (Vickers et al., 2000), with resulting benefit for catch-up growth. An alternative hypothesis for the authors is that the high leptin levels reflect adipocyte dysfunction as a consequence of altered adipose tissue development in IUGR. However, multivariate analyses did not show a role for leptin in the association of lower birth weight with lower glucose tolerance (Phillips et al., 1999). It is suggested that higher leptin concentrations reflect altered body composition or other physiological changes associated with small size at birth. It may reflect the hypercortisolemia resulting from resetting of the HPA axis, and hyperinsulinaemia, also associated with LBW. There is some evidence that catch-up growth in small babies is strongly related to cord blood level of leptin (Ong, Ahmed & Dunger, 1999).

The hypothesis that low leptin may be part of the phenotypic expression of the thrifty genotype could not be confirmed in a study on Pima Indians and non-Pima subjects in Mexico (Fox et al., 1998). While leptin concentrations were correlated with percentage of body fat and waist circumference in both groups, there was no differences in leptin concentrations between groups even after adjusting for percent body fat, waist circumference, age, and sex.

At this stage, there is therefore little evidence of a role for leptin in fetal programming of chronic disease, other than perhaps as a predictor of catch-up growth in individuals born with IUGR.

5.3 Structural impairment during fetal life, and later adaptation

As a result of impaired fetal growth, several structural changes may be implicated in early programming of chronic diseases, in addition to the resetting of major metabolic axes.

It is hypothesized that a reduced number of nephrons may explain the negative association of birth weight (or gestational age) with blood pressure (Brenner & Chertow, 1994), as suggested by experimental models in rats. Maintenance of renal haemodynamic functions following structural impairment during fetal life may require adaptations which raise blood pressure and promote a more rapid progression to renal failure (Nwagwu, Cook & Langley-Evans, 2000). Activation of the renin-angiotensin system is likely involved in an effort to preserve glomerular filtration (Dodic et al., 1998).

Vascular structure may be impaired in poor fetal growth, with loss of elasticity of vessel walls (Martyn et al., 1995). Leeson et al. (2000) observed that LBW was associated with vascular endothelial dysfunction, in young adults and in children. Poor vascularization of the skeletal muscles with an excess of type-1 fibers compared with type-2B muscle fibers has been suggested (Taylor et al., 1995). Reduced muscle glycolysis may result from fetal programming: it was indeed observed by magnetic resonance spectroscopy in adults who were thin at birth (Taylor et al., 1995). The observed differences in adult skeletal muscle metabolism were specific to PI at birth, and not to other birth measurements available. The evidence is consistent with a lower rate of glycolytic ATP (adenosine triphosphate) production. However, only when metabolic demand is increased to a level that cannot be satisfied with oxidative metabolism, does the inability to increase glycolysis appear. Such changes likely reflect slight shifts in regulatory enzymes. Persistent changes in the levels of GH and cortisol, which control substrate utilisation and metabolism in adult life, and also regulate fetal growth and maturation, may be responsible. Another metabolic adaptation would be an increased rate of fat oxidation, which was also observed in such adults (Wooton et al., 1994; Phillips et al., 1996). Apart from these fiber alterations, reduced capillary density and abnormalities of the capillary structure, such as thickened capillary basement membrane, may reduce the rate of diffusion of insulin to its receptor, thereby causing insulin resistance in people who were born small (Thompson et al., 1997).

Retarded fetal growth can result in a reduced number of β-cells and hence, the secretory capacity of the pancreas may be altered. There is, however, stronger evidence that it results in reduced insulin sensitivity and increased insulin resistance (Barker, 1997a; Ravelli et al., 1998).

Reprogramming of immunity may also be mediated by impaired organ differentiation and growth during fetal life. As proposed by Prentice (1998) and supported by observations in SGA-born adolescents (McDade et al., 2001), one mechanism may be the impairment of morphological development of thymus and lymphoid tissue. The author speculated that early thymic damage associated with fetal malnutrition might account for increased mortality observed among adults born in the hungry season in the Gambia. The thymus has an important function, and aberrations in lymphocyte processing may have life-long consequences. A defect in thymic-mediated immunity resulting from fetal programming could have serious consequences. For instance, the likelihood of contracting vertically-transmitted HIV infection could be increased, and the duration of survival within infected individuals markedly decreased, in children with a congenital "thymic defect profile" caused by thymus dysfunction (Kourtis et al., 1996). T-cell repertoire set-up and maintenance is another possible focus for programming. Failure to respond to certain antigens may create a hole in the repertoire, or a suboptimal response may generate a limited pool of circulating lymphocytes. There may also be an accelerated immunosenescence, a hypothesis involving the thymus, since it plays an important role in regenerating T-cells after lymphocyte depletion (Mackall et al., 1995; Prentice, 1998).

6. The role of fetal and maternal nutrition in programming of chronic disease

Fetal nutrition, understood as the net supply of metabolic substrates to the fetus, has been hypothesized to be the primary stimulus for intrauterine programming of chronic diseases. Recent reviews have helped clarify various aspects of this complex issue of nutritional programming (Godfrey & Barker, 2000; Harding, 2001; Rasmussen, 2001). Fetal nutrition, fetal growth, and birth size and proportions need to be distinguished. Furthermore, fetal nutrition does not necessarily mean maternal nutrition, although the latter is indisputably a major determinant of the former. It is important to determine to what extent maternal nutritional factors, and their timing, may have programming effects through, or independently from, effects on birth phenotype. Much information on the influence of maternal nutrition comes from animal models and famine studies. Another line of evidence supporting nutrition as a likely programming stimulus comes from its biological plausibility, based on the body of knowledge on the regulation of fetal growth (Harding, 2001). Animal studies are useful to clarify the effects of timing of intrauterine nutrient shortages or imbalances, in spite of species differences. For instance, based on rat studies, the teratogenic period for exposure to hyperglycemia would correspond in humans to a 6-week period between the second and eighth week of intrauterine life (Reece, 1999). The timing of nutritional incidents during pregnancy is of utmost importance, as demonstrated in human famine studies as well. The periconceptual, embryonic and fetal epochs of pregnancy are, in Paneth's words (1994), "as different as are infancy, adolescence, and older age periods of the life cycle". These periods must therefore be carefully distinguished. Dissimilar effects on fetal growth, birth weight, and body dimensions at birth have been observed depending on the timing (and nature) of nutritional inadequacies.

Maternal nutrition refers both to her nutritional status at the onset (and throughout) pregnancy, and to her energy and nutrient intake during pregnancy. The former is possibly even more critical than the latter for fetal growth, but the role of specific nutrients, their timing and their balance in reaching the fetus, is largely unexplored. Even if exposed to food shortage during the course of pregnancy, women with adequate energy and nutrient stores will provide for appropriate tissue synthesis and growth of the fetus. There is evidence for this in studies among populations exposed to famines (see Section 3.5.2.). Conversely, malnourished mothers may not be able to provide for adequate fetal growth even if diet is improved during pregnancy. This is a well-known phenomenon in animal husbandry. Furthermore, women who themselves were born growth retarded are at higher coronary risk, and they expose the next generation to similar risk, even more so if they gain excess weight.

In epidemiological studies on associations of birth weight with chronic disease in adulthood, small size in term newborns has often been equated with fetal and maternal malnutrition, which may be an oversimplification. There have been reports of links of CVD, diabetes, or insulin resistance features with other measures of restricted fetal growth than birth weight, including thinness, shortness, low placental weight or ratio, and small abdominal circumference. It may be appropriate to distinguish among these various indicators of size and proportions at birth, and to assess maternal influences thereupon. A commonly held presumption is that fetal growth is entirely reflected in birth weight, as underscored by Harding (1999; 2001). Birth weight is a crude measure of fetal growth (Poppitt et al., 1994) even with additional anthropometric measures such as just described. Furthermore, as animal studies suggest (Godfrey 1998; Langley-Evans 2000), size at birth is only an indirect proxy for fetal programming influences, as these may have only minor effects on its overall growth. Besides, different fetal growth trajectories may result in similar birth weights (Harding, 2001). Finally, birth somatic phenotype is the endpoint of a process which needs to be better understood in order to explain why and how the intrauterine experience may be associated with health risk later in life.

6.1 Impaired fetal growth, more than prematurity or clinical IUGR, predicts chronic disease risk

Fetal growth impairment may be identified by small size at birth, or disproportions, for instance, of placental/fetal growth, or in head circumference, length and weight. A consistent feature of most studies is that chronic disease risk is graded across the "normal" range of size at birth (birth weight and body proportions), and it is not only associated with LBW at the lower end of the spectrum of fetal growth. Low birth weight due to IUGR, and not prematurity, has usually been found to be related to higher chronic disease risk, but the fetal origins hypothesis cannot be equated with the long-term effects of IUGR as clinically defined. Besides, birth weight as such, without standardizing for gestational age, is inversely related to blood pressure (see Section 3.3.), and there are data suggesting that prematurity may also be associated with increased cardiovascular risk (Irving et al., 2000). There are diverse patterns of fetal growth retardation, depending on the timing, type and severity of fetal insult. It has been recommended, in order to better clarify this hypothesis, that impaired fetal growth be characterized by a combination of anthropometric, biophysical and biochemical measures as an alternative to appraising the ideal but impractical fetal growth trajectory (Henriksen, 1999). Growth restricted newborns are a heterogeneous group, and body proportions may be more informative than birth weight alone. Different classifications exist based on anthropometric proportions at birth, and on speculated timing and duration of fetal "insult". However, many assumptions about the type of fetal growth impairment reflected in proportions at birth according to type and duration of nutritional limitations are overly simplistic, according to Harding (2001). The classification of infants born SGA[5] based on PI (Villar, Belizan & Smeriglio, 1989) distinguishes proportionate and disproportionate IUGR. Newborns with proportionate IUGR (normal PI) are altogether of smaller size, or both thin and short, whereas those with disproportionate (or asymmetrical) IUGR (low PI) are thin, but their body length is nearly normal. Thinness is mainly due to a reduction in fat deposition, and to a lesser extent in skeletal muscle, as a consequence of fetal undernutrition in late pregnancy, whereas proportionate (or symmetrical) growth restriction is assumed to result from more chronic fetal growth impairment (Barker, 1995). However, the reliability of PI may be questionable because of technical errors of measurement of birth length.

[5] SGA taken as synonymous with IUGR in this paper, although subtle distinctions exist (Roth, 1996; Henriksen, 1999).

Newborns with a low PI are reportedly more likely than proportionately growth-restricted babies to experience catch-up growth during early postnatal life (Villar, Belizan & Smeriglio, 1989), but they appear to be more susceptible to CHD and insulin resistance in adulthood, and even more so if they have caught-up after infancy (see Section 7). In newborns with low abdominal circumference, and in those who were disproportionately short in relation to head size, persistent abnormalities in systems which are regulated by the liver, such as cholesterol and coagulation, have been attributed to programming of liver metabolism by fetal undernutrition (Barker et al., 1995). However, ultrasound measurements have not confirmed the assumed relationship between abdominal circumference and liver size (Roberts et al., 1999). Clear differences in timing and pattern of fetal growth changes that are assumed in the classification of symmetrical/asymmetrical growth restriction have not been confirmed either by ultasonography, which is consistent with a continuum of nutritional limitation affecting fetal growth, according to Harding (2001). Nevertheless, animal experiments consistently suggest that fetal malnutrition (undernutrition or nutritional imbalances) in early gestation results in small but normally proportioned offspring, whereas in late gestation, proportions of offspring at birth are altered, but not birth weight. Similarly, outside of famine situations, fetal undernutrition in late pregnancy in animals or humans is often the result of inadequate maternoplacental supply capacity established earlier in gestation (Robinson et al., 1995; Godfrey et al., 1996c; Gluckman, 1997; Godfrey & Barker, 2000).

Infants with proportionate (or symmetrical) growth impairment are likely to remain shorter and lighter than normal infants. It is postulated that by down-regulating growth in response to undernutrition in early uterine life, the fetus reduces its demands for nutrients, thereby reducing the risk of undernutrition in late gestation (Godfrey, 1998). According to Barker (1999a,b), this pattern of fetal growth may not be so strongly associated with chronic disease as in the case of asymmetrical IUGR, except for higher blood pressure. Children who are still small at one year are more likely to be of the symmetrical IUGR type because there is less potential for postnatal catch-up growth than in asymmetrical IUGR. The reported association of low weight at one year with chronic disease in later life would therefore be somewhat similar to that found in the case of chronically impaired fetal growth (or low fetal growth trajectory, see below).

Predominant phenotypes of fetal growth restriction may vary, depending on the prevailing causes. For in-

stance, in China, babies tend to be proportionately small, whereas in India, they tend to be thin (Barker, 1998). The long-term consequences of such differences may be geographical disparities in the prevalence of CHD, hypertension, and insulin resistance syndrome, as pointed out by James (1997). As discussed previously, adult CHD and type-2 diabetes appear to be more closely associated with body proportions at birth than birth weight as such (Lithell et al., 1996; Forsén et al., 1997).

6.2 Poor maternal nutrition as a predominant cause of impaired fetal growth in developing countries

A number of studies suggest that the fetal genome plays only a subordinate role in determining the growth that is actually achieved (Snow, 1989). For instance, in embryo transfer studies, the recipient mother influences birth size much more than the donor mother (Brooks et al., 1995). Birth weight correlations show that the dominant influences of fetal growth are indeed maternal, with little paternal effect, suggesting little autosomal influence (Gluckman, 1997). Fetal growth and development is determined by maternal nutrition, placental function and ability of the fetus to use the nutrients and oxygen provided. The main cause of placental insufficiency is inadequate blood flow on the maternal or fetal side, although other factors may affect transport mechanisms to the placenta. Inability of the fetus to use the substrates provided may be due to genetic or chromosomal factors, to infections or malformations (Henriksen, 1999). Godfrey & Barker (2000) provided a useful framework to understand maternal regulation of fetal development and programming. The basic elements are fetal demand, materno-placental supply, and fetal adaptations to inadequate supply to meet the demand. Fetal growth trajectory—and hence fetal nutrient demand—is set early in gestation. The nutrient supply is secured by the materno-placental line. The mother's body composition, nutritional status, and dietary intake will determine whether or not there is a balance between the nutrient demand and supply. Failure of the materno-placental supply line to meet fetal demand will result in fetal adaptations for survival. As noted by Gluckman & Pinal (2001), the fetal origins model represents this environmental adaptation process, whereby the fetus inteprets various signals in utero, and resets growth and metabolism in anticipation of the postnatal environment. Any mismatch between the expected and actual postnatal environment manifests in adult disease.

Nutrition of the fetus is indeed key, and as underlined by Hay (1999), fetal life is characterized as having nutrient-driven metabolism, with less dependence on hormones than in neonatal life. Harding (1999) sees the fetal endocrine environment as an important mediator of the nutritional regulation of fetal growth. The most common cause of impaired fetal growth is nutritional, that is, deficient supply of substrate (Gluckman & Harding, 1997; Lapillonne et al., 1997). In a study of term newborns in India, for instance, based on clinical assessment of their nutritional status, fetal malnutrition was present in 84% of SGA newborns (Deodhar & Jarad, 1999). Fetal malnutrition may be the result of inadequate maternal diet, maternal disease or, more commonly (at least in affluent populations), of abnormal utero-placental blood supply and placental function. Maternal hypertension is known to compromise the utero-placental blood supply. The majority of cases of idiopathic fetal growth impairment are also due to reduced nutrient delivery to the fetus (Lapillonne et al., 1997). It can therefore be assumed that in the large majority of cases, particularly in poorer population groups where maternal malnutrition is common, impaired fetal growth reflects fetal malnutrition, and maternal malnutrition as well. Differences in the rate of LBW among countries or groups indeed reflect various planes of maternal nutritional status, since the rate of prematurity does not fluctuate much and is little affected by maternal nutritional status (de Onis, Blössner & Villar, 1998). To interpret measures of fetal size as if they were a pure reflection of nutrition during fetal life, however, is a mistake (Paneth, 1994). Fetal nutrition is not simply a reflection of maternal nutritional status, as it involves the delivery of essential substrates to fetal tissues for both tissue accretion (growth) and oxidative purposes, following a cascade of events going from maternal nutrition and health status to fetal endocrine status (Gluckman, 1997).

The complex processes by which mothers regulate the development of fetuses are only beginning to be understood. Circulating fetal insulin and IGF-1 are considered to be the primary fetal hormones involved in the regulation of fetal growth, and their release is determined by nutrient delivery, matching growth with the materno-placental supply of nutrients (Gluckman, 1997). Partitioning of nutrients between the fetus, the placenta, and the mother is largely determined by maternal nutritional status. It is suggested that maternal diet may influence fetal growth primarily through placental growth in early pregnancy, and through nutrient supply in late gestation (Godfrey et al., 1996c; Robinson et al., 1997; Godfrey & Robinson, 1998). IGF-1 is the primary fetal growth factor in late pregnancy and its level is under acute nutritional regulation (Gluckman, 1997).

Setting the trajectory of fetal growth appears to be a major role of maternal nutritional status (Godfrey, 1998; Godfrey & Barker, 2000). In the developing embryo, cells are distributed between two masses: the embryo and the placenta. The distribution between the two appears to be influenced by periconceptional nutrition and hormonal status of the mother, according to animal studies (Kleeman, Walker & Seamark, 1994). In the rat model, protein deficiency during gestation primarily altered threonine levels in maternal serum and the fetus (Rees et al., 1999). This amino acid may have particular importance in setting the fetal growth trajectory. Resetting of fetal growth to a lower rate may be an important adaptation in early gestation in that it contributes to reduced nutrient demand in late gestation. Conversely, a high growth rate trajectory renders the fetus more vulnerable to a poor nutrient supply in late gestation (Harding et al., 1992). It is possible that this higher growth trajectory, accompanied with nutrient restriction in late pregnancy because of maternal constraint owing to her own small size, would contribute to the rise in CHD with westernization, and also to higher death rates in men (Godfrey, 1998). The growth trajectory is known to be higher in male fetuses, and it has been speculated that the lower rates of CHD among women may originate in their slower rates of growth *in utero* (Forsén et al., 1999).

In spite of the ability of the fetus to adapt to a broad range of nutritional conditions *in utero*, maternal nutritional factors remain the most important determinants of impaired fetal growth, but prevailing socioeconomic conditions make a difference. The role of maternal nutrition may appear modest in relatively well-nourished and affluent populations, but this is not the case in poorer population groups, where maternal malnutrition may be an important factor of fetal growth restriction. Mathews, Yudkin & Neil (1999) share this view. As pointed out by Kramer (1998), cigarette smoking is associated with the largest etiological fraction of IUGR in developed countries, followed by low weight gain in gestation and low maternal BMI; mother's height is another factor. Maternal smoking and height, however, were not shown to be independently related to cardiovascular risk factors in children (Law et al., 1991; Whincup, Cook & Papacosta, 1992), although there is at least one discordant report which indicates that maternal smoking was associated with both lower birth weight and high blood pressure (Williams & Poulton, 1999). In developing countries where undernutrition is widespread and women generally do not smoke, low maternal weight gain and BMI are relatively more important, followed by short stature.[6] In India, for instance, it was observed that a pre-pregnancy BMI <16, the incidence of LBW increased exponentially; and regardless of birth weight, infants whose mothers' pre-pregnancy BMI was <17, grew less in weight and height during the first 6 months of life (Kusin, Kardjati & Rengvist, 1994). In Jamaica, shorter and thinner women had babies with lower birth weight, who were shorter, had smaller heads, and lighter placentas (Thame et al., 1998). Thinner women also had babies with a lower placental:birth weight ratio, but there was no relationship with PI. In the Jamaican study, it was observed that maternal weight gain in pregnancy made no independent contribution to birth weight, length or head circumference. Based on a large number of studies throughout the world, it has been shown, however, that the energy costs of pregnancy could vary widely among communities; that total costs were correlated with pre-pregnancy fatness and pregnancy weight gain; and that marginally malnourished women conserved energy to protect human fetal growth by reducing metabolic rate and gaining little fat during pregnancy (Poppitt et al., 1994). Nevertheless, the limits of adaptation may be exceeded, which would link maternal nutrition to newborn status. The nutritional status of mothers may also affect their reproductive performance via leptin, the concentration of which is closely correlated with maternal BMI and birth weight (Helland et al., 1998).

There is a normal maternal constraint of fetal growth, and this is reflected in the strong association between birth weight and the mother's height and pelvic dimensions. Such factors may reflect malnutrition in the mother herself during intrauterine or early life (see Section 6.6.).

Based on a large body of evidence from multicentre studies of WHO and meta-analyses of data, it appears that the major maternal anthropometric predictors of birth weight are her height, her weight before pregnancy, her weight gain during pregnancy, and her arm circumference. The most powerful predictor of IUGR according to a WHO multi-centre study was attained weight at seven months of pregnancy, in women of below-average pre-pregnancy weight (Kelly et al., 1996).

Apart from overall maternal nutritional status as reflected in these anthropometric indicators, it is possible that her status in specific nutrients has an impact of birth phenotype, and is involved in programming. For instance, maternal protein turnover at around 18 weeks of gestation in Caucasian women was shown to be positively associated with length at birth, explain-

[6] Smoking, however, may become a more important factor of impaired fetal growth in certain developing populations (Sayers & Powers, 1997).

ing 26% of the variance, in addition to being associated with their own lean body mass; dietary protein did not show this association (Duggley & Jackson, 2001). Additionally, a few micronutrients appear critical for fetal growth and perhaps also for fetal programming, although mechanisms are still obscure. On the basis of available evidence, fetal (or placental) growth is influenced by maternal iron and folate status, and these nutrients may be involved in the programming of CVD and hypertension. Zinc probably plays an important role in fetal growth, but its implication in programming is only speculative. The same can be said about essential fatty acids and magnesium. Some findings suggest that vitamin C may play a role in fetal growth or programming, but evidence is even more limited than in the case of other nutrients. A specific programming effect has been reported only in the case of calcium (see Section 4.3.).

6.3 Maternal nutrition, placental growth, and chronic disease

The placenta plays a major role in the nutrition of the fetus, through transport of nutrients from the maternal to the fetal circulation, through its own demand for, and metabolism of, key nutrients, and because it produces hormones that influence fetal and maternal nutritional supply (Harding, 2001). Growth of the placenta occurs mainly during the first half of pregnancy, in contrast to fetal growth which is more rapid in the second half (Pardi, Marconi & Cetin, 1997). As a result, the ratio of placental to fetal weight normally decreases as gestation progresses. Thame et al. (2001) were able to measure placenta volume up to 20 weeks of pregnancy in over 500 pregnant Jamaican women, and found that it was the best predictor of birth weight status.

Maternal nutrition may influence placental growth and the ratio of placental weight to birth weight (placental ratio). Maternal pre-pregnancy weight is an important determinant of placental weight, and it is positively correlated with the fetal capillary surface area, while being inversely correlated with the volume of villous tissues within the placenta (Robinson et al., 1997). Placental volume at mid-pregnancy was shown to be positively related to maternal height, as well as to a high glycaemic index diet (Robinson et al., 1997). Placental ratio tended to be low in offspring of adolescent mothers, and in the lower range of birth weights (Lurie, Feinstein & Mamet, 1999). A placenta that is either too small or too large may adversely affect fetal growth. If the placenta is disproportionately small, the fetus may suffer as a result of an impaired placental supply capacity. Conversely, if the placental is too large, the fetus may suffer by experiencing fetal catabolism and wasting to supply amino acids to the placenta as a source of lactate. There is some evidence of a suppressive effect of high dietary intakes in early pregnancy on placental growth in humans, very much like in ewes (Godfrey et al., 1997; Robinson et al., 1995). In humans, maternal anaemia due to iron deficiency or to non-nutritional factors was found to be associated with increased placental weight or placental ratio (Godfrey et al., 1991; Lao & Wong, 1997). It has also been observed that whether or not the mothers have hypertension, the same decidual vascular and placental changes occur in impaired fetal growth (Pardi, Marconi & Cetin, 1997). Thus, the placenta may be an important determinant of maternal imprinting events through the control of nutrient supply to the fetus and hormonal interchanges between fetal and maternal tissues.

Although no consistent relations between placental ratio and measures of newborn size were found in a prospective study in Australia (Williams, Evans & Newham, 1997), placental ratio was positively associated with several maternal factors, including lower socioeconomic status, anaemia, and increasing number of cigarettes smoked daily. Also in Australia, it was found that maternal smoking was negatively associated with placental weight, and with growth and bone mass of children at age 8 years (Jones, Riley & Dwyer, 1999). Association of smoking with growth and bone parameters may be mediated by placental size and function, since these effects were no longer significant when adjusting for placental weight.

Cardiovascular disease appears to be predicted by an enlarged placenta (Barker et al., 1990). A U-shaped relation between placental ratio and later coronary disease was observed in Sheffield men born early in this century (Martyn, Barker & Osmond, 1996). A positive association of placental weight with blood pressure was reported in a birth cohort upon follow-up at 8 years of age in Australia (Moore et al., 1996), while birth weight showed an inverse association with blood pressure. This is in contrast with the report of Thame et al. (2000) who observed, in a longitudinal study of Jamaican mothers and their offspring up to age 3.5 years, that placental volume at 20 weeks of pregnancy was inversely associated with children's systolic blood pressure over the age range considered, and appeared as a powerful predictor of birth weight. However, placental size was measured at mid- pregnancy, and not at birth, at which time placental weight and placental ratio showed no association with blood pressure. This suggests again that higher placental growth early in

pregnancy has a favourable impact, whereas at the time of birth, a high placental:birth weight ratio can be negatively related to blood pressure. However, this requires further research. In this Jamaican study, measures of maternal nutritional status at first antenatal visit were not related to offspring's blood pressure, but they were strong predictors of birth weight and placental volume, in particular weight, BMI, and haemoglobin (Hb), which underscores the role of maternal nutrition, even indirectly. In a large retrospective study of live, singleton and term births in Jamaica, the same authors (Thame et al., 1998) found that placental weight (and birth weight) increased with increasing maternal Hb during the first trimester, but only up to 12.5 g/dl; Hb levels above 12.5 at any time during pregnancy were negatively associated with birth weights, size at birth and placental weight. However, an observational study in England (Perry et al., 1995) showed no evidence of a relation between placental to birth weight ratio and maternal Hb at any time during pregnancy, or maternal hypertension. The authors suggested that any association between high placental ratio and adult hypertension may be confounded by genetic and environmental factors associated with maternal obesity and possibly hypertension.

The role of the placenta in intrauterine programming of adult disease is still poorly understood as illustrated by the widely diverging data. Prospective studies controlling for potentially confounding variables are required to clarify this role, as well as maternal effects on placental growth.

6.4 Maternal diet, birth weight, and links with chronic disease

Information on the effect of maternal diet on size and proportions at birth is very limited, apart for dietary supplementation studies.

Available studies only reveal weak and inconsistent associations between maternal intake of macro-nutrients and size at birth. Imbalances may have more of an impact than absolute inadequacies. Data on micronutrient intake of pregnant women from food and from supplements are still scanty. The timing of dietary inadequacies (or supplements), in addition to the type of nutrients involved, and the status of mothers, all need to be considered. Still fewer studies link maternal diet with outcomes in the offspring other than weight or size at birth (see Section 6.5.). There is no attempt here at an exhaustive review of the association between maternal diet and birth weight, however, as the focus is on data linking maternal nutrition with chronic disease in the offspring.

6.4.1 *Dietary intake studies in pregnancy*

In southern England, a prospective study involving 693 nulliparous women with singleton pregnancies (Mathews, Yudkin & Neil, 1999) showed that placental weights and birth weights of term offspring were unrelated to the intake of any macronutrient, based on a one-week dietary diary around the second trimester of pregnancy, and a self-administered food frequency questionnaire during the last trimester. In the second trimester, vitamin C was the only micronutrient independently associated with birth weight after adjusting for maternal height and smoking. Vitamin C, vitamin E, and folate were each associated with placental weight after adjustment for maternal characteristics, but only vitamin C remained predictive in simultaneous regression, although the association was weak. In late pregnancy, no nutrient was associated with either birth or placental weight. The authors concluded, based on their findings and those of other studies (Godfrey et al., 1997), that at least in industrialized populations and among reasonably well-nourished women, maternal diet in pregnancy has, at most, a minor impact on birth and placental weights. However, nutritional status at the time of conception was not considered, nor dietary intake in late pregnancy. Furthermore, this may not be so in populations where maternal malnutrition is widespread. Doyle et al. (2000) commented that maternal diet early in pregnancy, and among women with lower socioeconomic status, may show more relationship with birth weight, although this is still not well demonstrated. In their study on nutrient intakes of over 500 women from East London, based on a 7-day dietary diary during the first trimester of pregnancy (Doyle et al., 1990), they found that mothers of LBW babies had lower energy intake and a lower intake from most food groups, although there was no evidence that any specific food or food group was related to birth weight. Nutrient intakes were significantly correlated with birth weight, birth length and head circumference, but only in infants below the median for these measurements. Adjusting for pre-pregnancy weight, which was associated with all three anthropometric parameters at birth, did not alter the relationship of intakes with size at birth. Data analysis suggested that intake of B-complex vitamins was important, while intakes of vitamins A, B12, C, D, and E were not significantly correlated with birth weight, head circumference or length at birth. Magnesium intake was the mineral nutrient most closely associated with birth length and head circumference; it was also correlated with intake of zinc, phosphorus, and to a lesser extent, iron. Interestingly, energy or protein intakes were not significantly correlated with body proportions (birth length or head

circumference), while micronutrients were. Social class was also correlated with birth weight, as well as with protein and micronutrient intakes, but not with prepregnancy weight.

Rogers et al. (1998) reported on the diet of as many as 12, 000 pregnant women from the Avon Longitudinal Cohort, according to their smoking habits and perceived difficulty to afford food (food insecurity). Based on a food frequency questionnaire at around 32 weeks of pregnancy, financial hardship was associated with significantly lower intakes of most nutrients, including zinc, iron, folate, vitamin C, and magnesium (but not calcium). The differences were particularly marked for vitamin C intakes, and in general, they were more pronounced in the nonsmoking than in the smoking groups. Women with financial difficulties were less likely to eat fish, fruits, and vegetables, and more likely to use highly saturated fats. In spite of decreasing dietary quality with increasing difficulty to afford food, there was no difference in birth weight according to financial hardship or diet, while smoking and parity were strong predictors of lower birth weight. The data, however, require cautious interpretation since self-administered questionnaires were sent by mail and completed by women themselves, some of whom had low standards of literacy.

There may be adverse effects from too high as well as too low dietary protein intake during pregnancy, which points to the likely importance of balance of nutrients. This is also suggested by observations in supplementation trials (see Section 6.4.2.). Campbell et al. (1996) found that at both extremes of maternal protein intake, alterations in placental weight could be observed, and were associated with higher blood pressure in men and women aged 40 years. In this follow-up study of adult offspring of mother who had participated in a dietary study in their 7th month of pregnancy, it was further observed that that a high percentage of total calories derived from protein, especially animal protein, was also associated with lower birth weight. Balance between protein and carbohydrate intake appeared to have a reverse impact on placental weight and on blood pressure in the offspring. At low animal protein intake, systolic blood pressure increased with increasing carbohydrate, while placental weight decreased. At high animal protein intake, a decrease of systolic blood pressure, and an increase of placental weight were seen with increasing dietary carbohydrate. While the findings of adverse effects of high protein intakes are consistent with results of dietary supplementation studies (see Section 6.4.2.), cautious interpretation is warranted as dietary intake assessment was based on a single 7-day weighted dietary diary in the 30th week of pregnancy. In this same group of subjects, Shiell et al. (2000) reported that high maternal protein and fat intakes were associated with a depressed plasma insulin increment following a glucose challenge. This was also observed in the offspring of mothers with a high BMI. The authors tentatively suggested that these high intakes might impair the development of pancreatic β-cells.

Additional data, based on two food frequency questionnaires, one in early and one in late pregnancy, in 538 British mothers, suggest an adverse effect of macronutrient imbalance during pregnancy (Godfrey et al., 1996b,c). The validated questionnaire covered the previous three months. Placental and birth weights were inversely related to energy intake in early pregnancy. This would corroborate the finding that in animals, moderate undernutrition early in pregnancy stimulates placental growth in previously well-fed individuals (McCrabb, Egan & Hosking, 1991). A diet high in carbohydrates in early pregnancy, and low in animal protein in late pregnancy, affected placental and fetal growth, which suggests that carbohydrate and protein intakes in early and late pregnancy may have specific and differing effects. High carbohydrate intakes in early pregnancy were reportedly associated with low birth weight and placental weight, and this inverse relationship seemed stronger with sugars than with starch. In late pregnancy, Godfrey et al. (1996c) observed that low animal protein intake relative to carbohydrate was associated with low placental weight (dairy protein) and low birth weight (meat protein), although protein intake could not be considered inadequate (Cosgrove & Davies, 1996; Doyle, Crawford & Costeloe, 2000). This pattern of intake and lower fetal growth was associated with reduced insulin secretion, as suggested by cord plasma levels of proinsulin, insulin, and C-peptide (Godfrey et al., 1996a,b), which is at variance with the report of depressed insulin in the offspring found to be associated with high maternal intake of fat and protein at 7 months of pregnancy (Shiell et al., 2000). In their own studies of infants with IUGR, Cosgrove & Davies (1996) found that mothers were less likely to have eaten green vegetables, root vegetables and fruit during their pregnancy (based on a food frequency questionnaire), which could mean a short supply of folate, but there was no difference in intake of protein, starch, cereal, and confectionery.

Interestingly, intakes of specific foods in later pregnancy were found to be related to birth weight, in a longitudinal study in India (Rao et al., 2001). Dietary assessment was done at 18 and 28 weeks of pregnancy, using a 24-hour recall combined with a food frequency questionnaire covering the previous 3 months. Con-

sumption of milk by rural Indian mothers at 28 weeks was strongly associated with birth weight after adjustment for potentially confounding variables, although energy and protein intakes were not. Consumption of green leafy vegetables and fruits was also significantly associated with birth weight (even after correcting for blood folate), as was erythrocyte folate, at 28 weeks. Among the macronutrients, only fat intake at 18 weeks showed a significant and positive association with birth weight (and length and triceps skinfold at birth). It appears that micronutrients may be important limiting factors for fetal growth in this undernourished population (31% of mothers had pre-pregnancy BMI <17). The relationship of green vegetables and fruit intake with birthweight was strongest among thin women. Part of the effect of micronutrient intake appeared mediated by lengthening of gestation, even if the study only pertained to term births.

Many studies show that low folate status or intake of mothers is associated with LBW, as reviewed by Scholl & Johnson (2000). Periconceptual folate status is important since neural tube closure occurs early in gestation, and severe deficiency is associated with neural tube defects. Sustained folate intake is needed in order for cell replication to be normal, since there is no long-term store of folate. James (1997) postulated that seasonal cycles of folate intakes may be relevant to cyclical changes in birth weight as observed in tropical countries, and that lower folate intakes in lower socioeconomic groups may be related to lower birth weights (James, 1997). Inadequate intake is compounded in a small proportion of the population with a genetic defect in an enzyme involved in folate metabolism. Low folate is associated with LBW; it is also associated with high serum homocysteinemia, which is associated with CVD risk (Vollset et al., 2000). This is further discussed in Section 8, as low folate may mediate the link between LBW and later CVD.

Anaemia in pregnancy, presumably due to iron deficiency, induces a compensatory placental enlargement that is disproportionate to fetal size, giving a high placental ratio (Godfrey et al., 1991; see Section 6.3.). However, anaemia and iron deficiency would require a clearer definition in pregnancy. In a retrospective study of over 2, 300 singleton births in Jamaica, maternal Hb early in pregnancy was positively associated with birth weight, length and head circumference (Thame et al., 1998). However, in the second and third trimesters, maternal Hb concentration higher than 12.5 g/dl was associated with lower size at birth. It was postulated that this reflected failure to hemodilute appropriately in chronically undernourished women, which would be associated with lower plasma volume and then lower birth weight. Similarly, Steer et al. (1995) observed, in a multiethnic study in England, that higher rates of low Hb concentrations did not account for higher rates of LBW in some ethnic groups. Rather, failure of Hb concentrations to fall during pregnancy was associated with a much increased incidence of LBW and preterm delivery. Iron intake or status has not been consistently associated with CVD (Corti, Gaziano & Hennekens, 1997; de Valk & Marx, 1999).

The fetus has a great demand for essential fatty acids for membrane synthesis during cellular development, and it is quite dependent upon maternal diet for its supply, since the placenta does not have the enzymes for synthesising them. Leskanich & Noble (1999) reported in their review that a high level of long chain polyunsaturated fatty acids (PUFA) in umbilical cord plasma phospholipid was found to be associated with a high placental weight, which was itself correlated with birth weight. By late pregnancy, there may be an obligatory requirement for two long chain PUFA, which are vital for growth and brain development (visual function and psychomotor development): eicosapentanoic acid (EPA), and docosahexanoic acid (DHA). As noted by Innis (1999), DHA concentration in fetal blood also increases with advancing gestation. Interesting relationships have been observed between fish oil consumption as a source of these essential fatty acids and birth weights. Fish oil supplements delay parturition and increase birth weights, as observed in Denmark (Olsen et al., 1992). An appropriate supply of these essential fatty acids during fetal life may be important for fetal development, but specific short- and long-term effects associated with circulating levels at birth need to be delineated by future research.

6.4.2 *Mitigated effects of nutritional supplementation during pregnancy on birth weight*

If fetal nutrition is the major regulator of fetal growth, then one would reasonably expect that dietary and nutrient supplements would benefit fetal growth, and conversely, that maternal undernutrition would have observable impact on birth size. However, maternal nutritional supplementation during pregnancy has shown rather mitigated effects, at least on fetal growth where the information is available, as reviews have suggested (Rush, 1989; Kramer, 1993; Gülmezoglu, de Onis & Villar, 1997; de Onis, Villar & Gülmezoglu, 1998; Gülmezoglu & Hofmeyr, 2001; Kramer, 2001a-c; Makrides & Crowther, 2001; Mahomed, 2001a, -d). Furthermore, maternal undernutrition as observed in famine situations in Europe during the last World War was not shown to have much impact on birth weights (see Section 3.5.2.).

Reviews of trials providing dietary supplements to pregnant women revealed that high protein supplementation was usually associated with lower birth weight and other adverse neonatal outcomes (Rush, 1989; Kramer, 2001b). According to a Cochrane review of 13 trials (Kramer, 2001a), however, balanced protein/energy supplementation (less than 25% of energy as protein) was associated with modest increases in maternal weight gain (17 g [5–29 g]/week), and birthweight 25 g (CI: 4–55 g), and a substantial reduction of risk of SGA births (OR: 0.64; CI: 0.53–0.78). There were also significant reductions in stillbirths and neonatal deaths. These effects did not appear greater among undernourished women, however, and another review (Kramer, 2001c) suggested that isocaloric balanced protein supplementation had no benefit for the mothers or the offspring.

Based on animal studies, it may very well be that nutrition can help prevent, but not reverse, impaired fetal growth (Harding, 1999). Furthermore, the timing of nutrition incidents (or supplements) is critical, as observations in famine situations suggest. The growth status of mothers themselves also appears critical, in addition to their general nutritional status. While food supplementation had little effect in well-nourished women, it was shown to increase birth weights significantly when targeting malnourished women (Ceesay et al., 1997). However, partitioning of energy and nutrients between mother and fetus according to maternal status is as yet unclear. Studies in humans and animals suggest that the partitioning may be in favour of mothers when they are depleted, or else, when they are still growing. In India, for instance, Kusin, Kardjati & Renqvist (1994) observed that mothers who had low BMIs initially had the lowest birth weight babies, but also that they had replenished their own stores during pregnancy, as suggested by their post-pregnancy BMIs. This may explain the modest effect of supplementary programmes on birth weights. Furthermore, prenatal energy supplementation might have no impact on birth weight while improving postnatal growth, as shown in one study in Indonesia (Kusin et al., 1992). This strongly suggests that other other markers of fetal nutrition than birth weight may have their importance.

In the mature woman or animal, the normal hormonal response in pregnancy seems geared towards optimising the flow of nutrients to the fetus, but the reverse seems to occur in adolescent pregnancy and supplemental feeding may further exacerbate the problem of the mother thriving at the expense of the fetus, resulting in a decrease in placental weight and birth weight (Wallace, Aitken & Cheyne, 1996; Fraser, Brockert & Ward, 1995; James, 1997). In adolescent pregnancy, maternal growth may have biological consequences similar to starvation, with negative consequences for fetal growth (Rees, 1999). It is speculated that the mitigated impact of supplementation interventions, which is of concern, may be partly due to the high proportion of supplemented mothers who are young and still growing, but this needs to be documented.

Multiple micronutrient inadequacies may limit fetal growth in poorer groups, as suggested by positive effects of supplements during pregnancy. Scholl et al. (1997) reported that multivitamin/mineral supplements during the first two trimesters resulted in a marked reduction of preterm deliveries and of low or very low birth weights in low-income urban women in the USA. Controlling for potential confounding variables further strengthened the effects. Similarly, a randomized, double-blind, placebo-controlled zinc supplementation trial in pregnant African-American women with low plasma zinc at booking in prenatal care resulted in a significant increase in birth weight of a mean of 126 g, and in head circumference (mean = 0.4 cm) (Goldenberg et al., 1995). In women with a BMI <26, the increase was even more marked, reaching 248 g for birth weight and 0.7 cm for head circumference. However, it is not known whether zinc deficiency during fetal life has permanent effects other than perhaps stunted growth, which needs further study. As already mentioned, zinc is a potential candidate for prenatal programming of the immune system. Data from large and well-controlled trials is scant, and further research should be conducted on folate, zinc, and magnesium supplementation in populations exposed to impaired fetal growth, while simultaneously addressing other factors of fetal growth retardation.

6.5 Relationship of maternal nutrition with chronic disease independently from size at birth

Maternal nutrition programming effects are not totally mediated by fetal/placental growth as reflected in size and proportions at birth, as suggested by independent associations of maternal nutritional status with chronic disease risk markers in the progeny. The best example is the calcium supplementation trial in pregnant women, which resulted in lower blood pressure in the children without any effect on birth weight (Belizan et al., 1997) (see Section 4.3.). It can be postulated that nutrients classified as type I and type II, depending upon their effect on growth (Golden, 1988), may programme the fetus differently, through a growth effect in the case of type II (which includes protein, threonine, zinc), and independently in the case of nutrients

such as calcium, B-vitamins, etc. To a large extent intergenerational effects also appear independent from birth size (see Section 6.6.).

In a study of adults aged 45 in Beijing (Mi et al., 2000), birth weight was positively related to both maternal weight and height, and there was also an independent and inverse association of maternal BMI in early and late pregnancy with adult offspring's 2-h serum glucose, insulin, and triglycerides, but no association with blood pressure and LDL. Therefore, adults whose mothers were thin appeared more likely to develop metabolic syndrome, which was also noted by Shiell et al. (2000) in their Aberdeen study. Similarly, in men and women from southern India (Stein et al., 1996), the highest rates of CHD were observed in LBW adults whose mothers weighed less than 45 kg. Low maternal body mass, or weight early in pregnancy, were also found to be independently associated with elevated blood pressure at the age of 10 years in Jamaican children (Godfrey et al., 1994). This is somewhat similar to the protein deficiency model in animals, with direct correlation of maternal undernutrition with offspring's systolic blood pressure.

In contrast, higher rates of CHD were found in Finnish individuals (Forsén et al., 1997) who were thin (low PI) at birth, but whose mothers had a high body mass. Multivariate regression analyses showed that both PI and maternal BMI had a significant effect in the opposite direction. However, after stratification of men according to height of mothers, a significant positive effect of maternal BMI was only seen among men whose mothers were of below average height. According to the authors, poor maternal and fetal nutrition in Finland was common at the beginning of the century and was reflected in very high infant death rates. With improvements in nutrition, the immediate consequence is that mothers' weights increase, although they remain short in stature. This could lead to a steep increase in CHD. The authors speculate that increased maternal BMI leads to an increased fetal demand for nutrients, but this higher demand cannot be met because of the intergenerational constraint on placental growth owing to short stature. With continued improvement in nutrition in the population, mothers become taller and heavier, constraints on placental growth diminish, and maternal fatness no longer increases the risk of CHD, resulting in a decline in CHD. This view of past sequential events of the nutrition transition in Europe likely describes what is currently occurring in many developing countries. In the south of India, for instance, higher rates of type-2 diabetes were observed in men and women who were short and had a low PI at birth (Fall et al., 1998). It was found that mothers of subjects who developed diabetes were heavier than average, but their heights were not known.

6.6 Multigenerational effects of maternal nutrition

Independent associations of maternal nutritional status with chronic disease risk in the offspring were just reviewed. There is also evidence from experimental and observational data that maternal nutrition may affect more than one generation, which makes the distinction between genetic and environmental (intrauterine) influences increasingly difficult.

Animal studies have shown, for instance, that undernutrition can have cumulative effects on reproductive performance over several generations, with progressively greater fetal growth retardation. Upon refeeding, it may take many generations to normalize growth and development (Stewart et al., 1980). In humans, we know that a woman's own birth weight influences that of her offspring (Emanuel, 1992; Emanuel et al., 1992). Furthermore, LBW mothers tend to have thin, low PI babies, which may reflect impaired placentation in women who themselves had poor fetal growth and perhaps altered uterine vasculature development during their fetal life. Babies of LBW mothers were found to have lower placental weights (Godfrey et al., 1996c), which suggests that uterine or ovarian development may have been impaired during the mother's own fetal life, and as a consequence, may constrain fetal growth (Barker, Gluckman & Robinson, 1995). Low paternal birth weight has less relationship with fetal growth, although the crown-heel length of the baby was reported to be more strongly related to paternal birth weight than to the mother's (Godfrey et al., 1997).

Data on the Dutch Famine suggest that maternal nutrition may influence fetal growth of the second generation. Undernutrition in the first trimester of pregnancy had a negative impact on fetal growth of progeny from the second generation (Lumey, 1992), while it did not have an effect on birth weight of the first generation offspring. While there is a normal increase in offspring birth weight with increasing birth order, the opposite effect was seen in women who had been exposed to intrauterine undernutrition during the first trimester of their own fetal life (Lumey, 1998). A decreased efficiency of women's uterine circulation with successive pregnancies would provide an explanation, but the mechanisms are not known.

The intergenerational cycle of growth failure was reported for the first time in a developing country through the findings of the prospective intergenerational study in Guatemala Ramakrishnan et al.,

1999). Data were available for 215 mother-child pairs. The children have been followed over time, and now many girls have a family of their own. Birth size of these girls was a significant predictor of child's birth size, after controlling for maternal age, height, prepregnancy weight, sex of child, and socioeconomic status. Adjustment for maternal height, prepregnancy weight, and current SES did not alter the association to a great degree. There was a 26 g increment of child's birth weight for every 100 g increase in maternal birth weight, nearly twice the effect reported in developed countries. There was also an increase in birth length with increasing maternal length or weight at birth. It will be interesting to uncover the associations with chronic disease risk markers.

Barker et al. (2000) did a follow-up study in Lancashire of blood pressure at 18–40 years in individuals whose parents' size at birth was recorded. A negative and marked association was found between maternal weight and head circumference at birth, and both systolic and diastolic blood pressure of male and female offspring (-2.4 mmHg per pound increase, and -4 mmHg per inch of head circumference). These associations were little changed by adjusting for length of gestation, sex, age, BMI, or alcohol consumption, and they were independent of maternal blood pressure. Furthermore, this relationship between maternal birth weight and blood pressure was largely independent of the significant association between maternal and child birth weights. Poor nutrition during a mother's own childhood may also contribute to impaired fetal growth and associated chronic disease risk, as speculated by Martyn, Barker & Osmond (1996), by interfering with pelvic bone growth and subsequently, with maternal ability to sustain growth of the fetus in late pregnancy.

To summarize this section on the role of maternal nutrition, it may be said that short supplies of nutrients and oxygen to the fetus, combined or not with maternal constraint of fetal growth, are predominant causes of IUGR. Concurrent and past maternal nutrition is therefore important, and there may be consequences of unbalanced maternal diet independently from, and even in the absence of, effects on size or proportions at birth. Intergenerational influences of maternal malnutrition were depicted in studies among populations exposed to famines, and more recently, in longitudinal studies in Central America. Calcium supplementation trials in pregnant women provided the first experimental evidence of fetal programming of (reduced) blood pressure through maternal nutrition without any change in size at birth. Preventing impaired fetal growth as well as promoting nutritional health in women may therefore benefit present and future generations.

7. Fetal programming of increased susceptibility to postnatal influences?

Genes set the potential body size, metabolic competence, and functional capacity of individuals. To what extent this potential is achieved is determined by environment experiences, including the intrauterine environment, and it is expressed in the physical, hormonal, and metabolic phenotype (Jackson, 2000). Throughout the course of life, the interactions of genes and phenotype factors determine the response of the body to environmental challenges, for instance stress, diet and other lifestyle patterns, or else obesity. Depending on the outcome of interest, prenatal or postnatal influences may predominate. The influences may be additive, and there may be interactions between them. Postnatal factors may modulate, or be modulated by, the association of small size at birth with chronic disease (they may also confound the association, as discussed in Section 8). Three types of modifications are plausible:

1. Small size at birth may increase vulnerability or risk through catch-up growth during childhood, and there may a timing issue.
2. Small size at birth may increase the propensity to obesity in childhood and later life, which goes beyond catch-up growth in height or weight (although discussed jointly below); in this case, size at birth and current body mass are negatively correlated.
3. Small size at birth may enhance the risk associated with current obesity in childhood or in later life, in which case an interaction is observed, so that the association differs significantlty according to size at birth.

7.1 Catch-up growth associated with higher risk of chronic disease

Is a higher risk of chronic disease associated with catch-up growth in childhood? An increasing number of studies suggest that this is so in people born SGA, which indicates impaired fetal growth; but it is not known whether the association is with the increased fat mass, the catch-up growth process itself, or the intrauterine resetting of endocrine axes that control growth. Catch-up growth is hypothesized as being a key mechanism underlying fetal programming of chronic disease (Cianfarani, Germani & Branca, 1999). It has been associated with increased hypertension (Levine, Hennekens & Jesse, 1994; Leon et al., 1996), CHD (Osmond et al., 1993; Eriksson et al., 1999; Forsén et al., 1999), and insulin resistance (Crowther et al., 1998). According to Leon et al. (1996) the important risk factor is being small at birth in relation to one's growth potential. Failure to achieve this potential in utero could be indicated by being relatively small at birth, but tall as adult.

Catch-up growth may be defined as accelerated gain in height, or weight, or both in postnatal life in order to compensate for intrauterine growth impairment. Ong et al. (2000) describe it as a property of human growth whereby children return to their genetic trajectory after a period of growth arrest or delay. While it may occur at any time during growth, it normally occurs primarily during the first 2 years of life, and it is particularly marked following severe IUGR. Catch-up growth occurs in 80–90% of IUGR children (Karlberg & Albertsson-Wikland, 1995). Catch-up growth in height takes place early, with more than two-thirds of the final height increase (expressed in standard deviation scores relative to reference population) being achieved by the age of 2 months (Karlberg & Albertsson-Wikland, 1995). Catch-up growth in early infancy may not be associated with increased chronic disease risk, in contrast with later accelerated growth. Infant growth failure was found to be associated with CHD risk in the early studies of Barker and his colleagues (Barker et al., 1989b). More recently, it was found in the Finnish birth cohorts that low weight, height, and BMI at the age of 12 months, irrespective of birth weight, increased coronary risk, which suggests that poor early growth is an independent risk factor (Eriksson et al., 2001). Furthermore, the same study showed that rapid growth in weight and BMI after the age of one year increased the risk only in subjects born thin.

Catch-up in weight and height does not necessarily

imply full recovery at organ level, as animal models show. For instance, Garofano, Czernichow & Breant (1998) observed that rat neonates with moderate IUGR which were appropriately nourished postnatally had normal organ weights and insulin contents in adulthood. Offspring with severe IUGR but well fed postnatally also recovered normal body and pancreatic weights, but liver and kidney weights were reduced at adult age. In contrast, severe IUGR at birth resulted in decreased insulin content at adult age, irrespective of postnatal nutrition, and of organ weight catch-up. Thus, normalization of adult size does not necessarily mean that all organ weights are normalized, and altered insulin stores in adulthood are more dependent on the severity of IUGR at birth than on postnatal catch-up in organ growth. Furthermore, catch-up growth may be associated with shortened lifespan (Hales et al., 1996)

In a study on postnatal growth of LBW babies of diverse ethnic groups, Seed, Ogundipe & Wolfe (2000) observed that by the age of 2–3 years, there was substantial catch-up growth only in infants born at 32 weeks or more of gestation. Black infants tended to put on more weight than White infants, particularly when born preterm. In a cohort study on postnatal catch-up growth in relation to obesity at 5 years of age, Ong et al. (2000) identified predictors of catch-up growth in subjects born lighter and thinner: primiparous pregnancies, lower maternal birth weights, taller fathers, and smoking during pregnancy (trend only). They reported that children who had caught-up in height or in weight had, at 5 years of age, a higher waist circumference. The results were not affected by adjusting for type of postnatal feeding (breastmilk or formula). It is postulated that increased food intake mediated though hormonal effects is responsible for postnatal catch-up, at least partly, but this requires further evidence. For example, postnatal weight gain was found to be inversely related to the level of cord blood leptin (Ong, Ahmed & Dunger, 1999), a hormone involved in satiety regulation. This study therefore suggests that children who were growth retarded at birth are at increased risk of becoming obese. Likewise, a higher percentage of body fat was found to be associated with LBW independently from body mass (Barker et al., 1997; Jaquet et al., 2000). Growth acceleration and cell hyperplasia is also observed when there is an early adiposity rebound in children (Rolland-Cachera et al., 1984), and this early adiposity rebound has been associated with increased risk of adult obesity (Whitaker et al., 1998). There is frequently "over catch-up", and IUGR children are considered at particularly high risk of metabolic syndrome in later life because they tend to overcompensate for their prenatal growth deficit and gain more weight, particularly during prepuberty and puberty (Nicolino et al., 1999). Léger & Czernichow (1999) observed that in IUGR subjects BMI increased significantly more during the puberty growth spurt.

There is further evidence of a relationship between postnatal catch-up and metabolic disease risk in childhood, beyond increased likelihood of high body mass, but statistical evidence is still scant. The insulin response in IUGR children with catch-up growth is higher than in those without catch-up growth (Colle et al., 1976). Therefore, the secondary insulin resistance, when associated with risk factors such as obesity or genetic predisposition, may lead to diabetes, which would then represent a long-term consequence of catch-up growth in children born with impaired fetal growth.

A strong correlation between size at birth and final height has been reported (Karlberg & Albertsson-Wikland, 1995), although the extent of postnatal catch-up growth, and of growth faltering during the early years, may vary depending on various factors including the environment, and therefore, the strength of the correlation may vary between countries and population groups.

The study among men of the 1924–33 birth cohort in Helsinki (Forsén et al., 1997) revealed that the highest death rates from CHD were observed in those who had low PI at birth and who had caught up weight by age 7 (Eriksson et al., 1999). This suggested that poor fetal nutrition, followed by improved postnatal nutrition, may further increase the risks of heart disease. Since serial measurements were taken initially at age 7, it was possible to assess growth in childhood and examine the relationship with CHD while correcting for birth weight. The highest risk ratio (5.3) for CHD death was for men who had the lowest PI at birth, combined with the highest BMI from the age of 7 to 11 years. This compares with a risk ratio of only 1.2 in for those who only had a high BMI in childhood, without being small size at birth. This worsening of the risk associated with small birth size may be that accelerated postnatal weight gain is intrinsically damaging, or else, that due to fetal programming, body composition of weight gain is altered in later life. Another possibility is that catch-up growth is linked with CHD through programmed changes in the IGF-1-insulin axis. Catch-up growth (in weight) was attributed to improved nutrition in childhood and not to living conditions, based on maternal BMIs. In the corresponding cohort of women, Forsén et al. (1999) reported that shortness at birth, more than LBW, was a risk factor for CHD, and that there was a strong interaction with tallness at age

7, particularly among daughters of tall mothers. Hence, catch-up growth during childhood appears as a risk factor, but whether catch-up in weight or height is involved may vary according to sex, and perhaps other factors as well. In these cohorts, subjects who later developed hypertension exhibited accelerated growth compared to non-hypertensive individuals at the age of 7 years but not from age 7 to 15, in addition to the higher risk associated with being smaller, shorter, and thinner at birth (Eriksson et al., 2000). In contrast, those who developed type-2 diabetes had normal heights and weights at age 7, but their weights, heights, and BMIs increased faster between 7 and 15 years than in subjects without diabetes; the risk also increased with decreasing birth weight, birth length, PI, and placental weight. In these cohorts, high BMI in childhood was associated with increased risk of type-2 diabetes in girls, and of CHD in boys.

In keeping with the Scandinavian studies, observations in children from southern India supported the idea that catch-up growth, alone or in combination with fetal growth restriction that preceded it, contributed to increased insulin resistance (Bavdekar et al., 1999). Among 8-year-old healthy children, the highest levels of insulin resistance markers were observed in those who were born small but who had the highest current weight and height, as well as short parents. Similarly, in South African Black children aged 7, those with LBW whose weight was in the upper two quartiles at age 7 exhibited more insulin resistance than those who remained in the same low range for weight at birth and at 7 years of age (Crowther et al., 1998). In Finland, a retrospective study in over 400 men and women showed no relationship of birth weight with metabolic syndrome as adults, but children who at age 7 were in the upper quartile of BMI had a fourfold risk of metabolic syndrome in adulthood compared to the other three quartiles (Vanhala et al., 1999). Even after adjusting for age, sex, and current obesity, the risk of metabolic syndrome was still twice as high in children with high BMI at age 7. Body proportions at birth, however, are not available to determine the extent of "centile crossing" (see Section 7.2.) of height and weight since birth. This, however, does not exclude *per se* that obesity in childhood could have been programmed *in utero*, but for the authors, it suggests that increased weight gain during infancy and childhood, owing to lack of physical activity combined with excess dietary energy, poses a new threat, in developing countries and in developed ones (Vanhala, 1999).

In spite of controversial findings, there is some evidence showing that small size at birth is a risk factor for obesity later on in life; but according to Martorell, Stein & Schroeder (2001), it is still inconclusive. In both cohorts of American nurses, for instance, Curhan et al. (1996a,b) found that subjects whose birth weight was (4.5 kg were at increased risk of being in the upper quintile of BMI as adults. Similarly, Barker et al. (1997) reported a positive association of birth weight with current BMI in Southampton White adolescent girls. However, in this last study, an interesting observation is the association of birth weight with body fat distribution. After adjusting for current BMI, birth weight was found to be inversely related to subscapular skinfold thickness, and to subscapular to triceps skinfold ratio. The association was independent of gestational age and socioeconomic status, and it was particularly strong in girls whose BMI was (25, with a 27% increase in the skinfold ratio for every kilogram decrease in birth weight. This suggests that small size at birth tends to be associated with a central pattern of body fat distribution, which is a known independent risk factor for diabetes and CVD. Small size at birth may also be associated with a higher percentage of body fat, as observed by Hediger et al. (1998; 1999) in SGA children, and by Jaquet et al. (2000) in 25-year-old men and women born with IUGR, compared to subjects of normal birth weight. At any obesity level, Law et al. (1991) observed more abdominal fat (based on waist-hip ratio) in those who weighed less at birth.

According to Eriksson et al. (1999), catch-up growth may enhance chronic disease risk in different ways: 1) altered body composition, with more fat than muscle deposition; 2) overgrowth of limited cell mass resulting from impaired fetal growth; 3) hormonal changes, including insulin resistance.

Adequate early nutritional management would appear important for optimal catch-up growth, but it is not known whether early reprogramming is possible, although some adverse effects appear irreversible according to animal studies. This needs further investigation.

7.2 Interaction of small size at birth and current obesity

In order to elucidate the independent association of birth size with cardiovascular risk factors later on in life, it has become standard practice to adjust for potential confounding factors, in particular, current body size. However, this raises the issue of whether a given parameter such as current body size is really a confounder or whether it is a mediator of the effect. Adjustment for current body size may not be appropriate. As conceptualized by Waterland & Garza (1999), correcting for current body weight or BMI in order to

determine the magnitude of the birth weight effect on chronic disease risk would require that the variance of BMI be partitioned into two components, one related to birth weight, and an unrelated one. Since this partition cannot be estimated, it is suggested to report associations adjusted and non-adjusted for current BMI. The complex relationship of birth weight with BMI indeed complicates the studies reporting associations between birth weight and adult outcomes associated with BMI. In quite a few studies reporting both uncorrected and corrected associations, the findings and conclusions were not affected by the adjustment, which suggests that there is no spurious link between birth weight and CVD because of the birth weight-BMI relationship. What can also be suggested is to test the interactions of birth weight with BMI in the multivariate models with CVD or other outcomes as dependent variables. More detailed measures of size and proportions at birth such as PI and length are unrelated to BMI in adult life (Forsén et al., 1997; 1999), and therefore, as pointed out by Leon et al. (1996), adjustment for current BMI is less of an issue.

Lucas, Fewtrell & Cole (1999) contributed an interesting discussion on this issue of adjusting for current size and the statistical implications. Adjusting for current body weight or size has usually been justified on the grounds that birth weight (or size) is positively related to later size, and that current weight (or fatness) is also correlated with the outcome of interest, be it blood pressure or insulin resistance. Omitting to adjust for current size would therefore obscure the relationship of birth weight with the outcome variable. However, several alternatives have to be considered. If adjustment attenuates or suppresses the effect of early size, then it may be that later size is more relevant than size at birth in the causal pathway. In contrast, if the outcome is amplified with adjustment, Lucas, Fewtrell & Cole (1999) consider that the determinant factor may be the magnitude of size change with age, that is, the magnitude of centile crossing during postnatal growth. Questions that can only partly be answered are then:

1. Does small size at birth increase the propensity to centile crossing?
2. Is the outcome of centile crossing in individuals born small more serious than an equivalent centile crossing in people who were of normal size at birth?

One difficulty is that small babies tend to show greater centile crossing than larger babies by virtue of regression to the mean which would be reflected in catch-up growth—in other words, there is an inherent correlation between lower birth weight and centile crossing. Lucas, Fewtell & Cole (1999) therefore recommend to adjust both for birth weight and later size. This means that results of four separate regression models should be provided for appropriate interpretation of the findings:

1. the early model (birth weight alone)
2. the late model (current or later size alone)
3. the combined model, obtained by adding current or later size to the early model
4. the interaction model, which adds the interaction of early and later size to the combined model.

Several studies report that the effect of small birth size on chronic disease markers is amplified with age (Law et al., 1993), and that it is further enhanced by high current body mass. For instance, among adults born small, the obese had the highest risk profile for metabolic syndrome (Fall et al., 1995a), showed a higher prevalence of impaired glucose tolerance (Hales et al., 1991; Lithell et al., 1996), were the only ones to show increased coronary risk (Frankel et al., 1996a,b), and had lower insulin sensitivity (Flanagan et al., 2000). In a child cohort in India, risk markers for insulin resistance syndrome at age 8 were only related to lower birth weight in the heavier children (Bavdekar et al., 1999). Regarding the relationship between birth weight and blood pressure, it was shown to almost double in strength between the ages of 5–7 and 9–11 years (Whincup, Cook & Adshead, 1996). The relative contribution of birth weight and childhood PI to levels of blood pressure and insulin at 10–11 years of age was reviewed (Taylor et al., 1997; Whincup et al., 1997). It was found that for each unit increase in PI, the increase in blood pressure was three times higher than that observed with an equivalent decrease in birth weight (1 SD or inter-quartile range). This suggests that the effects in children are dominated by the influence of childhood obesity. However, Whincup et al. (1997) also note that the relationship between birth weight and blood pressure is particularly strong in the most obese children, which typifies the interaction between small size at birth and obesity later on with respect to blood pressure. This is supported by the observation of a stronger correlation of blood pressure and plasma cortisol among obese people, in different population groups (Phillips et al., 2000). In a longitudinal study in Australia, it was found that the inverse association of birth weight and blood pressure was stronger at age 20 than at age 8 (Moore et al., 1999). Furthermore, there was an interaction with current size, with enhanced effects among heavier individuals. In a cross-sectional study of nearly 600 Australian adolescents aged 18 (Milligan et al., 1997), it was found that systolic blood

pressure was negatively related to birth weight, as well as to present physical fitness, while being positively related to current weight for height and male sex. In Argentina, Bergel et al. (2000) found that LBW was a risk factor for high blood pressure only in overweight children in the 5–9 years age range. In the Scandinavian longitudinal study of men born in the '20s, it was found that the inverse relationship of size at birth with mortality was strengthened when adjusting for current BMI, which again suggests an interaction of small size at birth with large size in adulthood, and that it was not mediated through an increase in blood pressure in those born small (Koupilova et al., 1997).

In a cohort study in New Zealand, Williams & Poulton, (1999) reported that the total effect of birth weight on blood pressure was small once the indirect effect through concurrent measures of height and BMI was taken into account, using the path analysis. The regression coefficient for the direct (inverse) effect of birth weight, for example, on systolic blood pressure at 9 years, was significant (-1.93; CI: -2.89 -0.96). The complex statistical analysis using the path analysis quantifies, and therefore illuminates, sequences of variables which, for the purposes of the model, the analyst must already assume do in fact hold. Actually, birth weight was more strongly and positively related to concurrent height and BMI, which have a direct positive effect, than it was negatively associated with blood pressure, so that the total negative effect was small. Nonetheless, the negative correlation, although modest, is still compatible with the fetal programming hypothesis (Susser & Levin, 1999).

It has been postulated that the increased risk associated with obesity among people having suffered impaired fetal growth resulted either from the metabolic resetting or from structural changes *in utero*. Based on data from India, James (1997) proposed that mothers on a low-protein diet before and during pregnancy not only establish a low growth trajectory for the fetus, but also that the effects on corticosteroid metabolism may programme the propensity to abdominal obesity and diabetes if excess weight occurs in adulthood. Alternatively, it was suggested that there is a more limited capacity to withstand the stress of obesity owing to decreased β-cell mass as a result of intrauterine malnutrition (Barker et al., 1993c; Phillips et al., 1994; Jackson, 2000).

One practical implication of these observations is that obesity prevention or reduction is even more critical for those children who were thin (or small) at birth. Since impaired fetal growth is more widespread in developing countries, these data suggest that obesity in childhood would carry proportionally more cardiovascular risk in adulthood than in population groups with low rates of impaired fetal growth.

8. Controversial areas and related hypotheses

Associations of chronic disease markers with size at birth as an indicator of fetal growth are now established. Considering the delay between exposure and outcome, such associations are undeniably robust, but their existence does not imply that they are causally related (Kramer, 2000). Fetal programming has been proposed to explain this relationship, and there is accumulating evidence from animal models, some twin studies, and a few experimental trials in humans to support this theory. Compelling evidence comes not only from many studies being consistent with each other (Paneth & Susser, 1995), but also from a growing body of experimental data. Epidemiological studies cannot provide definitive evidence, be it only because of the time lag between exposure and effects, of the many other influences during the course of life, and the sometimes unreliable measurement of exposure. Longitudinal studies extending over many decades of life, while necessary to support the theory of fetal programming, are remarkably difficult and therefore, there are not many. Until now, the large majority of studies on fetal programming originate from Europe and refer to people born between the early '20s and World War II. Cohorts born after that time in western countries may not demonstrate an association between early life events and adult chronic disease because of better overall postwar socioeconomic and nutritional conditions. Cohorts from developing countries with high rates of undernutrition and LBW may be more appropriate to further test the independent contribution of impaired fetal growth to chronic disease.

However, there are still areas of uncertainty and controversy. In particular, many researchers object that small birth size and chronic disease are not causally related, but that both reflect a common denominator. Other hypotheses are proposed as alternatives to the "early origins" theory, or else, as complementary theories.

8.1 A common causal factor for impaired fetal growth and chronic disease in adulthood?

The pervasive influence of poverty throughout the life cycle is seen as a major confounding factor for the association of small birth size and chronic diseases later on in life. Other socioeconomic factors may be in the common causal pathway. Folate deficiency has also been proposed as a common risk factor for both LBW and CVD.

8.1.1 Low socioeconomic status as a confounding factor of impaired fetal growth and chronic disease

The question is, to what extent is small size or disproportions at birth (or high placental ratio) a mediator of the association of poverty with chronic disease, rather than poverty acting as a confounding factor of the relation between size at birth and risk of chronic disease. The same adverse environment may be responsible both for LBW and high infant mortality, as well as for high rates of CVD and diabetes, as several studies suggest. It is therefore not surprising that many authors, including Kramer & Joseph (1996), contend that the reported association of small size at birth and higher risk of chronic disease is confounded with low socioeconomic status. Adjusting for socioeconomic status may be inadequate, with much residual confounding, owing to the fact that this variable is notoriously difficult to control for (Signorello & Trichopoulos, 1998). "If one cannot accurately measure a confounding factor then one cannot adequately control for it" (Cox, 2000). Twin studies partly eliminate socioeconomic confounding, and more such studies are needed.

Vagero et al. (1999), comparing social determinants of size at birth and gestational age in Sweden in 1920s and 1980s, found that social circumstances of the mother are always linked to biological processes during the fetal period, but in different ways. For instance, household social class had a weaker effect on PI and preterm birth in the 1980s than the 1920s, while its importance for birth weight remained. This supports

the view that socioeconomic status can hardly be fully accounted for, and that residual confounding is likely.

Davey-Smith et al. (1998) observed that education and occupational social class are not equivalent as indicators of socioeconomic status and of mortality risk. Education is more strongly (inversely) associated with cardiovascular causes of death than occupational social class, which is more closely associated with non-cardiovascular, non-cancer deaths. Similarly, in their rigorous analysis of growth data during the first year in a cohort study in Aberdeen, Baxter-Jones et al. (1999) found that residual confounding may be important if social class is controlled only on the basis of parental occupation. Based on their results, they suggested that other adverse environmental conditions, such as overcrowded housing and maternal parity, should be considered when investigating the association of chronic disease in later life and early experiences.

Socioeconomic status markers are strongly associated with risk of adult chronic diseases and mortality, particularly markers of social status in early life (Davey-Smith, 1997; Davey-Smith et al., 1997; Koskinen, 1994). When examining the father's social class (on the basis of type of occupation) as a marker of social conditions in early life, and its relationship with CVD in middle-aged men, Wannamethee et al. (1996) found that the father's social class was significantly related to the individual's social class, height, and obesity, but not to blood glucose or cholesterol. Men whose fathers were manual workers were shorter, more obese, had higher systolic blood pressure, and lower HDL-cholesterol. They also tended to have less healthy lifestyles (more cigarette smoking, heavy drinking, and less physical activity), but this was more closely associated with their own social class (manual work). Nonmanual workers whose fathers were manual workers had higher rates of nonfatal myocardial infarction and ischaemic heart disease, and this persisted after adjustment for lifestyle factors, height, blood pressure and cholesterol. In this study, men who moved upwards in social class did not have a significantly different risk than those who remained in the manual-working class. This suggests that socioeconomic status early in life has some persistent influence on the pattern of chronic disease and risk factors in later life. Smoking was found to be associated with low socioeconomic status and poorer school achievement; it may therefore be a proxy for poorer home environment and poorer nutrition (Logan & Spencer, 1996). Kramer (2000) also holds that low socioeconomic status may predispose both to suboptimum fetal growth and to later lifestyles that increase chronic disease risk, for instance, dietary and physical activity patterns, and tobacco smoking.

Socioeconomic status has consistently been positively associated with height, and inversely related to CHD. Achieved height is also an indicator of early nutritional status. Wannamethee et al. (1998) observed this trend in middle-age men from the UK, even after adjusting for lifestyle and other risk factors. Similarly, social stratification is reflected in rates of fetal growth and hence, on size at birth. According to Paneth (1994), birth weight is not only a marker of what happened before birth, but also of events occurring after birth, because the social and environmental conditions that produce LBW are likely to be still operating in the infant and child. Socioeconomic status is strongly related to birth weight (fetal growth), as found by Kramer (1987) in a meta-analysis. A higher ratio of placental weight to birth weight, which may be a useful marker of suboptimum fetal nutrition and uteroplacental function, was also found to be related to lower socioeconomic status (Davey-Smith et al., 1997). According to the authors, this ratio is possibly a surrogate for factors in the maternal environment related to social status, and to which the growing child may be exposed.

The observation of a substantial association between birth weights and mothers' mortality from all causes and from CVD (Davey-Smith et al., 1997; Davey-Smith, Harding & Rosato, 2000) also suggests a common cause, such as poor social circumstances, or maternal health, nutrition, and health related behaviours. Or else, intergenerational genomic and epigenetic processes underlying the link between mothers' and children's birth weights could influence cardiovascular risk. Smith, Pell & Walsh (2001) reported, in a large retrospective cohort of more than 100, 000 births in Scotland, that maternal risk of ischaemic heart disease was associated with delivering a baby in the lowest quintile of birth for gestational age. Compared with mothers giving birth to a baby weighing more than 3,500 g, those delivering LBW babies were at 11 times greater risk, which is much higher than the risk increment reportedly associated with LBW in the offspring, suggesting a genetic link. However, as noted earlier, it may be difficult to distinguish genetic and non-genetic influences. In southern India, the inverse association of birth weight with CHD rates was no longer significant when controlling for several variables linked with socioeconomic status (Stein et al., 1996). In other studies, however, the birth size effect was little modulated by social status (Leon et al., 1996; Lynch et al., 1994; Barker et al., 1993c; Koupilova, Leon & Vagero, 1997; Frankel et al., 1996a,b). In the cohort study of Caerphilly (Frankel et al., 1996a,b), which involved a follow-up period of 10 years of men aged 45–59 years at age of recruitment, it was possible to document socioeconomic and

behavioural risk factors that operate in adult life, in addition to evidence on birth weight and later fatal and nonfatal coronary events. It was found that adult height, BMI, triceps skinfolds, and percent body fat were all positively associated with birth weight, and that correcting for these factors further strengthened the reverse association of birth weight with incidence of CHD. Of the socioeconomic variables studied, the only significant dietary parameter was vitamin C intake which showed a positive association with birth weight. Smoking, drinking, exercise, type of bread eaten (indicator of fibre intake), own and parental occupation, and birth order were not significant.

In Leningrad, the cross-sectional study of people exposed or nonexposed to the siege of 1941–4 while *in utero* showed that glucose intolerant subjects were overall shorter, after adjustment for exposure to siege, age, and sex (Stanner et al., 1997). However, this difference did not persist after further adjustment for adult social class and education, which suggests that socioeconomic status was a major confounder. As noted by Rich-Edwards & Gillman in their commentary (1997), the absence of effect in this study, after considering all possible sources of bias, may support the view that intrauterine programming is totally confounded by social class, considering that the poor and the rich starved for a long period of time during the Leningrad Siege.

Another potentially important source of confounding is that the factor underlying fetal growth impairment is also the underlying factor of the chronic disease risk marker in later life (Kramer, 2000). As pointed by Leon (2001), reverse causality explanations need to be considered. Folate deficiency, maternal hypertension, and insulin resistance provide such examples.

8.1.2 *Folate deficiency as a common cause of small birth size and high homocysteine concentrations—a known risk factor for coronary heart disease?*

There is a genetically inherited abnormality in an enzyme involved in folate metabolism, 5,10-methylenetetrahydrofolate reductase, which makes about 6% of women susceptible to neural tube defects in their progeny, as the body needs more folate in such circumstances to prevent hyperhomocysteinemia and ensure adequate nucleotide synthesis for cell replication. Results of epidemiological studies suggest that moderately high levels of blood homocysteine may be quite prevalent and are associated with higher risk of CHD and stroke, independent of classic cardiovascular risk factors (Boushey et al., 1995; Eikelboom et al., 1999). However, a causal relationship between high homocysteine concentrations and CHD risk remains to be demonstrated. A deficiency of folate (and also vitamin B6 or vitamin B12) can cause an increase in blood homocysteinemia. Vollset et al. (2000) recently reported that elevated serum homocysteine concentrations in women were strongly associated with previous pregnancy complications, and poor outcomes including low and very low birth weights. James (1997) hypothesized that folate deficiency, particularly when associated with the genetic defect, may explain the relationship between LBW and CVD, and the risk would be further enhanced if folate intakes were limited in individuals themselves. This would be a genetic, rather than programming basis for the link between birth weight and adult CVD. A causal relationship, however, is not fully established and trials on the effectiveness of folate, vitamin B6 and vitamin B12 in preventing hyperhomocysteinaemia are in progress.

8.1.3 *The thrifty genotype and genetic polymorphism as a cause of impaired fetal growth and type-2 diabetes?*

The same genetic factors that cause impaired insulin secretion or insulin resistance may alter both intrauterine growth and glucose tolerance in adulthood. This is the basis of the "fetal insulin hypothesis" of Hattersley & Tooke (1999) who observed LBW and neonatal hyperglycemia in human mutations of glucokinase, much like in mice with a similar mutation (see Section 4.1.). It was found that neonates with a glucokinase mutation had lower birth weights than those without, and that reduced birth weights were associated with reduced insulin levels. The same group also observed, in support of their hypothesis of impaired insulin action during embryogenesis as a cause of LBW and hyperglycemia, that mice suppressed for insulin receptor substrate-1 had LBW. However, in humans these mutations are too rare to explain the association of LBW and insulin resistance and diabetes in adult life. Other more common alleles altering insulin secretion/sensitivity need to be identified for genetic factors to explain the wide variance in birth weight (see Section 8.3.). In Belgium, for instance, Haelterman et al. (1997) observed that chronic uncomplicated hypertension in women was associated with an increased risk for SGA birth. Small size at birth would then be a confounder for maternal hypertension as a factor of higher blood pressure in the offspring. However, some studies showed that the negative association of birth size and blood pressure, mainly systolic, was independent from maternal blood pressure (see Section 3.3.).

There are other examples of intricate genetic and

early environmental influences on CVD risk factors, for instance, atherosclerosis. There are often fatty streaks in the aortas of children aged only 3–4 years. The formation of these fatty streaks, as well as LDL oxidation, can even occur during fetal development, and it has been observed by Napoli et al. (1997) that both phenomena are enhanced by maternal hypercholesterolemia. It was observed by the same authors (Napoli et al., 1999) that birth weight correlated independently and negatively with cumulative lesion size. However, children of normocholesterolemic mothers had noticeably fewer lesions, and the rate of lesion progression in the arch and abdominal aorta was strikingly greater in children of hypercholesterolemic mothers. There is likely a genetic component, but the mechanisms by which maternal hypercholesterolemia modulates the expression of specific genes in the fetus remain to be established.

Terauchi et al. (2000) consider that there is a complex mix of genetic and environmental effects on birth size, and on CVD risk. Lifestyle adds to the intrauterine effects, as Barker (1999b) recognizes. Regarding diabetes, for instance, whether based on the thrifty genotype or phenotype (Hales & Barker, 1992) theory, it appears to be highly prevalent (>10%) among adults in several developing countries, or among minority populations who were plausible candidates for natural selection for the thrifty gene, and/or who have quite high rates of impaired fetal growth, and who have undergone rapid socioeconomic and lifestyle changes (King & Roglic, 1999; King & Rewers, 1993).

8.2 Other criticisms of the fetal programming theory of chronic diseases

Until recently, Barker's hypothesis may have been weakened by the fact that most studies pertained to Europeans born in the '20s and '30s. The reasons for fetal growth restriction, or its consequences, in the western world early in this century may not be the same as those that apply today in industrialized or in developing countries. However, there are more recent supportive data on younger people, and from developing countries as well, notably India and China. The long-term effects of impaired fetal growth also may not be the same in different settings, depending on the causes (Henriksen, 1999). In other words, it is not known whether IUGR due to maternal malnutrition or due to placental insufficiency have the same consequences, although both cases would be referred to as fetal malnutrition. The timing, the nutrients involved, and whether or not oxygen supply has been impaired (this mainly in placental insufficiency) are likely to vary in different ecological settings. The practical implications could also be very different where maternal malnutrition is an important factor of LBW.

Longitudinal designs are undoubtedly the most appropriate for the study of accumulation of risk, or early influences (Kuh & Ben-Shlomo, 1997), but such studies are expensive and do not yield immediate results. Historical cohorts, where new data are collected on a population for whom data was collected earlier (like birth weights) for another purpose, often lack detail on early life factors, and additional information on the intervening years has to be based on recall, with its associated unreliability and uncertainty. For both longitudinal and historical cohort studies, losses to follow-up are inevitable and raise the possibility of selection bias due to migration and nonparticipation (Joseph & Kramer, 1996). This is a factor of error if migrants and nonparticipants are different from remaining cohort members for the characteristics being studied. There are indications that this may the case. In the UK between 1965–85, for instance, likelihood of migration was positively related to social class and inversely related to maternal systolic blood pressure (Jones & Swerdlow, 1996). However, in a study by Pharoah, Stevenson & West (1998) in a county of England, all LBW children from a geographically defined area were included in the follow-up with a resulting rate of 95%, and still, the inverse relationship between birth weight and systolic blood pressure of adolescents was significant, and controlling for potential confounders further strengthened the relationship. What was seen as a possible bias in this study is the high rate of neonatal mortality among the very LBW babies.

Barker's hypothesis has been criticized for being molded according to the data set (Kramer & Joseph, 1996). Significant inverse associations with chronic disease in later life were first reported for birth weight. In subsequent studies, thinness, shortness, and other measures of body proportions at birth rather than birth weight were linked with chronic disease, and in other cases, a high placental ratio was the indicator of future risk. Birth weights were not consistently a significant variable. However, it is argued that these variations represent refinements of the hypothesis as data become available, rather than changes. The consistency is in the inverse association of one or many markers of impaired fetal growth with future CVD risk, and the nature and extent of the risk depend upon the nature and timing of the intrauterine incident as reflected in body size or proportions. Nevertheless, a better definition and measure of early experience or "exposure" (Terry & Susser, 2001) is warranted in future work. Anthropo-

metric parameters at birth are crude indicators of fetal growth and furthermore, size and proportions at birth may only be an epiphenomenon, since fetal programming does not necessarily entail substantial variations in fetal growth.

Present ecological trends in CHD are difficult for Kramer & Joseph (1996) to reconcile with Barker's hypothesis, notably the rise in CHD in most industrialized countries, and the high rates in some countries (Scotland, Norway, Finland) whose birth weights have been among the highest in the world for some time, and the striking recent increases in Eastern Europe. However, a counter-argument is that the declining rates of CHD as currently observed in highly industrialized countries, and the sharp increases in CVD and diabetes in developing countries undergoing a rapid demographic and "nutrition transition", are highly congruent with the early origins hypothesis. The observed recent decline in diabetes rate in Nauru, a Pacific Island where obesity and diabetes soared with rapid economic growth, also supports the hypothesis. The decline was too fast to be consistent with the genetic hypothesis (Ozanne & Hales, 1998). Dowse et al. (1991), remarked that the decline is associated with improved prenatal nutrition of today's adults, not with a decrease of obesity.

8.3 Alternative or complementary theories

The early origins hypothesis (thrifty phenotype) appears as a symmetrical alternative to Neel's hypothesis of a thrifty genotype, which is based on observations of very high rates of type-2 diabetes and obesity among aborigenal populations having undergone drastic changes in their diet and lifestyle, notably the Pimas and the Nauruans. This genotype would have been advantageous for survival in times of irregular food supply, but would become detrimental in times of food plenty (King & Roglic, 1999). In spite of the intuitive validity of the broad concepts, which may explain the continued popularity of the thrifty gene hypothesis, little solid evidence is available, and the mechanisms suggested by Neel (1962; 1982) have not been substantiated by experimental data (Swinburn, 1996). Insulin resistance and/or insulin hypersecretion would be the expression of the underlying thrifty genotype which would then promote obesity and diabetes. Rather than non-Europeans having been exposed to pressures promoting natural selection of the thrifty genotype as a predisposition to obesity and diabetes, the European population may be the unusual one in having low rates of diabetes (Swinburn, 1996), owing to a "non-thrifty genotype" (Allen & Cheer, 1996). This somewhat parallels the observations on lactase deficiency, which would appear to be the norm, and lactase activity remaining in adulthood as the exception only to be found in Europeans and herd tribes (Allen & Cheer, 1996). The main difference between Neel's and Barker's hypotheses is that the former ascribes predisposition to obesity and diabetes to genetic factors, whereas the latter ascribes it to fetal programming. Insulin resistance may be the common denominator. McCance et al. (1994) propose that there is a high mortality among LBW babies, and the survivors may be more insulin resistant, as this confers a survival advantage in conditions of fetal malnutrition. The end result might be the same, and whether the people are born with the thrifty genotype or phenotype, they are likely to be vulnerable to overnutrition and physical inactivity as amplifiers of initial risk (Swinburn, 1996). Neel's hypothesis remains relevant, and it may explain ethnic differences in obesity and diabetes prevalence under similar conditions of diet and physical activity. No specific genes have been identified and the putative hereditary component is now believed to be polygenic.[7]

Hattersley & Tooke (1999) offer a complementary explanation of the association of LBW with diabetes and CVD, with their "fetal insulin hypothesis". Insulin resistance would be genetically determined, and would be responsible for impairment of insulin-mediated fetal growth and insulin resistance in adult life. They proposed that as a result of insulin resistance, abnormal vascular development during fetal life and early childhood, and adverse body fat distribution, could increase risk of hypertension and vascular disease. It is plausible that both fetal programming as proposed by Barker and this "fetal insulin hypothesis" have a role in explaining the links between fetal growth and adult disease. In order to test the "fetal insulin hypothesis", insulin resistance of the father should be inversely related with birth weight and more specific measures of insulin-mediated fetal growth. Future studies should assess the respective role of genetics and fetal malnutrition in LBW children. It may be conceivable to reprogramme systems that have been affected during fetal life in the neonatal period, based on partial reversal of ill effects of fetal malnutrition in animal models.

Regarding nutrition *in utero* and the development of the metabolic syndrome, McKeigue (1999) postulates that the "small baby syndrome" is a subset of the broader group of disturbances that make up the syndrome. He argued that reduced size at birth does not predict lipid disturbances (high triglycerides and low

[7] Twelve genetic regions linked to diabetes were recently identified by Eli Lilly's Consortium for Diabetes and Obesity according to Reuters Medical News, May 5, 2000.

HDL-cholesterol) associated with insulin resistance and central obesity in the general population.[8] He also suggests that ethnic variations in diabetes prevalence are at least partly attributable to genetic factors, although the "thrifty phenotype" explanation is compatible with the increasing rates of diabetes in some Pacific and South Asian populations.

With reference to most chronic diseases, and CVD in particular, Kuh & Ben-Shlomo (1997) proposed that programming at best could create predisposition and vulnerability to life course experience, and early experience would surely be complementary, for so much is already attributable to other factors of the life course, notably lifestyle and diet. They question whether early influences act on adult health through independent, synergistic, or intermediary mechanisms. Their alternative model hypothesizes that adult chronic disease reflects cumulative differential lifetime exposure to damaging physical and social environments. At variance with programming, accumulation of risk does not require (nor does it preclude) the notion of a critical period. It places greater emphasis on a wider range of biological and social experiences in childhood, adolescence, and early adulthood than the lifestyle model (behaviours from childhood to early adulthood) or the programming model (prenatal and early infancy factors). The observation that birth weight is a strong predictor of risk of CHD, particularly among obese adults, is in keeping with this theory (see Section 7). It is believed that biological and social risk factors at each life stage may be linked to form pathways between early life experiences and adult disease (Wadsworth, 1997), and the important concept of the chain of risk describes how certain experiences in early life increase the likelihood of future events, which in turn lead to a change in risk of adult disease. Perry (1997) integrated nutritional, hormonal, metabolic, and circulatory components of fetal programming, along with genetic, maternal, and postnatal environmental influences in a broad conceptual framework. Järvelin et al. (1998) similarly emphasized a life course approach to the etiology of CVD.

[8] Although there are studies showing that thinness, shortness, and low abdominal circumference at birth are associated with altered liver development and higher cholesterol levels in adulthood.

9. Conclusions and recommendations

Based on evidence reviewed, it may be concluded that intrauterine programming is likely a third underlying factor of CVD and major markers of risk, along with genetic predisposition and lifestyle. The links between suboptimum fetal growth and higher risk of CVD, hypertension, and insulin resistance syndrome or type-2 diabetes are now demonstrated in several populations and age groups. Fetal "insults" reflected in lower birth weight or disproportion at birth or altered placental ratio were successively found to be associated with later disease risk markers. Furthermore, fetal nutrition may also impact on later risk without much effect of birth weight phenotype, as supported by a few studies. Although there are still controversial areas and information gaps, the weight of evidence for programming by metabolic adaptation of the fetus to its environment as the main underlying mechanism is increasingly convincing, based on animal models and other experimental data. In addition to the resetting of major hormonal axes of fetal growth regulation, there may be some permanent structural changes, further increasing the vulnerability to metabolic stress in later life. Maternal nutrition, including her nutritional status and dietary intake, likely plays a more important role in fetal programming of these diseases than heretofore suspected. Although not reviewed as yet, there is accumulating data in support of a programming effect of poor growth and nutrition in early infancy as well, which is a less-well documented component of the early origins hypothesis in its initial formulation in the late '80s. Furthermore, catch-up growth in height or weight in childhood appears to increase chronic disease risk associated with impaired fetal and/or early infancy growth. This is an area where much research effort is focused at this time. Additionally, suboptimum fetal or early growth may predispose to excess adiposity, as well as further increase the cardiovascular risk associated with obesity.

Regulation of fetal growth and development is extremely complex, and many experimental and epidemiological data linking prenatal events and chronic disease risk in later life challenge the view that the fetus is little affected by maternal nutrition. A much more sophisticated understanding of human fetal development, and of maternal regulation of fetal development is needed. Maternal nutrition may have long-term effects in offspring that are not reflected in birth weight, or any other measure of body size at birth. In other words, these may be poor proxy measures of maternal nutritional status, and of the quantity or quality of a woman's diet during pregnancy. Based on Dutch Famine cohort findings, on a rapidly growing number of epidemiological studies, and on several decades of animal research, it is now proposed that programming by fetal undernutrition can occur even without alterations in size at birth.

Although it is not specifically addressed in this review, smoking during pregnancy may be a major factor of impaired fetal growth and increased cardiovascular disease in later life, as suggested in the study by Williams & Poulton (1999). This is an increasing concern, in particular, in developing countries where tobacco smoking in women is escalating. Therefore, promoting non-smoking behaviours, in particular during pregnancy, is warranted as an important means of preventing impaired fetal growth. In addition, the specific effect of maternal smoking on infant body composition, postnatal growth, and chronic disease risk later in life needs to be further elucidated.

Evidence for fetal origins of CVD disease and risk markers suggests that a "developmental" model (Godfrey, 1998) may be more appropriate than the models that focused primarily on adverse influences acting only in adult life. It also indicates a new focus for disease prevention. Research and intervention on promotion of fetal growth and development, and on prevention of "over catch up" growth among children born growth retarded, may then improve health at all ages. A model that links impaired fetal growth with other adverse influences in the life-course and diet-related chronic diseases is proposed in Appendix B. The model to illustrate nutrition throughout the life cycle, developed by the Commission on the Nutrition Challenges of the 21st Century (2000), also integrates the increased chronic disease risk associated with inadequate fetal nutrition.

The early origins of later disease has much more important public health implications in developing than industrialized countries, because in the former, a larger proportion of birth weights are in the range found to be associated with adult disease. It is of utmost importance in those countries undergoing epidemiological transition, as risk factors for CVD and diabetes are on the rise, particularly obesity, while childhood malnutrition continues to be highly prevalent. Fetal programming may have dramatic consequences, further contributing to the increase in noncommunicable diseases associated with growing income, urbanization and westernization of diets and lifestyles. That obesity may be a time bomb was emphasized (Walker, 1998). Changes in diets, physical activity, and lifestyles that are typical of this transition now occur at a lower level of country income, which make the populations undergoing the process that much more vulnerable. With rising incomes, an initial upsurge in CVD in many population groups is to be feared because of atherogenic lifestyles; it will take time before healthier lifestyles bring about a decline. This initial increase may be even higher because of fetal programming associated with malnutrition and poverty early in life, and/or because of genetic susceptibility.

The is an urgent need at this time to better estimate the potential contribution of impaired fetal (and early infancy) growth, and its reduction, to CVD in developing countries and populations in transition. Further research on various aspects of the early origins model is also needed to feed into appropriate policies and programmes.

9.1 Implications for intervention strategies

The development of chronic disease has to be conceived as resulting from cumulative risks throughout the course of life, an approach that may easily reconcile apparently conflicting theories based on genetic susceptibility, fetal (and early postnatal) programming, or lifestyle risk factors. Whether the predisposition to CVD and type-2 diabetes is genetic or the result of fetal programming, or both, it remains that this predisposition will be expressed when diets and lifestyles are conducive to it.

9.1.1 Public health importance of fetal programming for cardiovascular disease

The public health importance of the links between fetal growth and chronic diseases is still controversial. Joseph & Kramer (1996), for instance, believe that interventions to improve fetal (and infant) growth would have, at best, limited impact on the occurrence of adult chronic disease, while having potential adverse effects, particularly an increased risk of cesarian section, if interventions were indeed successful in improving birth weights. Reported benefits associated with higher birth weights are considered very small, for enormous birth weight differentials (Kramer, 2000). However, their focus tends to be on industrialized country settings, and the calculations are only based on birth weight, while studies in Sweden (Lithell et al., 1996) and Finland (Forsén et al., 1999) show the larger effects on CHD when using more precise measures of size at birth. Using data from the 1993 Canadian birth cohort for a simulation exercise, they estimated that a 100 g increase in birth weight would only result in a 2.5% and 1.9% decrease in CHD deaths for women and men respectively. These figures do not take into account, however, the much higher rate of impaired fetal growth reflected by lower birth weight in developing countries and therefore, the potentially more favourable cost-effectiveness of interventions to improve fetal growth in these countries.[9] Also, they do not consider the apparently higher effectiveness of interventions designed to reduce LBW when malnourished women are targeted. The impact has to be assessed, therefore, in terms of changes in chronic disease rates, and in terms of maternal and infant mortality rates, which are likely to result from improved fetal growth in settings with high rates of malnutrition among women.

The magnitude of the associations between birth parameters and later disease risk requires assessment in comparison with those attributed to behaviours and lifestyle. The findings of the Finland cohort studies suggest, for instance, that variations in CHD predicted by size at birth and at 11 years are large compared with smoking (Eriksson et al., 1999). Dietary and physical activity patterns that promote obesity may compound the risk associated with impaired fetal nutrition, as there is evidence showing that impaired fetal growth may further increase obesity and enhance its adverse effects. As suggested by Yajnik (1998), fetal programming represents an adaptation that will continue to be beneficial only to the extent that the environment continues to be meager. When there is a change of lifestyle towards relative plenty, these metabolic adaptations become detrimental, and contribute to excess body fat deposition, deterioration in the function of overworked β-cells with precipitation of diabetes, and to several other aberrations in lipids and coagulation pathways. If fetal growth restriction amplifies other risk factors, then their indirect or intermediate effects must be considered.

[9] (in addition to improved maternal and child health and survival)

9.1.2 *Further impetus to improve maternal nutrition*

Unlike the genetic theories, fetal programming of common adult diseases provides additional justification, if needed, for emphasis on optimal fetal growth and development. The long-term adverse impact of fetal malnutrition is an additional and compelling argument to concentrate on improving nutritional status of young girls and women, preferably before, but if not, as early as possible, and throughout pregnancy. As stressed by Barker (1998), if the blueprint for our cardiovascular health is really established before birth, improvement in maternal nutrition may lead to reduction in adult cardiovascular risk.

Rasmussen (2001) estimates that the optimal birth weight for the lowest CVD mortality appears high (around 4,000 g), and higher than that associated with the lowest perinatal mortality (between 3,500–4,000 g). It is concluded in that review that the evidence is as yet too limited to use the research on fetal origins of adult disease as a basis for new interventions directed at pregnant women. We concur with this view, given that interventions to prevent impaired fetal growth are essentially the same, whether the focus is mother and child survival only, or whether the longer-term dimension of potential reduction of cardiovascular risk is also considered. Indeed, prevention of impaired fetal growth through improved nutrition of girls and women not only contributes to lower maternal mortality, and better child survival and development, it may also help to prevent chronic disease, and in particular, the obesity, diabetes, and CVD epidemic in developing countries. Although the portion of chronic disease that can be explained by fetal programming (and prevented by optimal fetal growth) may appear small, it must be emphasized that intrauterine growth impairment affects 30 million children annually, of whom 75% are in Asia and 20% in Africa. Furthermore, the benefit of improving maternal (and fetal) nutrition may go beyond what may be projected based on birth weights since intrauterine programming may occur without verifiable effect on size or proportions at birth. However, in view of available evidence, new interventions directed at women for the specific purpose of reducing the risk of chronic disease in the offspring do not appear relevant as yet, given the present status of knowledge, beyond early action to ensure that women enter pregnancy with an adequate nutritional status, and appropriate nutrition monitoring and promotion throughout pregnancy.

We can only concur with the joint statement of WHO/UNFPA/UNICEF/World Bank (1999) pleading for a commitment by nations-states to the special needs of girls and women, and particular attention to their nutrition and education needs. The key biological and social role of women is also highlighted in the Final Report to ACC/SCN of the Commission on the Nutrition Challenges of the 21st Century (2000).

9.1.3 *Promoting adequate growth in early infancy, and preventing obesity in childhood*

The fact that children who showed impaired prenatal or early infancy growth are at enhanced risk of chronic disease by virtue of catch-up growth, and particularly so if they become obese, may have practical implications for programmes. Better data bases on birth weights (with information on gestational age) should be developed and maintained, possibly with WHO support. Furthermore, children born small should be targeted by nutrition promotion and obesity prevention activities, especially those administered through the school system.

It may be difficult to undertake chronic disease prevention interventions based on lifestyle and "prudent" eating in countries where the focus has been on undernutrition in mothers and children. However, as suggested by Vorster et al. (1999), a promising strategy could be to focus on optimal nutrition through programmes designed to address both undernutrition and overnutrition. For instance, emphasis could be on preventing obesity in children and adolescents, along with preventing impaired fetal growth, and promoting optimal nutrition in early infancy.

There is evidence that stunted growth in infancy, whether or not it originates *in utero*, is associated with childhood obesity (Popkin, Richards & Monteiro, 1996), and with the same longer term adverse effects as impaired fetal growth (Eriksson et al., 2000), but this requires further testing. Influence of the early nutritional environment of the fetus on its growth trajectory may have implications for the amount of catch-up growth that can be expected and that should be the target in early infancy.

The implication of catch-up growth in childhood and obesity in later life as amplifiers of the risk associated with impaired fetal growth raises a critical issue that urgently needs to be addressed through research. The potential for early nutritional intervention to reprogramme these infants following poor intrauterine growth, in order to ameliorate the risk, needs to be assessed (Lucas, 1998). The issue involves two reciprocal aspects: critical periods for adverse and long-term effects of nutritional inadequacies in fetal and early life, and critical and likely narrow windows in prenatal and early postnatal life for nutrition intervention to pre-

vent or reverse disease programming. It can be speculated that catch-up growth in early infancy offers some benefit, based on the findings of increased CVD risk associated with poor growth in the first year (see Section 7.1.), and that breastfeeding may be protective (Roberts 2001; Singhal, Cole & Lucas 2001).

9.2 Research needs in humans on the basis of available evidence

The link between weight or proportions at birth and CVD risk (CHD, stroke, type-2 diabetes, hypertension, metabolic syndrome) is now considered sufficiently demonstrated to avoid replicating any further observational studies on the associations. However, knowledge gaps are immense, particularly on the process of programming itself, on the role of maternal nutritional status and diet at specific times, on fetal (and placental) growth assessment, and on effective measures to attenuate the risk in children born with suboptimum fetal growth.

The effects of fetal malnutrition on different organs and systems in the human fetus need to be better understood. The factors that modulate the growth of the fetus and permanently programme its metabolism may be the key to the effective prevention of CVD in adult life. As stressed by Barker (1997a), if we are to use the information on "early origins" of chronic disease for prevention, we need to know what factors limit the delivery of nutrients and oxygen to the human fetus; how the fetus adapts to a limited supply; how these adaptations programme the structure and physiology of the body; and by what molecular mechanisms nutrients and hormones alter gene expression. Future research needs to mesh epidemiological, clinical and animal studies. Accordingly, Langley-Evans et al. (1999) consider an urgent research priority to be the elucidation of the role of maternal diet as a programming stimulus in order to generate relevant and effective public health guidelines. The ever-growing body of data on fetal origins of chronic disease points to the need to better understand fetal nutrition and identify the critical periods for specific nutrients, and for placental and fetal growth, as well as the interaction between genes and nutrient supply *in utero*. At present, there is a serious paucity of reliable and representative data on dietary intakes of pregnant women in relation with chronic disease markers in the progeny.

Interventions may be crucial in populations with high rates of fetal growth impairment. More studies must therefore be conducted in developing countries. In order to adequately prevent fetal malnutrition, it is of utmost importance to better assess the impact of a combination-type of nutritional interventions during, and preferably even before, pregnancy, as strongly recommended by de Onis, Villar & Gülmezoglu (1998) when considering the limited knowledge and mitigated results of such interventions. More placebo-controlled, randomized trials are required, especially those including adolescent mothers. The effects of micronutrient intakes from food or from supplements on chronic disease risk markers, and not only on pregnancy outcome and birth weight, urgently need to be studied or further documented, in particular zinc, folate, iron, calcium, magnesium, and vitamin C.

The short (reproductive performance and size of infant at birth) and long-term (chronic disease in later life) effects of maternal nutrition may be quite different, in the sense that programming effects may not be correlated with birth size effects. It will be important to re-examine the nature and timing of nutritional deficiencies, imbalances, or supplements on both fetal (and placental) growth and metabolism, on early infancy growth, as well as on chronic disease, in order to advocate for relevant preventive policies. It is possible that some nutrition interventions during pregnancy and in early infancy could modify chronic disease risks through programming, but not necessarily in a positive manner, as suggested, for instance, by potentially adverse effects of high protein supplements during pregnancy, or food supplementation in pregnant adolescents who are still growing. Another major question to be answered through intervention trials is whether it is possible through prudent diets and healthy lifestyles to cancel out the extrasusceptibility to noncommunicable diseases due to prenatal factors.

Most early cohorts were born in the early twentieth century, at a time when environmental conditions during pregnancy and childbirth were more adverse than those prevailing today. There are more recent studies, but cohorts with prenatal and postnatal growth data are required in different populations living in different conditions; in northern Finland, for instance, such a cohort study has been underway since the '60s (Järvelin et al., 1998). These longitudinal studies could examine whether or not the impaired fetal growth risk factor is amplified between adolescence and adulthood, and also examine the relative contribution of birth weight and contemporary factors of risk. As stressed by Grivetti et al. (1998), the ultimate proof of causality will require further evidence from experimental longitudinal designs. Follow-up components of intervention trials designed to examine short-term outcomes, or of individuals involved in nutritional and nonnutritional intervention trials having produced variations in fetal growth, are seen as possibilities, as well as

trials routinely using ultrasound in pregnancy to document fetal growth. They also see as relevant, studies in adults to assess whether size at birth affects the effectiveness of interventions to treat or prevent hypertension, type-2 diabetes, and we should add, obesity. While risk of disease in later life may be programmed *in utero* by impaired fetal development due to suboptimum nutrition, infancy and childhood events may also determine risk independently of prenatal and adult factors, and the infancy component of the early origins hypothesis urgently needs testing. Impaired growth in early infancy appears to be an independent risk factor, and a recent report highlights the early faltering of growth in length, that is, in the first year of life, in all developing regions (Shrimpton et al., 2001). Determinants of adult disease ultimately have to be studied across the whole life course (Kuh & Ben-Shlomo, 1997), in order for interventions to break the biological and social chains of risk by targeting those life stages that are known to be particularly critical, notably prenatal life, infancy, childhood, and adolescence.

To summarize, the following appear to be particularly pressing research needs:

- Conjunct analysis of available population data on birth weights, the prevalence of obesity, and the prevalence and death rates from CVD and type-2 diabetes
- Respective role of fetal and placental growth in predisposing to adult diseases
- Effect of suboptimum maternal nutrient intake, and its timing, on fetal and placental growth, in adolescent and adult mothers, with a clear definition and measure of prenatal "exposure"
- Effects of deficiencies in specific micronutrients, and of their timing, on fetal growth and chronic disease markers, in particular iron, folate, magnesium, calcium, zinc, and vitamin C
- Extent of spontaneous and controlled catch-up growth in infancy according to type of fetal growth impairment, including that due to maternal smoking and parental size
- Potential for "reprogramming" of growth-restricted newborns through nutrition-controlled catch-up growth in the first years
- Effectiveness of pilot interventions promoting simultaneously improved nutrition for the prevention of undernutrition/impaired fetal growth, and for the prevention of obesity/chronic diseases.
- Effects of maternal smoking on infant body composition, postnatal growth, and chronic disease risk later in life

The issue of fetal programming of chronic diseases is progressively attracting more interest and concern in health and development circles. As aptly described by Vorster et al. (1999), the issue of increased susceptibility to CVD, hypertension and insulin resistance because of impaired fetal nutrition has to be placed in the overall framework of the "nutrition transition". The early origins model triggers challenging strategies of simultaneously addressing undernutrition and "overnutrition". Owing to its inherently multidisciplinarity, it calls for collaboration among academic institutions, international agencies, and countries, as well as among several clusters of WHO, in particular reproductive health, chronic diseases, ageing, and nutrition. An ACC/SCN Working Group on Life Cycle Consequences of Fetal and Infant Malnutrition was created in 1999 to help respond to this issue. The First World Congress on Fetal Origins of Adult Disease held in Mumbai (India) in February 2001 provided an opportunity to share knowledge on the issue, and to discuss roles and responsibilities in research, clinical application, and public health action. It is to be hoped that action-oriented research will be conducted at an accelerated pace with a particular focus on transition countries and populations in order for relevant intervention programmes to be undertaken with the aim of simultaneously addressing early undernutrition and later lifestyles, that is, two modifiable factors of CVD risk. Following this initial desk-review intended to serve as background discussion paper, an expert consultation should be convened to further examine the evidence and to draft a research and policy agenda.

APPENDIX A

Characteristics of main epidemiological studies on fetal origins of cardiovascular disease and risk markers of last decade

A. Coronary heart disease, type-2 diabetes, hypertension, metabolic syndrome

Site	Key outcome	Ref.	Study type	Sample description	Birth period	Age	Results
Hertfordshire, UK	CHD	Barker et al., 1989; Osmond et al., 1993	Historical cohort	16,000 men and women	1911–30	?	– Death rates from CHD decreased twofold from the lower to the upper end of the birth weight (BW) distribution – LBW was associated with an increased risk of stroke – Low rates of infant weight gain were associated with higher rates of CHD in men, not women: men small at 1 y 3 times more likely to have CHD
	CHD	Vijayakumar et al., 1995	Historical cohort	290 men born there, whose weights were recorded at 1 year and still living there	1920–30	65–75y	– Low weight at 1 year associated with hypertrophy of left ventricle, after controlling for age, body size and systolic systolic blood pressure (BP) of older men – Concentric left ventricular enlargement as observed is a known risk factor for CHD
	Metabolic syndrome	Fall et al., 1995a	Historical cohort	297 women born and still living there, with oral glucose tolerance test	1923–30	60+y	– Lower fasting insulin, glucose, pro-insulin with increasing BW (correction for current BMI) – Similar trends for 2-h glucose and insulin – Inverse association of systolic BP, triglycerides, waist-hip ratio with BW and position association of HDL-cholesterol with BW – Highest risk profile in those born small and currently obese – Contrary to men, no relationship of risk markers with low growth rate in infancy
	Cortisol	Phillips et al., 1998	Historical cohort	370 men	1920–30	60+y	– Fasting plasma cortisol was related to systolic BP, fasting and 2-h plasma glucose, triglycerides, and insulin resistance. – Plasma cortisol fell with increasing BW, independent of age and BMI
Preston, UK	CHD, hyper-tension, insulin resistance	Phillips et al., 1994; Taylor et al., 1995	Historical cohort	People with detailed birth records	1935–43	60+y	– Thinness at birth (low PI) associated with insulin resistance and its associated disorders – Rates of muscle glycolysis was reduced – BPs increased with increase of placental weight at any given BW – Alterations of placental to BW ratio typical of iron deficiency associated with CHD and hypertension in later life

Site	Key outcome	Ref.	Study type	Sample description	Birth period	Age	Results
Sheffield, UK	CHD	Barker et al., 1993	Historical cohort	1, 586 men with detailed obstetric records	1907-24	?	– Those of LBW because of fetal growth retardation, not prematurity, were at increased risk of CHD – PI inversely associated with CHD mortality
	Impaired glucose tolerance	Hales et al., 1991	Historical cohort	400 Men	1920-30	59-70y	– Impaired glucose tolerance and diabetes more frequent in LBW men (OR: 6.6) – Prevalence still higher in obese adults born small
	Serum cholesterol, blood clotting	Barker et al., 1992b; 1995	Historical cohort, hospital-based	219 men and women	1939-40	50-53y	– People disproportionately short for head size at birth even within normal BW range had persisting disturbances of cholesterol metabolism and blood coagulation – Small abdominal circumference in particular predicted raised LDL-cholesterol and plasma fibrinogen concentrations
Both Hertfordshire and Sheffield cohorts, UK	CHD	Martyn, Barker & Osmond, 1996	Historical cohort	13, 249 men; deaths from stroke and CHD (77% of men born in Hertfordshire, 66% in Sheffield)	1907-30	?	– Standardised mortality ratios fell by 12% for stroke and by 10% for CHD between each of the 5 groupings of increasing BW – Death rates from CHD and stroke also related to low weight at 1 year, irrespectiveof feeding and weaning practices – Mortality from stroke was most strongly associated with a high ratio of head circumference to BW and low placental weight-to-head size, pattern encountered with mothers having flat bony pelvises – Mortality from CHD was associated with small head circumference, thinness or shortness at birth, and an altered (too high or too low) ratio of placental weight to BW
Newcastle, UK	Carotid intima-media thickness	Lamont et al., 1998, 2000	Longi-tudinal (Newcastle thousand families)	154 men and 193 women from original cohort of 1,142 subjects, followed up until age 15	1947	49-51y	– BW in men and social class at birth in women were negatively associated with carotid intima-media thickness. BW in men was not associated with thickness independently of adult biological risk markers, but social class in women remained significant – Most variation was explained exclusively by factors operating or measured in adulthood (lifestyle and biological risk markers) – Little evidence that suboptimal growth *in utero* leads to increased intimal thickening of the carotid artery in later life independent of adult lifestyle and risk markers

Site	Key outcome	Ref.	Study type	Sample description	Birth period	Age	Results
Caerphilly, South Wales	CHD, obesity, lipids, bp	Frankel et al., 1996a,b	Cohort study with 10-year follow-up	1,258 men aged 45–59 at screening (1979–83), and who could provide BW data. 10-year follow-up	1920–34	55–69y	– Inverse association of BW with incident fatal and nonfatal CHD in follow-up period, restricted to subjects in the top tertile of BMI – Associations not changed substantially after adjustments for age, father's and own socioeconomic status, systolic BP, smoking history, fibrinogen and cholesterol level – There were strong graded (positive) associations between BW and current BMI, triceps skinfold, height, and % fat – Inverse association between triglycerides and BW – No association between BW and BP – Positive association between BW and fibrinogen
Aberdeen, Scotland	BP; Insulin and glucose	Campbell et al., 1996; Shiell et al., 2000	Follow-up study of offspring of mothers who participated in a dietary survey in their 7th month of pregnancy	253 men and women for BP; 168 men and women for women for glucose	1948–54	?	– Maternal macronutrient intake at 30 weeks of pregnancy was associated with BW, placental weight, BP, and plasma insulin and glucose – A high % of calories from protein, especially animal protein, was associated with lower BW – At high animal protein intake, higher BP was associated with low carbohydrate intake; and at low animal protein intake, higher BP was associated with high carbohydrate intake, suggesting a role for dietary imbalance – High protein and fat intakes, and high maternal BMI, were independently associated with a decrease in plasma insulin increment between fasting and 30-min post-glucose challenge, suggesting an adverse effect on insulin metabolism – Low maternal BMI and low placental weight were associated with raised fasting insulin
Arizona, Pima Indians, USA	Type-2 diabetes	McCance et al., 1994	Follow-up study	1,179 Pima Indians	1940–72	20–39 y	– Age-adjusted diabetes prevalence according to BW was 30% under 2,500g, 17% between 2, 500–4,499g, and 32% at 4,500g or more (U-shape) – However, most diabetics of normal BW, so that other factors are involved – Genetic predisposition to insulin resistance hypothesized as underlying mechanism
USA	CHD	Rich-Edwards et al., 1995a, b	Prospective	80,000 women of the Nurses Health Study I, aged 30–55 in 1976 and followed up for 14 years	1921–46	44–69	– Significant positive association between BW and CHD – Adult height was negatively associated with CHD risk; % LBW was also inversely related to height category – Stratification by BW did not change the association of CHD with current height

Site	Key outcome	Ref.	Study type	Sample description	Birth period	Age	Results
USA	Hypertension and obesity	Curhan et al., 1996	Prospective	71,100 women of the NHS I aged 30–55 in 1976; 92.940 of the NHS II who were aged 25–42 in 1989	1921–46 (I); 1947–64 (II)	30–55 (I) 25–42 (II)	Hypertension – NHSI: OR for BW<5 lb compared with women in middle BW category (7–8.4 lb): 1.39 (1.29–1.50) – NHSII: Or for BW<5.5lb, compared with middle BW (7.1–8.5 lb): 1.43 (1.31–1.56) No change after adjusting for confounding factors. Obesity – In both studies, those with BW>10lb had an OR ratio of above 1.6 of being in the highest BMI quintile (>29.2) vs. the lowest quintile (<21.9)
	Type-2 diabetes	Rich-Edwards et al., 1999	Prospective	69,526 women in the NHS free of diabetes in 1976	1921–46	60+y	– Reverse J-shaped association between BW and age-adjusted risk of type-2 diabetes – Inverse association between BW and type-2 diabetes across the entire range of BW, after further adjusting for current BMI and maternal diabetes – Stronger inverse association of BW and type-2 diabetes in women without parental history of diabetes: almost fourfold gradient – The inverse association observed in all current BMI strata, and in all 3 birthyear groups
Copenhagen, Denmark	Insulin sensitivity	Clausen et al., 1997	Prospective	331 Caucasians from cohort	1961–73	18–32y	– Significant, but modest relationship between BW and insulin sensitivity index (ISI); PI did not show a relation; – LBW was not associated with features of insulin resistance syndrome – BMI and waist-hip-ratio (WHR) were much more strongly (and inversely) related to ISI than BW – There was no association between BW and BMI
Helsinki, Finland	Fatal and non fatal CHD	Forsén et al., 1997; Eriksson et al., 1999	Prospective (hospital-based birth cohort)	Follow-up of 3,641 men born in Helsinki and with a mean of 10 height-and-weight measurements in childhood	1924–33	65+y	– CHD death was associated with LBW and more particularly, low PI at birth: increase of 14% of risk ratio for each unit decrease in PI – Higher BMI at 11y associated with higher CHD death risk: 22% increase per BMI unit increase – Maternal BMI in pregnancy was positively associated with death rate, but only among men whose mother was below average height – Highest death rates in boys, born thin, and whose weight had caught up by age 7y.
		Eriksson et al., 2001	As above	4,630 men, as above	1934–44	55+y	– Low weight, height, and BMI at 12 months independently associated with higher CHD risk – In subjects born thin only, rapid gain in weight and BMI after infancy increased CHD risk

Site	Key outcome	Ref.	Study type	Sample description	Birth period	Age	Results
Helsinki, Finland	Fatal and non fatal CHD	Forsén et al., 1999	Prospective hospital-based birth cohort)	Follow-up of 3,447 women (same as for men, see above)	1924–33	65+y	– CHD was inversely related to BW, and particularly so after adjusting for placental weight – Shortness at birth was strongly related to CHD, with a 10.2% decrease per cm increase in birth length – Higher rate of CHD in women who were born short and who had caught up in height at 7y, but BMI showed no relation ship – The interaction between shortness at birth and tallness in childhood in increasing CHD risk was stronger in daughters of tall mothers
	Hypertension	Eriksson et al., 2000	Same as above	1,958 men and women from the 1924–33 birth cohort, treated for hypertension	Same as above	Same as above	– Cumulative incidence of hypertension fell with increasing BW, length, and PI at birth, and it rose as the ratio of placental weight:BW increased – Subjects developing hypertension had accelerated postnatal growth, and had caught up in height and weight at age 7y – In those developing hypertension and diabetes, growth rates in weight and height between 7–15y were higher than in those developing only hypertension, and this was particularly marked in girls
	Type-2 diabetes	Forséen et al., 2000	Same as above	471 men and women from the 1924–33 birth cohort, who developed type-2 diabetes	Same as above	Same as above	– Cumulative incidence increased with decreasing BW, PI and length at birth, and placental weight; stronger trend in men – Faster growth rates observed between age 7–15y, and not up to age 7y – With decreasing BW, increasing likelihood of weight gain, height gain, and BMI gain between age 7–15y
Piek-sämäki, Finland	Metabolic syndrome	Vanhala et al., 1999	Population-based	712 subjects (72%)	1947, 1953, 1957	?	– No association between BW and metabolic syndrome as adult – Among children in the highest BMI quartile at age 7y, OR of metabolic syndrome was 4.4 (CI: 2.1–9.5) – After adjusting for current obesity, age and sex, OR still 2.4 (1.1–5.6)
Stockholm (Sweden)	Insulin resistance, glucose tolerance abnormalities	Carlsson et al., 1999	Population-based cross-sectional study	2,237 men born in 1938–57, 50% with a family history of diabetes	1938–57	?	– BW ≤3kg associated with an OR of 2.3 for diabetes and 3.3 for impaired fasting glucose in subjects without a family history; similar findings in those with a family history, except that the OR was much higher for diabetes (5.4) compared with about 2 in those without diabetes in close relatives. – Those with BW ≤3kg and a family history were 10 times more at risk that those of higher weight and without a family history – Adjusting for family history did not remove the relationship of diabetes with BW – Insulin resistance prevalence increased with decreasing BW in a dose-response manner.

Site	Key outcome	Ref.	Study type	Sample description	Birth period	Age	Results
Uppsala, Sweden	Insulin resistance, glucose tolerance abnormalities	Lithell et al., 1996	Cohort	1,333 living in Uppsala in 1970	1920–4, in Uppsala or elsewhere in Sweden	50–60y	– Weak inverse association of PI and 60-minute insulin concentrations at age 50y; stronger association in the upper tertile of BMI – Association unchanged after adjusting for current BMI, as it was not related to PI (but BW was positively correlated with adult BMI) – Stronger association of PI than BW with diabetes at 60y; – Highest prevalence of type-2 diabetes and IGT in people who were also obese as adults
	Mortality from circulatory diseases	Koupilova, Leon & Vagero, 1997	Cohort	Same as above	Same as above	Up to 75y	– Inverse association of BW with mortality: rate ratio of 0.67 (CI:0.50–0.89) per kg increase in BW – Not affected by adjusting for socio-demographics and smoking – Slightly strengthened by adjusting for BMI at age 50 and 60y – Adjustment for BP slightly reduced the inverse association of BW with death from ischaemic heart disease, but no effect on death from stroke, so that the inverse association does not seem to be mediated through increased BP
France	Insulin resistance	Léger et al., 1997	Regional cohort study	236 SGAs and 281 AGAs	1971–8	20y	– Proinsulin and insulin concentrations following a glucose load were sign. higher in SGAs, although there was no IGT, suggesting changes in insulin sensitivity – No difference of BP, fibrinogen, and blood lipid concentrations – SGAs were significantly shorter
		Jaquet et al., 2000	Case-control	26 IUGR-born subjects and 25 controls, men and women	1970–75?	25y	– % body fat higher in IUGR group, in spite of similar BMI – Significantly lower insulin-stimulated glucose uptake in IUGR subjects adjusting for BMI, total body fat and WHR – After adjusting for insulin resistance, no difference in insulin secretion
Australia	Insulin sensitivity and secretion	Flanagan et al., 2000	Subset of birth cohort	163 men and women born at term	1975–76	20y	– Small size at birth was associated, but only in male subjects, with increased insulin resistance and hyperinsulinemia independently from BMI or % body fat – Glucose tolerance was however not affected, because of compensatory increased insulin secretion and glucose effectiveness – Obesity added to the effects of shortness or LBW on insulin sensitivity in men; obesity was the major determinant of insulin sensitivity in women.

Site	Key outcome	Ref.	Study type	Sample description	Birth period	Age	Results
Philadelphia (USA)	Metabolic syndrome compo-nents	Hulman et al., 1998	Prospec-tive study	137 African Americans	1959-65	Follow-up until 30-35y	– No relationship between BW and adult BMI, BP, or impaired insulin-stimulated glucose metabolism
Jamaica	Metabolic syndrome compo-nents	Forrester et al., 1996	Retrospec-tive cohort	1,610 school children	?	6-16y	– Systolic BP was inversely related to BW and directly related to current weight – Glycated Hb was related to shortness at birth and high triceps skinfold – Serum cholesterol was inversely related to length at birth and current height, and directly related to triceps skinfold and socioeconomic status
Mysore, South India	CHD	Stein et al., 1996	Hospital-based restrospec-tive cohort	517 men and women with detailed obstetric record	1934-54	38-60y (mean 47)	– CHD prevalence of 15% in those weighing ≤2.5 kg at birth, 4% in those who weighed ≥3.2kg, subjects aged 45 and above – Higher CHD in those short and with low head circumference at birth – Highest rate in LBW subjects whose mothers weighed (45 kg in pregnancy (20%) – Inverse relationship of CHD and social class (many criteria), in men but not women; controlling for socioeconomic status suppressed the association of BW with CHD
	Type-2 diabetes	Fall et al., 1998	See above	506 men and women with detailed obstetric record	1934+	39-60y	– 15% prevalence of type-2 diabetes – Higher rate in those who were short and had low PI at birth – Mothers heavier than average during pregnancy – Higher PI associated with slower insulin increment at 30 minutes post glucose load, marker of reduced β-cell function
Rural Indians, Pune	Metabolic syndrome	Yajnik, 1998	Cross-sectional	321 adults above 40 (85% of the eligible)	?	>40y	– Based on OGTT, 4% had diabetes and 4% IGT – 2-h glucose positively related to BMI and WHR, but negatively to height (men) or head circumference (women) – Insulin, and other markers of metabolic syndrome interrelated
Urban setting, India	Insulin resistance syndrome markers	Yajnik et al., 1995	Hospital-based cohort	379 children born in local hospital, with BW data	?	4y	– Following OGTT, significant inverse relation between BW (or head circumference) and insulin at 30 min independent of current weight

Site	Key outcome	Ref.	Study type	Sample description	Birth period	Age	Results
Urban setting, India	Insulin resistance syndrome markers	Bavdekar et al., 1999	Mixed, longi-tudinal and cross-sectional	190 children from above cohort, born full-term, and additional children born full-term, with BW in a specific range to complete the set. Total: 477 boys and girls	?	8y	– BW only marginally higher in children with higher socioeconomic status , but at age 8y, anthropometric measures rose sharply with increasing socioeconomic status – Many outcome variables higher in children with higher current weight: systolic BP, plasma insulin, pro-insulin, insulin resistance, β-cell function, total and LDL-cholesterol, triacylglycerol; fat mass is the component more strongly associated with risk factors – Plasma insulin and pro-insulin, as well as total and LDL-cholesterol, were higher in taller children – After adjustment for current weight and socioeconomic factors, lower BW was associated with clustering of the insulin resistance syndrome factors, although current weight showed a stronger effect – Inverse trends with BW were stronger in high current weight, and positive trends with current weight were stronger in lowest BW group. – Insulin resistance was higher in taller children, and the most insulin resistant were those children whose parents were short but who had grown the tallest at 8y – Risk variables were related to BW only in the heavier children

B. Blood pressure only

Site	Ref.	Study type	Sample description	Birth period	Age	Results
England	Barker et al., 1990	Retrospec-tive cohort	449 men and women	1935–43		– Inverse association of BW and adult systolic BP
	Whincup et al., 1999	Pop.-based longi-tudinal study	1,860 singleton children	1994–6	3y	– Graded inverse relationship of BP (both systolic and diastolic) with BW after adjusting for current weight – No independent association of other birth measure ments with BP – No observed association between BP and rapid postnatal growth; rather, BW was more strongly associated (inversely) with BP in shorter children
	Pharoah, Stevenson & West, 1998	Case-control	172 very LBW infants born in 1980–1, with school matched controls	1980–1	15y	– Systolic BP significantly higher in cases than controls – Controls were significantly heavier, taller, with larger head circumferences – Adjusting for current height, weight or BMI increased the difference between cases and controls
England and Wales	Taylor et al., 1997; 1998	Cross-sectional school-based survey	3,010 singleton children with BW information	?	8–11y	– Negative relationship of BW and BP, but particularly in girls (apparent after correction for current body size) girls (apparent after correction for current body size) – No association with other neonatal measurements – Association independent of maternal BP – Current body size is a much more important determinant of BP

Site	Ref.	Study type	Sample description	Birth period	Age	Results
Edinburgh, Scotland	Walker et al., 1998	Cross-sectional	452 young adults with BW data, and whose parents had BP measured 7 years previously	?	16–26y	– +2.24 mmHg of systolic BP per kg decrease in BW – Higher maternal blood pressure positively related to offspring blood pressure and negatively related to BW – After correction for maternal BP, weaker negative association of BW and blood pressure
Netherlands	Uiterwall et al., 1997	Longi-tudinal study	330 subjects initially aged 5–21 years followed for 14 years	?	19–35y	– Inverse association of BP with BW throughout the follow-up period – BW showed a significant interaction with BMI, with LBW combined with high BMI increasing the risk
France	Zureik et al., 1996	Retrospec-tive cohort	210 subjects with BW and growth information	?	8–24y	– Systolic BP inversely related to BW – Left ventricular mass unrelated to BW, but was increased in infants with reduced growth (weight at 8mo and 2y)
	Said et al., 1998	Cross-sectional survey, school-based	1,296 children randomly selected	?	3–4y	– Inverse association between systolic BP and PI at birth: -0.67 mmHg per PI z-score adjusted for gestational age, after adjustment for current height and BMI – No relationship with diastolic BP
Italy (Torino)	Rabbia et al., 1999	Cross-sectional study, school-based	1,310 randomly selected adolescents	?	12–14y	– Weak negative association of BW and BP – Stronger negative association when including with confounding factors maternal diseases or environ-mental conditions leading to placental hypoperfusion
Uppsala, Sweden (see also Lithell et al., 1996)	Leon et al., 1996	Cross-sectional with birth size data from obstetric records	1,333 men	1920–4	5y	– Inverse relationship of BW and BP – Much stronger reverse effect in those in the last tertile of BMI – Those who weighed <3,250g at birth but who were above the median adult height had particularly high BP – Highest adult BPs found in men with gestational age <38 weeks
	Koupilova et al., 1997	Same as above	Subset of 615 men with data on social circumstances	Same as above	5y	– Adjustment for socioeconomic status, education level and marital status at age 50y did not reduce the strength of the BMI-adjusted association between BW and systolic blood pressure – Controlling for smoking and drinking at 50 did not affect the relationship – Simultaneous adjustment for sociodemographic circumstances at birth and at 50y, and for behaviours at 50 led to only a slight reduction of the relationship between BW and BPat age 50y
Göteborg, Sweden	Sewert-Delle & Ljungman, 1998	60% random screening of men aged 49 born in Göteborg	430 subjects with full birth records (25% of eligible)	1926–7	49y	– No association found between BW and BP – Gestational age was inversely associated with BP in the whole sample, and the association was particularly strong in preterm or LBW individuals – Only in term or post-term was current BMI associated with BP

Site	Ref.	Study type	Sample description	Birth period	Age	Results
Sweden	Leon, Johansson & Rasmussen, 2000	Record linkake study (retropective)	>165,000 male conscripts born after 35–44 weeks gestation	1973–6	18y	– Inverse association of BW and systolic BP – BW for gestational age (proxy for fetal growth) independently and inversely associated with systolic BP, but not birth length for gestational age – Independent but small inverse association of gestational age with systolic BP
Dunedin, New Zealand	Williams & Poulton, 1999	Longitudinal	Children from health and development study cohort 818 seen at age 9, and 879 at age 18	1972–3	18y	– Using path analysis, the total effect of BW on systolic BP was small (inverse association), after its indirect effect through concurrent height and BMI was taken into account
Adelaide, Australia	Moore et al., 1999	Longitudinal	584 men and women followed up		20 years	– Current weight-adjusted systolic blood pressure was inversely associated with BW in men and women – Shortness at birth, thinness at birth, and high placental ratio were also associated with elevated BP at 20y – The inverse association with BW was stronger at age 20y than at age 8y – An interaction of size at birth and current size was observed, with enhanced effects in individuals of larger body size
Israel	Seidman et al., 1991;	Cross-sectional	33.545 subjects	1964	1y	– Positive association of BW with BP
	Laor et al., 1997	Cross-sectional, pop.-based	>10,000 army draftees, 40% women	1974–6	17y	– No association of BP with BW – Positive association of systolic and diastolic BP with BMI, mother's BMI before pregnancy, but not maternal weight gain in pregnancy – Contrary to other studies, those who were small at birth and became overweight were not at higher risk
USA (Louisiana)	Donker et al., 1997	Longitudinal study (Bogalusa) and cross-sectional study data	2 data sets: 1) 233 from birth cohort 1873–74, examined in 84–85; 2) 1,213 subjects aged 7–11 examined in 87–88, with birth data retrospectively collected		7–11y	– When comparing LBW and normal BW children, LBW was a risk factor for high diastolic BP , but the OR was high only for Black boys (2.66) (CI:1.25–5.70) – When analysing only full-term births, BW was not significantly associated with BP – Current BMI was significantly and positively associated with BP
Argentina	Bergel et al., 2000	Prospective cohort	518 children out of 614 eligible	1987–90	5–9y	– BP was not significantly associated with BW or other measurements at birth, nor with maternal characteristics during pregnancy, including her BP, smoking and weight gain – BP was significantly and positively associated with current size of the child, and with maternal haemoglobin during pregnancy, and BP outside of pregnancy – BW was negatively associated with BP among tall and heavy children, although this association became non significant when adjusting for maternal BP

Site	Ref.	Study type	Sample description	Birth period	Age	Results
Kingston, Jamaica	Thame et al., 2000	Longitudinal, hospital-based study	428 newborns, 5 subsequent follow-ups	?	Up to 3.5y	– Inverse association of systolic BP with BW at ages 2.5 and 3y – Inverse association also with placental volume at 17 and 20 weeks of pregnancy and abdominal circumference at 20 weeks – Maternal nutritional status was predictor of BW and placental volume, although it was not a direct predictor of children's BP
China	Mi et al., 1999	Cross-sectional study with birth size data from obstetric records	600 men and women	Around 1950	45y	– Inverse relationship of BW and systolic BP: for each kg increase in BW, BP drops by 3 mmHg – Inverse association also with blood glucose, which dropped 5% per kg of increase of BW – Lower BW correlated with maternal thinness (weight for height) during pregnancy
China (Hong Kong)	Cheung et al., 2000	Longitudinal hospital-based birth cohort	122 men and women	1967	30y	– Inverse relationship of PI, and length SD-score at birth with systolic BP at age 30y – PI changes between age 6–18 mo inversely associated with systolic BP – Birth length SD score inversely associated with diastolic BP at age 30y
Harare, Zimbabwe	Woelk et al., 1997	Retrospective cohort	756 school-children	?	Mean age 6.5y	– Systolic BP inversely related to BW after adjusting for current weight – Inverse association also with head circumference, but not birth length or gestational age
Johannesburg, South Africa	Crowther et al., 1998	Longitudinal cohort subset	152 Black African children born at term	?	7y	– Following an OGTT, inverse correlation between BW and insulin secretion or blood glucose – Children with lower BW but high weight velocity as shown by high BMI at 7 showed more insulin resistance than those remaining in the lower weight range – Like BW, height at age 1 and 7y was inversely related to blood glucose 30 min post glucose load
Soweto, South Africa	Levitt et al., 1999	Prospective cohort	849 children	?	5y	– Systolic BP was inversely related to BW, independent of current weight and height: mean decline of 3.4 mmHg per kg increase in BW
R.D. Congo	Longo-Mbenza et al., 1999	Cross-sectional	2,648 school-children (randomly selected)	?	Mean age 11y	– Higher likelihood of high systolic BP (OR: 2, CI: 0.9–8.2) and of high diastolic BP (OR: 2.3; CI: 0.6–11.5) in LBW children – Strongest association in females and in adolescents.

C. Famine studies

Site	Key outcome	Ref.	Study type	Sample description	Birth period	Age	Results
Holland	Obesity	Stein et al., 1975; Ravelli et al., 1976	Cross-sectional	Male army draftees exposed/not exposed to famine	1944–5	19y	– Those exposed in first trimester of gestation: no effect on BW, but +80% chance of obesity at 19y, compared to nonexposed – Those exposed after 5 months of gestation: lower BW, but lower likelihood (-40%) of obesity at 19y
		Ravelli et al., 1999	Cross-sectional	702 people born during the Dutch Famine, with detailed prenatal and birth records	1943–7	50+y	– Mothers exposed in early to mid-pregnancy and adequately nourished during the rest of pregnancy gained more weight than mothers exposed in late pregnancy – Babies of mothers exposed in late pregnancy had lower BWs and heights than those of mothers exposed early in their pregnancy – However, at age 50y, those whose mother had been exposed early in pregnancy had higher body weight, BMI, and waist circumference than those exposed late. – Such effect observed only in women. No difference in men. Adjustment for potential confounders hardly changes the findings.
	IGT, insulin resistance	Ravelli et al., 1998	Cross-sectional	Same as above, 741	Same as above	Same as above	– Following OGTT, higher glucose concentrations in exposed than non exposed individuals – Effect particularly marked in people exposed in late gestation – Early exposure resulted in higher BMI in adulthood – Thin babies that became obese had highest concentrations – Increased pro-insulin and 2-h insulin levels in exposed individuals suggest an association with insulin resistance
	Blood lipids and coagu-lation	Roseboom et al., 2000a,b	Case-control	700–725 subjects exposed to famine *in utero*; 650 randomly selected controls in people born the year before, and 650 born the year after the famine	1943–7	50+y	– More atherogenic blood lipid profile among subjects exposed early in intra-uterine life (first 4 mo) compared to those exposed later, or not exposed – Factor VII concentrations but not plasma fibrinogen significantly lower in subjects exposed early in intrauterine life, compared to those expose later, or not exposed
	BP	Roseboom et al., 1999; 2001	Case-control	400 subjects exposed to famine while *in utero*; 442 unexposed subjects (born the year before, or the year after, the famine)	1943–7	50+y	– No effect of prenatal exposure to famine per se on systolic or diastolic BP – Adult systolic BP inversely associated with BW – Adult systolic BP inversely associated with the protein: carbohydrate ratio of maternal diet in weeks 32–38 of gestation, independent of famine exposure

Site	Key outcome	Ref.	Study type	Sample description	Birth period	Age	Results
Holland	CHD	Roseboom et al., 2000c	Case-control	196 subjects exposed *in utero*; 440 unexposed (see above)	1943–7	50+y	– Higher CHD risk in those exposed to famine in early gestation than in nonexposed individuals, independent of maternal weight or size at birth – People with CHD were born to lighter mothers and tended to have lower BW and head circumferences at birth
Finland	Mortality (all causes)	Kannisto, Christensen & Vaupel, 1997	Observational cohorts	Cohorts born during the famine (1866–8), during the 5 previous years, or during the 5 following years	1861–73		– Cohorts born before or during the famine had reduced survival from birth to 17y – No effect on survival in later life (No data on BWs and on cause-specific mortality)
Leningrad	Insulin resistance factors	Stanner et al., 1997	Case-control	169 subjects exposed to rationing *in utero* (and early infancy) during the siege (1941–4); 192 born just before; 188 born outside the siege area	1941–4	50–55y	– No difference in glucose tolerance, insulin, lipids, BP, coagulation factors – Subjects exposed to fetal undernutrition showed evidence of endothelial dysfunction and a stronger influence of obesity on BP – Short adult stature was associated with higher insulin and glucose 2-h post-load, irrespective of siege exposure, but association no longer significant when adjusting for socioeconomic status

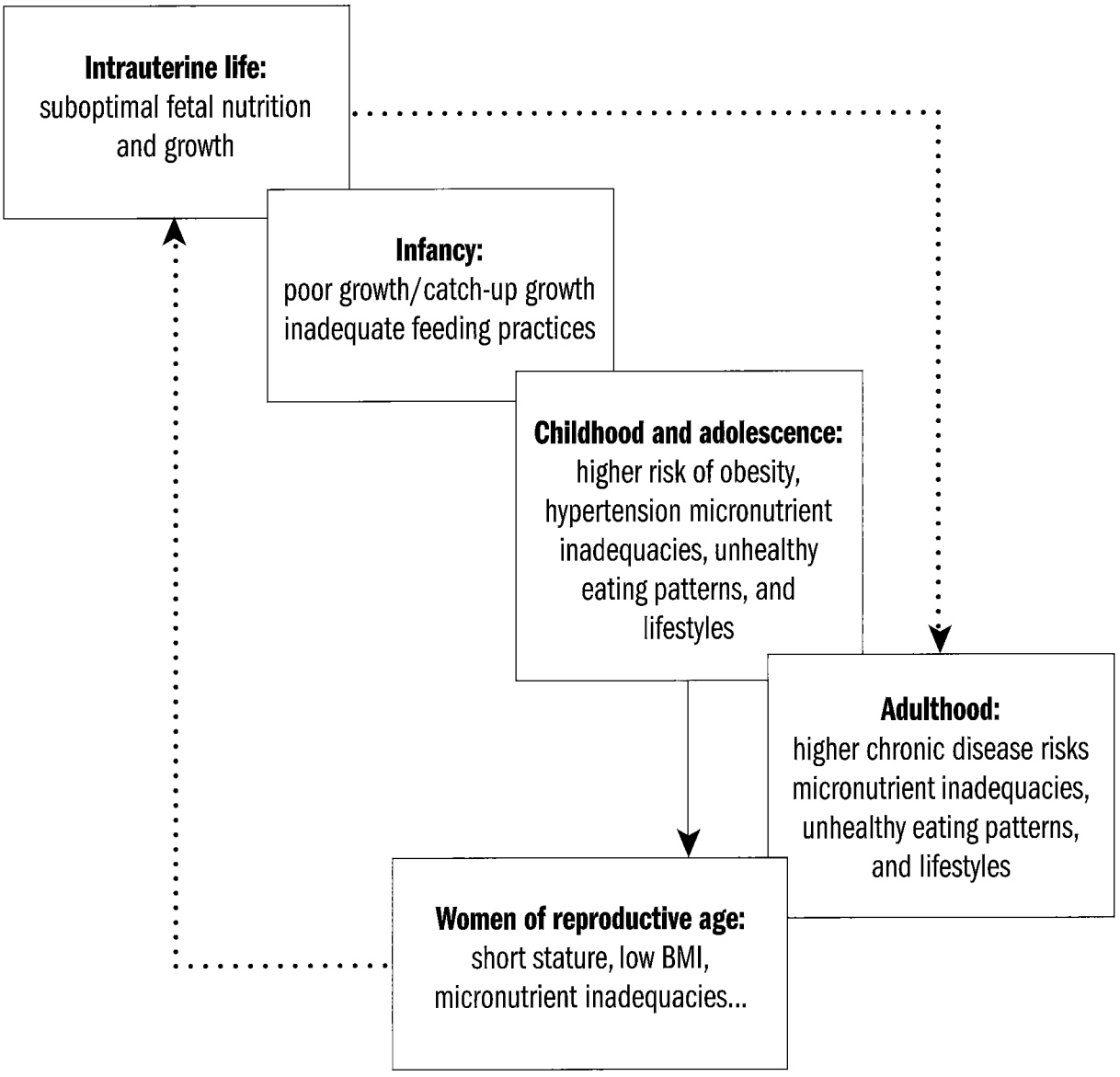
D. Twin studies

Site	Key outcome	Ref.	Study type	Sample description	Birth period	Age	Results
Sweden	Ischaemic heart disease	Vagero & Leon, 1994	Case-control (and nested case-control study among mono- and dizygotic twins)	8,174 female and 6,612 male twins	1886–1925	All those alive in 1971; follow-up for 5y	– Ischaemic heart disease mortality not higher in twins than in singletons – Shorter member of the pair more likely to die of ischaemic heart disease than taller twin, in mono- and dizygotic twins
	Acute myocardial infarction	Hübinette et al., 2001	Case-control	132 same-sexed twin pairs; 118 individually matched control twins	1886–1958		– Cases had significantly lower BW, birth length, and head circumference than external matched twins, but – No anthropometric difference between cases and healthy twins, in within-pair comparisons
New-York, USA	Obesity	Allison et al., 1995	Cross-sectional	2,880 monozygotic twins		40y	– No correlation of weight differential at birth with BMI differential at age 40 – Significant correlation of BW differential with weight, and height differential at 40

Site	Key outcome	Ref.	Study type	Sample description	Birth period	Age	Results
Denmark	Diabetes	Poulsen et al., 1997; 1999	Cross-sectional pop-based study	125 monozygotic twin pairs; 178 dizygotic twin pairs of same sex	1921–40	55–64y	– In twins with normal glucose tolerance and no family history of diabetes, monozygotic twins had higher insulin and glucose concentration 30 min after a glucose load than dizygotic twins – In monozygotic pairs discordant for diabetes, the diabetic members tended to be lighter at birth
Tasmania (Australia)	Systolic BP	Dwyer et al., 1999	Cohort study	55 pairs (including 16 monozygotic pairs)	1988	8y	– In monozygotic twins (16 pairs), non sign. higher BP in the lighter members of pairs – Only trend for higher BP in lighter twins, when mono- and dizygotic twins are combined
New Zealand	BP	Williams & Poulton, 1999	Longi-tudinal study	>800 subjects	1972–3	9 & 18y	– At age 9 and 18y, twins had lower systolic BP than singletons, even after adjusting for direct and indirect effects of BW, sex, maternal height, socioeconomic status, maternal smoking, and concurrent size
England	Systolic blood pressure	Poulter et al., 1999	Historical cohort	492 women twin pairs (including 167 monozygotic pairs)	1940s	Mean age 54y	– In monozygotic twins non sign. higher BP in lighter twins of pairs – When monozygotic and dizygotic twins are combined, sign. higher BP in lighter twins (492 pairs)
Florida, USA	Blood pressure	Levine et al., 1994	Prospective twin cohort	166 viable twin pairs (67 monozygotic)	1976–89	12 months	– Positive correlation of systolic and diastolic BP with body weight from birth to one year of age, but declining from birth to 12 mo – Greater increase in BP during the first year in LBW twins so that differences were smaller at 1y

APPENDIX B

Life cycle chain of risk for diet-related chronic diseases



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