

CHAPTER 2

Developmental Origins of Cardiovascular Disease, Type 2 Diabetes and Obesity in Humans

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Abstract

Fetal growth restriction and low weight gain in infancy are associated with an increased risk of adult cardiovascular disease, type 2 diabetes and the Metabolic Syndrome. The fetal origins of adult disease hypothesis proposes that these associations reflect permanent changes in metabolism, body composition and tissue structure caused by undernutrition during critical periods of early development. An alternative hypothesis is that both small size at birth and later disease have a common genetic aetiology. These two hypotheses are not mutually exclusive. In addition to low birthweight, fetal 'overnutrition' caused by maternal obesity and gestational diabetes leads to an increased risk of later obesity and type 2 diabetes. There is consistent evidence that accelerated BMI gain during childhood, and adult obesity, are additional risk factors for cardiovascular disease and diabetes. These effects are exaggerated in people of low birthweight. Poor fetal and infant growth combined with recent increases in childhood adiposity may underlie the high rates of disease in developing countries undergoing nutritional transition. Sub-optimal maternal nutritional status is a major cause of low birthweight globally but its impact on fetal growth in 'well-nourished' western populations has been inadequately studied. In experimental animals hypertension and insulin resistance can be programmed in the offspring by restricting maternal diet in pregnancy but there are currently insufficient data to determine whether maternal nutritional status and diet programme cardiovascular disease risk in humans.

Low Birthweight and Adult Cardiovascular Disease

The concept that events in early life have long-term effects on human health life is not new. In 1934, Kermack showed that death rates from all causes in the UK and Sweden fell between 1751 and 1930 with each successive year-of-birth cohort.¹ He rejected one possible explanation, that babies were born healthier in successive generations, and concluded that it was the result of social reforms and better childhood living conditions. In 1977, Forsdahl discovered a geographical correlation in Norway between coronary heart disease (CHD) mortality in 1964-67 and infant mortality rates 70 years earlier (1896-1925).² He suggested that growing up in poverty caused 'permanent damage' perhaps due to a 'nutritional deficit', which resulted in 'life-long vulnerability' to an affluent adult lifestyle. Studies in the UK a decade later shifted the

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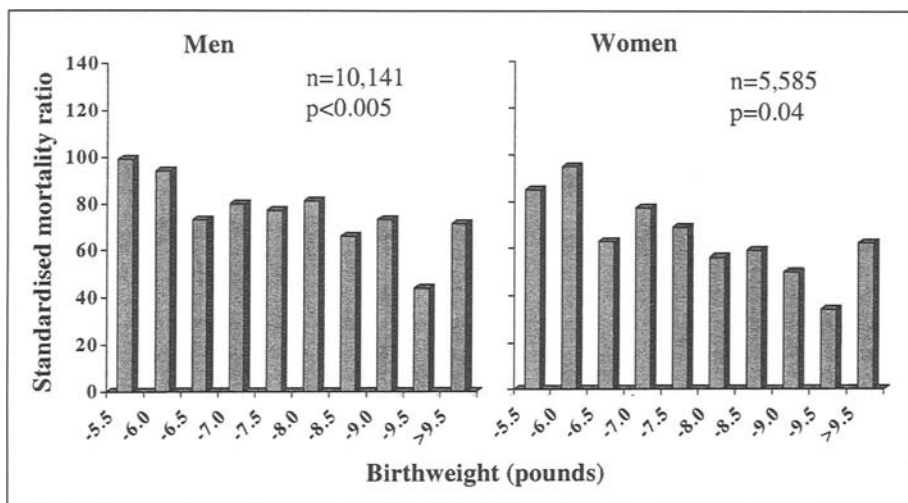


Figure 1. Standardised mortality ratios for cardiovascular disease in men and women born in Hertfordshire, UK, according to birthweight.⁶

focus back to prenatal rather than childhood events. Blood pressure was found to be inversely related to birthweight in young men and women³ and Barker showed that regional differences in stroke and CHD mortality in the UK in 1968-78 were predicted by neonatal mortality (a marker for low birthweight) in 1921-25.⁴ He went on to propose that the roots of cardiovascular disease (CVD) lay in the effects of poverty on the mother and undernutrition in fetal life and early infancy.

Using birth records dating back to 1911-1930 from one English county (Hertfordshire), Barker showed that lower birthweight and weight at one year were associated with an increased risk of death from CHD and stroke.^{5,6} There was an approximate doubling of mortality from the highest to the lowest extremes of birthweight (Fig. 1), similar in men and women. Since then, studies in the UK, Europe, and the USA have confirmed these findings⁷⁻¹⁴ and shown that it is restricted fetal growth rather than preterm delivery which carries the risk of CVD.¹² The effects are linear, graded across the whole range of birthweight (Fig. 1) and independent of adult socio-economic status.^{9,10,12} Many studies were limited to birthweight as a measure of fetal growth but there is evidence that body proportions at birth show stronger associations with CVD. For example low ponderal index (weight/ length³) predicted CHD better than birthweight in Finland,¹¹ and a low birthweight/head circumference ratio predicted stroke mortality in the UK.⁸

CVD Risk Factors

Subsequent work has shown that lower birthweight and other measures of small size at birth are also associated with higher levels of CVD risk factors.

Metabolic Syndrome

Hypertension, type 2 diabetes, insulin resistance, and combinations of these (the Metabolic Syndrome, Insulin Resistance Syndrome or Syndrome X) are consistently related to low birthweight in a large number of studies in different populations.¹⁵⁻²⁵ The strength of these associations led Barker and Hales to suggest that the Metabolic Syndrome should be renamed the 'small baby syndrome'.¹⁶ It is notable that the associations are stronger for disease outcomes, such as hypertension (Fig. 2)²⁶ than for blood pressure measurements.

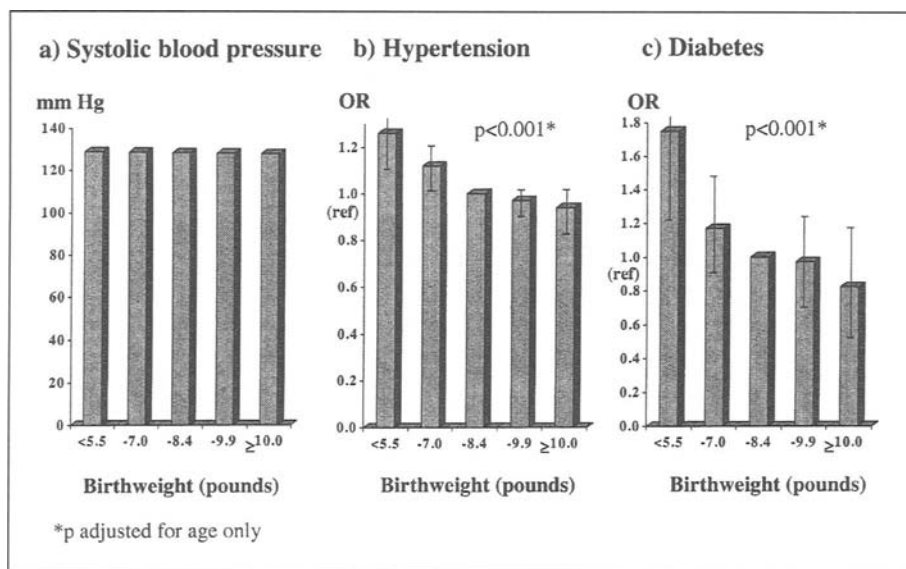


Figure 2. Mean systolic blood pressure and odds ratios for hypertension and incident diabetes in 22,846 US men aged 48-83 years.²⁶

Serum Lipids and Clotting Factors

Although serum lipid concentrations show some associations with size at birth, these are less consistent. Total cholesterol shows a weak inverse association with birthweight.²⁷ HDL-cholesterol concentrations are positively, and triglyceride concentrations inversely, related to birthweight in some²⁸ but not most studies.^{18,21-23,29,30} Post-prandial lipid concentrations, and Lp(a), fibrinogen and factor VII concentrations were unrelated to birthweight in Hertfordshire.^{28,31,32} Total- and LDL-cholesterol, apolipoprotein B and fibrinogen concentrations were associated with smaller abdominal circumference at birth, recorded in obstetric records in Sheffield, UK.^{33,34} PAI-1 was increased in low birthweight men in one published study.²²

Measurements of Cardiovascular Structure and Function

Martyn et al showed that arterial intima media thickness (IMT) and the risk of carotid stenosis, examined using ultrasound, were increased in lower birthweight men and women.³⁵ In a follow up of the Newcastle (UK) 1000 Families Study, carotid IMT was increased in lower birthweight men and in women of lower socio-economic class at birth.³⁶ In the only study to examine peripheral vascular disease in relation to size at birth, ankle brachial pulse index, was not significantly related to birthweight.³⁵ Pulse wave velocity, a measure of poor arterial compliance, was increased in UK men and women with small head and abdominal circumferences at birth,³⁷ but showed no association with size at birth in a study in India.³⁸ Left ventricular mass was unrelated to birthweight in three studies.³⁸⁻⁴⁰ Flow-mediated dilatation, a measure of endothelial function, and indices of microvascular function, are reduced in children and young adults of lower birthweight.⁴¹⁻⁴⁴

Obesity

People of higher birthweight tend to become 'fatter' adults as measured by body mass index^{22,45} (Table 1, Fig. 3). However, there is growing evidence that this reflects increased lean mass rather than adiposity.⁴⁶⁻⁵¹ Higher birthweight men had higher lean but not fat mass, measured using DEXA at the age of 70 years⁴⁹ (Fig. 4). Using anthropometric measurements of

Table 1. Birthweight and adult obesity: Uppsala, Sweden (men, n = 1268)²²

	Birthweight (kg)				p	p*
	<3.25	-3.75	-4.25	⊕4.25		
50 years						
Triceps skinfold (mm) (TR)	10.3	10.9	11.2	11.3	0.02	0.2
Subscapular skinfold (mm) (SS)	17.4	16.6	16.7	16.6	0.5	0.001
SS/TR	1.78	1.60	1.57	1.54	<0.001	<0.001
70 years						
BMI (kg/m ²)	25.9	26.4	26.6	26.8	0.007	–
Waist (cm)	93.7	94.9	95.5	96.2	0.01	0.8
Hip (cm)	99.2	100.4	101.4	101.7	<0.001	0.02
Waist/Hip	0.94	0.94	0.94	0.94	0.9	0.03

p values adjusted for age; p* for age and BMI. Reproduced with permission from Byberg et al. Birthweight and the insulin resistance syndrome: Association of low birthweight with truncal obesity and raised plasminogen activator inhibitor-1 but not with abdominal obesity or plasma lipid disturbances. *Diabetologia* 43:54-60. ©2000 Springer-Verlag.

thigh diameter and skinfold thickness in young men, Kahn showed that the birthweight-BMI association was attenuated by 68% after adjustment for thigh muscle+bone area, but only by 30% after adjustment for subcutaneous fat area.⁴⁷ There is no evidence from these studies that low birthweight leads to increased adiposity, but leptin concentrations were increased in low birthweight men and women in one study.⁵²

There is some evidence that small size at birth is associated with an increased risk of later central obesity (indicated by high waist circumference, waist/hip ratio and subscapular/triceps skinfold ratio). The subscapular/triceps ratio (SS/TR) is consistently higher in adults and children of lower birthweight (Table 1).^{22,53-55} In contrast, although waist circumference and waist/hip ratio are inversely related to birthweight in some studies^{22,56,57} this is

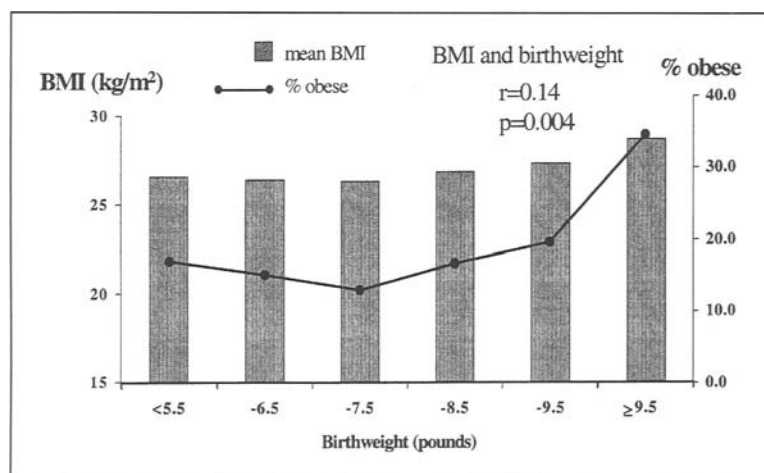


Figure 3. Adult body mass index (BMI) according to weight at birth; Hertfordshire men aged 60-70 years (n = 845).

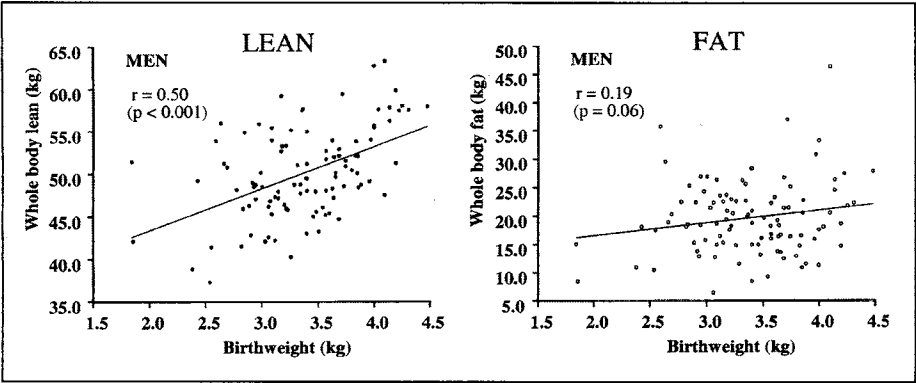


Figure 4. Lean and fat mass measured using dual energy absorption (DEXA) in men aged 70-75 years, born in Sheffield, UK ($n = 102$).⁴⁹ Reproduced with permission from Gale C et al. Intrauterine programming or adult body composition. *J Clin Endocrinol Metab* 86:267-272, ©2001, The Endocrine Society.

weaker and less consistent.¹⁷ Where present, the association may reflect larger hip circumference (and therefore frame size and muscle mass) in higher birthweight individuals, rather than abdominal obesity in people of low birthweight (Table 1).

Post-Natal Growth and Adult Obesity

In addition to size at birth, cardiovascular disease and its risk factors also show associations with patterns of growth in infancy and childhood. In Hertfordshire, men with lower weight at the age of one year had increased cardiovascular disease mortality^{5,6} (Fig. 5) and type 2 diabetes.¹⁵ There are few adult cohorts with infant data but these findings were confirmed in men born in Helsinki, Finland and men and women born in New Delhi, India^{58,59} (Fig. 6). In Hertfordshire, men who had a low weight at one year also had higher left ventricular mass,³⁹

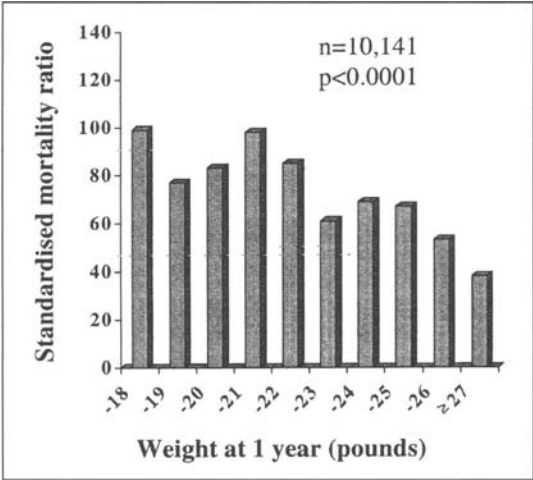


Figure 5. Standardised mortality ratios for cardiovascular disease in men born in Hertfordshire, UK, according to weight at the age of one year.⁶

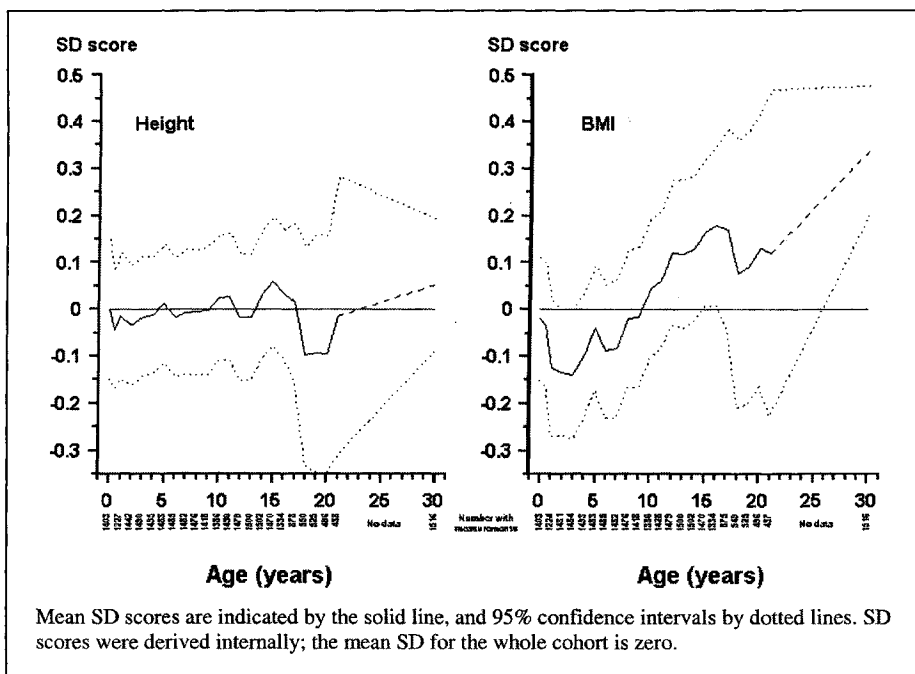


Figure 6. Sex-specific SD scores for height (left) and BMI (right) at every age from birth to 21 years and at 30 years, for men and women in New Delhi, India who developed IGT or diabetes.⁵⁹ Reproduced with permission from Bhargava SK et al. Relation of serial changes in childhood body mass index to impaired glucose tolerance in young adulthood. *N Eng J Med* 350:865-875. ©2004 Massachusetts Medical Society. All rights reserved.

and fibrinogen³² and cholesterol concentrations.²⁹ Adult blood pressure is not related to infant weight.^{15,60}

The relationship between infant weight and weight gain and later health requires further research. It is current pediatric practice to encourage weight gain in low birthweight babies, and this is associated with increased infant survival in some populations.⁶¹ The data described above suggest that infancy may be an accessible stage of the lifecourse in which improved nutrition could benefit adult health. This is controversial however, as studies in children show higher levels of CVD risk factors in children who gained weight rapidly in infancy.⁶²

Greater weight or BMI gain in childhood (after the period of infancy) is consistently associated with an increased risk of later disease. Accelerated childhood weight gain (upward crossing of centiles) was associated with higher blood pressure in young adults in the UK.⁶⁰ Similarly, in the Finland and New Delhi birth cohorts, an increase in BMI SD score between birth and adolescence was associated with an increased risk of CHD and/or type 2 diabetes.^{13,59,63-66} In both cohorts, early adiposity rebound was also associated with increased adult diabetes.^{59,66} The determinants of age at adiposity rebound are unknown, but both studies showed that lower weight at one year predicted an earlier rebound.^{59,66}

Increased BMI in childhood and adult obesity add to, and in some studies interact with, the effects of low birthweight and infant weight. In Finland, an increase in BMI from birth to seven years was only associated with an increased risk of adult CHD in those who were small at birth (Fig. 7).⁶³ The most adverse cardiovascular disease risk profile is consistently

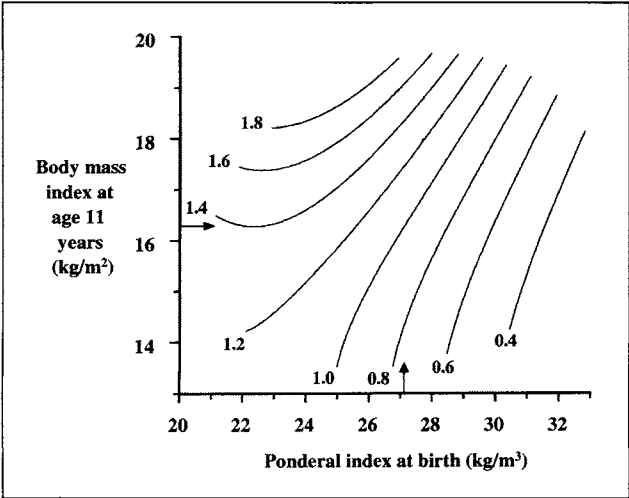


Figure 7. Hazard ratios for death from CHD for men born in Helsinki 1924-33 according to ponderal index at birth and BMI at age 11 years. Arrows indicate average values.⁶³ Reproduced from Eriksson JG et al. Catch-up growth in childhood and death from coronary heart disease: Longitudinal study. *BMJ* 1999; 318:427-431, with permission from the BMJ Publishing Group.

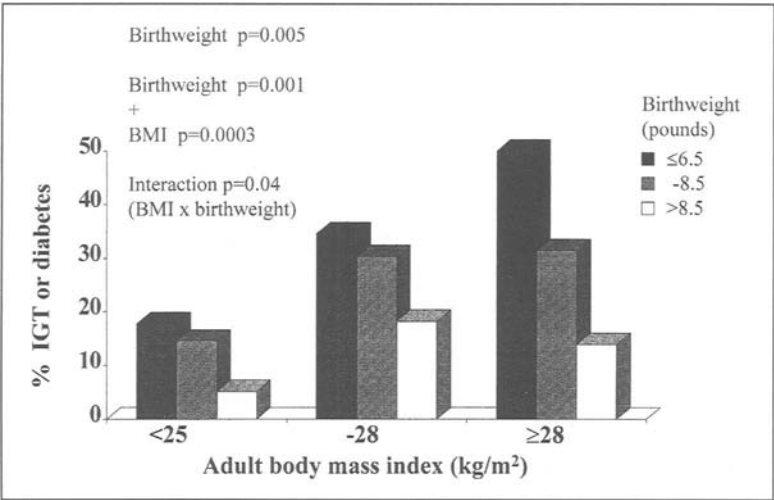


Figure 8. Prevalence of impaired glucose tolerance (IGT) and Type 2 diabetes (%) in Hertfordshire men aged 60-71 (n = 370).¹⁵

found in men and women who were small at birth but became obese adults (Fig. 8).¹⁵ The intriguing corollary of this is that high birthweight may protect against the adverse effects of adult obesity. Similar additive and/or interactive effects have been described between size at birth and other aspects of adult lifestyle, for example between ponderal index at birth and adult socio-economic status on CHD⁶⁷ and between weight in infancy and the effects of smoking on fibrinogen concentrations.³¹

Variation with Sex

In general, relationships between small size at birth and adult cardiovascular disease and risk factors are similar in both sexes. However, in Finland, CHD was most strongly associated with low ponderal index at birth in men and with short birth length in women.^{11,13} The strong associations of type 2 diabetes and cardiovascular disease mortality with low weight at one year in the Hertfordshire men were not seen in women.^{6,15,28} Similarly, apolipoprotein B, fibrinogen and factor VII concentrations, which were inversely related to small abdominal circumference at birth³³ and low weight at one year²⁹ in men, showed no associations with either size at birth or infant weight in women.²⁸

Variation with Ethnicity

Studies from India, Jamaica, China, and Japan, and among US Hispanics and black South Africans have shown associations between lower birthweight and higher blood pressure, glucose intolerance and insulin resistance.⁶⁸⁻⁷³ Higher SS/TR ratios have been shown in Indian children⁵⁵ and white, black and hispanic US children of lower birthweight.⁵⁴ There are some inconsistencies, however. Type 2 diabetes was associated with low birthweight in young Indian adults^{59,74} but with a high ponderal index at birth in older men and women.⁷⁵ A study of blood pressure in children in 5 countries showed differences in associations with birth measurements.⁷⁶ In China and Central and South America, higher blood pressure was associated with 'proportionate' smallness at birth (reductions in birthweight, length and head or chest circumferences), while in Sweden it was associated with 'asymmetrical' smallness at birth (low ponderal index). In Nigeria, blood pressure was not related to size at birth.

Studies in India have shown differences in neonatal body composition from UK babies (Fig. 9).^{77,78} Indian newborns were lighter by almost 2 standard deviations (SDs) and nonfat soft tissues such as muscle (mid-upper-arm circumference) and abdominal wall and viscera (abdominal circumference) showed a similar deficit. Measurements of fat, however, were

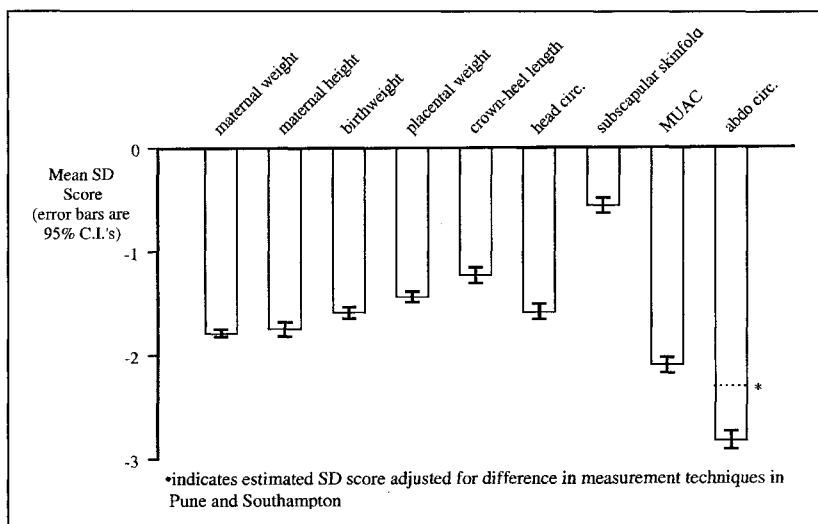


Figure 9. Mean SD scores for maternal prepregnant weight and height, and measurements of the babies, in Pune, India compared with Southampton, UK.⁷⁷ The Southampton mean is represented by 0. Reproduced from Yajnik CS et al. Neonatal anthropometry: The thin-fat Indian baby; the Pune Maternal Nutrition Study. *Internat J Obes* 2003; 27:173-180 with permission of Nature Publishing Group (<http://www.nature.com>).

substantially 'spared'; although small and thin, the Indian babies were relatively adipose. The aetiology and long-term implications of this 'muscle-thin but adipose' or 'thin-fat' phenotype are unknown. However the neonatal findings are of interest because the high rates of type 2 diabetes and CHD among South Asian populations are related to a similar body phenotype in adults.⁷⁹⁻⁸²

The 'Developmental Origins of Adult Disease' (DOHaD) Hypothesis

Barker proposed that the associations between small size at birth and cardiovascular disease reflect permanent effects of fetal undernutrition⁸³ (Fig. 10). The fetus is dependent on the transfer of nutrients from the mother and adapts to an inadequate nutrient supply in a number of ways: prioritisation of brain growth at the expense of other tissues such as the abdominal viscera, reduced secretion of and sensitivity to the fetal growth hormones insulin and IGF-I, and up-regulation of the hypothalamo-pituitary-adrenal (HPA) axis. Barker's 'fetal origins' hypothesis proposed that although occurring in response to a transient phenomenon (fetal undernutrition) these changes become permanent or 'programmed' because they occur during critical periods of development.

The mechanisms by which this could occur at a cellular and tissue level have been reviewed.^{84,85} Programmed changes may include reduced insulin sensitivity,⁸⁶ low muscle mass,⁴⁶ pancreatic beta cell mass⁸⁷ and nephron numbers,⁸⁸ altered arterial structure⁸⁹ and increased left ventricular mass,³⁹ and up-regulation of the HPA axis⁹⁰ and sympathetic nervous system⁹¹ (Fig. 10). The fetal origins hypothesis proposes that these changes not only lead directly to adult cardiovascular disease, but also make the individual more susceptible to environmental stressors such as obesity in later life. The hypothesis is supported by examples in experimental

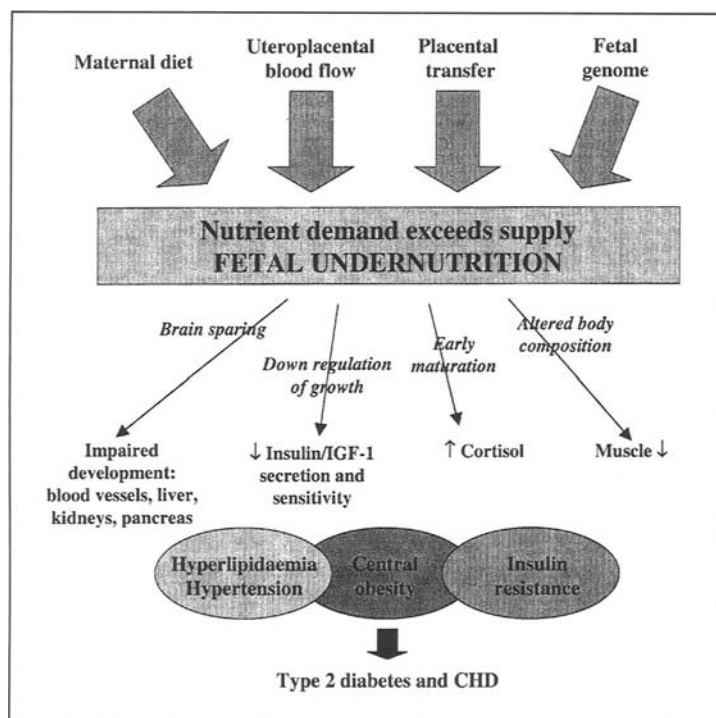


Figure 10. The fetal origins hypothesis.

animals of permanent structural, metabolic, endocrine and behavioural effects resulting from transient nutritional insults in utero, including undernutrition of the mother (reviewed extensively in other chapters in this book).

Associations of cardiovascular disease and risk factors with different body proportions at birth may reflect undernutrition during particular periods in gestation when different tissues and organ systems develop.⁹² It has been suggested that male and female fetuses have different growth priorities and thus adapt differently to undernutrition, reflected in sex differences in associations with neonatal body proportions.⁹² Since size at birth is a strong determinant of infant growth, the associations with low infant weight may reflect prenatal events. Alternatively, since the hyperplastic development of many tissues continues in early infancy, the infant as well as prenatal environment may have programming effects.

There are several reasons why weight gain in childhood, on a background of fetal restriction, might be associated with disease. Low birthweight babies tend to catch-up (compensatory growth), and the rapidity of post-natal growth may simply indicate the severity of fetal growth restriction.⁹³ Alternatively the process of catch-up may be disadvantageous in itself.^{62,94,95} There may be excess demand on other tissues which are not capable of compensatory hyperplasia, such as the pancreas.⁸⁷ Another adverse effect may be altered body composition. McCance observed excessive fat gain in pigs if they were placed on a high plane of nutrition after a period of early post-natal undernutrition. He suggested that this emphasised the development of fat which maintains the capacity for growth throughout life but could not recover muscle tissue which develops earlier and lose the capacity for cell division.⁹⁶ Another possibility is that the hormones driving catch-up growth have adverse cardiovascular and metabolic effects.⁹⁷ Low birthweight children who catch up in weight or height have higher insulin-like growth factor-1 (IGF-I) concentrations, and these in turn correlate with blood pressure.⁹⁸

Because adult disease is linked to both post-and prenatal growth, and because a number of other health outcomes show associations with growth in early life, the term 'developmental origins of adult health and disease' (DOHaD) has supplanted 'fetal origins of adult disease' (FOAD) in recent years.

Genes 'versus' Environment

The fetal origins hypothesis has also been called the 'thrifty phenotype' hypothesis, a name coined by Hales and Barker⁸⁷ after Neel's 'thrifty genotype' hypothesis.⁹⁹ 'Thrifty' can mean 'saving' (storing resources in times of plenty in preparation for leaner times) or 'economy' (making judicious use of meagre resources). Neel suggested that diabetes is caused by 'thrifty' genes that were selected for in mankind's distant past when the supply of food was precarious.⁹⁹ He proposed that they conveyed a 'fast insulin trigger' and thus the ability to store food rapidly as fat (savings) which became diabetogenic in modern times. The thrifty phenotype hypothesis, on the other hand, suggests that the undernourished fetus develops insulin resistance and other metabolic changes as a strategy for immediate survival, to down-regulate and prioritise growth (economy) for which it pays a price later in life, generally after the reproductive period. Both thrifty genes and the thrifty phenotype could become detrimental on exposure to plentiful nutrition. Variations on the thrifty genotype hypothesis are the strongest contenders to the 'fetal origins' hypothesis as an explanation for the associations between low birthweight and CVD risk.

Correlations between parent and offspring birthweights and between birthweights of half-siblings related through either the mother or the father show stronger maternal than paternal effects, which suggests that the 'maternal environment' is a more powerful influence on fetal growth than genes.^{100,101} The birthweights of babies born after ovum donation are strongly related to the weight of the recipient mother but not that of the donor mother.¹⁰² Nevertheless there are significant genetic effects on size at birth.¹⁰³ Hattersley proposed that, since insulin is a major growth hormone in fetal life, genes associated with either insulin resistance or reduced insulin secretion would lead to reduced fetal growth as well as an increased risk of adult diabetes (the 'fetal insulin hypothesis').¹⁰⁴ That this is biologically feasible

is shown by the fact that birthweight is reduced in a number of genetic syndromes causing impaired insulin secretion or insulin resistance.¹⁰³ These are too rare to explain the observed birthweight-disease associations but more frequently occurring polymorphisms, linked both to small size at birth and adult diabetes, have recently been described.¹⁰⁵⁻¹⁰⁷ The robustness of these associations remains to be tested.

Twin studies have classically been used to distinguish between genetic and environmental effects. Studies linking CVD risk to the difference in birthweight within twin pairs have shown inconsistent results. For example a study using the Danish twin registry showed that the smaller of monozygous twin pairs was more likely to become diabetic,¹⁰⁸ but this has not been confirmed elsewhere.¹⁰⁹ The mechanisms underlying the growth restriction of twins differ from those limiting growth in singleton fetuses. Higher disease concordance rates for monozygous than dizygous twins may reflect their shared intra-uterine environment as well as shared genes. Twin-twin interactions, for example the diffusion of steroid hormones from one twin to another, may reduce within-pair differences in programming effects. These features of the biology of fetal growth in multiple pregnancies limit the conclusions that can be drawn, in relation to the fetal origins hypothesis, from twin studies.¹¹⁰

Recent reports of associations between low offspring birthweight and an increased risk of CVD and insulin resistance in the parents (both mothers and fathers) could be evidence of common genetic factors.¹¹¹⁻¹¹⁴ However, intergenerational effects may also have environmental explanations. Assortive mating and shared lifestyle (socio-economic status, nutrition, smoking, and stress) could lead to both low birthweight and later CVD in both parents. Some but not all of these were taken into account in these studies. Associations shown between low offspring birthweight and type 2 diabetes in fathers but not mothers is more powerful evidence of genetic effects.^{115,116} The lack of effect in mothers argues against these resulting from a shared environment. Fathers of low birthweight babies did not, however, have increased insulin resistance or diabetes in two other recent studies from India.^{117,118}

Time trends in CVD and type 2 diabetes in western countries during the 20th century, and the recent rise in developing countries suggest a susceptibility to environmental changes that could have a either a genetic basis or arise from early-life programming. However these would make different predictions for the future. The former would predict continuing high levels of disease unless people reduce their lifestyle risk factors and become less obese. The thrifty phenotype hypothesis would predict a slowdown or downturn in disease as better nutrition of girls and mothers leads to improved fetal nutrition. CHD has been falling in the USA and Europe for 35 years despite increasing adult obesity, and only modest reductions in lifestyle-related risk factors. The incidence of stroke has also fallen since the early 1950s in the UK. In contrast, type 2 diabetes is increasing in all populations worldwide. However, the increase has been less marked in developed than developing countries¹¹⁹ and a fall in incidence has been reported in one population.¹²⁰

With increasing understanding of epigenetic effects and gene-environment interactions, it is no longer possible to think of diseases as being *either* 'genetic' *or* 'environmental'.¹²¹ It was recently shown that an allele of the PPAR- γ gene is associated with increased insulin resistance, but only in men and women of low birthweight.¹²² It is clearly possible to permanently alter gene expression by manipulation of intra-uterine nutrition.¹²³ Such epigenetic effects may persist across generations. For example, feeding 'agouti' mice with a methyl-supplemented diet during pregnancy leads to permanent and heritable effects on offspring coat colour, which is regulated by genes.¹²⁴ Imprinted genes, several of which play a role in fetal growth, are thought to be particularly susceptible to epigenetic effects. It seems likely that environmental effects, genes and interactions between the two contribute to the observed associations linking birthweight to adult disease, and that the DOHaD and fetal insulin hypotheses are not mutually exclusive.

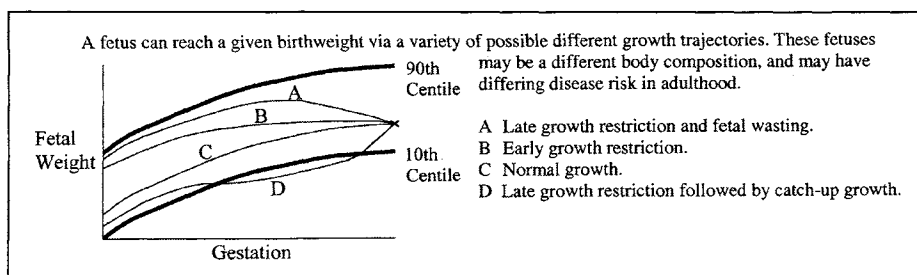


Figure 11. Different fetal growth trajectories.¹²⁸ Reproduced from: Harding JE. The nutritional basis of the fetal origins of adult disease. *Int J Epidemiol* 2001; 30:15-23, by permission of Oxford University Press.

Clinical Importance of the Effects of Poor Fetal Growth

It has been argued that fetal undernutrition is of little clinical importance because statistically birthweight explains little of the variation in adult disease.¹²⁵⁻¹²⁷ Effects are most marked at the extremes of birthweight, where there are relatively fewer individuals. Based on the Hertfordshire data Joseph estimated that 26% of CHD deaths would be averted if all babies weighed 9-9.5 pounds at birth, 9% if babies were born one birthweight category (approximately 1 pound) heavier, and 2% if more realistic increases in birthweight (100-200g) were achieved.¹²⁵

These calculations are potentially misleading. Crude birth measurements and imprecise estimates of gestational age at birth would lead to under-estimation of birthweight effects. Birthweight is an insensitive marker of the dynamic process of fetal growth¹²⁸ (Fig. 11) and does not describe body composition or the development of specific tissues. Babies born to mothers exposed to the Dutch Famine of 1944-45 during early gestation had normal birthweights, and yet an increased risk of adult obesity and dyslipidaemia (see below). The true impact of intra-uterine undernutrition will not be known until there are better markers of programming than birthweight.

A further reason why calculations based on birthweight alone may underestimate the importance of intra-uterine growth is that, as described above, effects of size at birth are conditioned by childhood growth and adult obesity. Data from Finland, show that combinations of birth, infant and childhood measurements predict large differences in the risk of CHD, hypertension and diabetes^{63,64,129} (Table 2).

The Role of Maternal Nutrition

If maternal nutritional status has important programming effects on adult disease, correlations would be expected between measures of maternal nutrition and CVD in the offspring. There are limited data to test this, especially in populations old enough to measure disease outcomes. Those that are available are limited to maternal anthropometry recorded in clinical obstetric notes (usually only weight and height), old diet and nutrition surveys, and famine studies.

Maternal Anthropometry

Several studies have shown that low maternal weight gain, BMI or skinfolds in pregnancy are associated with higher offspring blood pressure,^{130,131} though not consistent in all studies.^{70,132} Low maternal weight or BMI is associated with increased adult insulin resistance in the offspring,⁷⁰ and a study in India showed that CHD was associated with low maternal weight.⁶⁹ Conversely, in Finland, mortality from CHD was increased in men and women whose mothers were short and had a high BMI¹¹ and in India type 2 diabetes in older men and women was strongly associated with higher maternal weight and pelvic diameters.⁷⁵ It is possible that these associations with large maternal size or obesity reflect the effects of gestational diabetes, but this is speculative.

Table 2. Odds ratios (95% CI) for type 2 diabetes and hypertension, and hazard ratios for coronary heart disease according to birthweight and body mass index at 11 years; 13,517 men and women born in Helsinki, Finland, 1924-1944¹²⁹

Birthweight (kg)	Body Mass Index at 11 Years (kg/m ²)			
	-15.7	-16.6	-17.6	>17.6
No. of men and women				
-3.0	991	719	581	560
-3.5	1394	1422	1264	1246
-4.0	827	984	1122	1110
>4.0	167	254	413	463
Type 2 diabetes (698 cases)[†]				
-3.0	1.3 (0.6-2.8)	1.3 (0.6-2.8)	1.5 (0.7-3.4)	2.5 (1.2-5.5)
-3.5	1.0 (0.5-2.1)	1.0 (0.5-2.1)	1.5 (0.7-3.2)	1.7 (0.8-3.5)
-4.0	1.0 (0.5-2.2)	0.9 (0.4-1.9)	0.9 (0.4-2.0)	1.7 (0.8-3.6)
>4.0	1.0 (ref)	1.1 (0.4-2.7)	0.7 (0.3-1.7)	1.2 (0.5-2.7)
Hypertension (2997 cases)[†]				
-3.0	2.0 (1.3-3.2)	1.9 (1.2-3.1)	1.9 (1.2-3.0)	2.3 (1.5-3.8)
-3.5	1.7 (1.1-2.6)	1.9 (1.2-2.9)	1.9 (1.2-3.0)	2.2 (1.4-3.4)
-4.0	1.7 (1.0-2.6)	1.7 (1.1-2.6)	1.5 (1.0-2.4)	1.9 (1.2-2.9)
>4.0	1.0 (ref)	1.9 (1.1-3.1)	1.0 (0.6-1.7)	1.7 (1.1-2.8)
Hospital admissions for coronary heart disease and deaths (1235 cases)*				
-3.0	1.4 (0.8-2.4)	1.6 (0.9-2.8)	1.8 (1.0-3.2)	2.1 (1.1-3.8)
-3.5	1.3 (0.7-2.2)	1.5 (0.9-2.7)	1.5 (0.8-2.6)	1.6 (0.9-2.9)
-4.0	1.3 (0.7-2.3)	1.4 (0.8-2.4)	1.3 (0.8-4)	1.4 (0.8-2.6)
>4.0	1.0 (ref)	1.2 (0.6-2.3)	1.1 (0.6-2.1)	1.0 (0.5-1.8)
Deaths from coronary heart disease (480 cases)*				
-3.0	1.4 (0.5-4.0)	1.8 (0.6-5.1)	2.1 (0.7-6.2)	3.0 (1.0-8.6)
-3.5	1.4 (0.5-3.9)	1.9 (0.7-5.2)	2.2 (0.8-6.1)	2.7 (1.0-7.6)
-4.0	1.9 (0.7-5.3)	1.8 (0.7-5.2)	1.7 (0.6-4.8)	1.6 (0.6-4.5)
>4.0	1.0 (ref)	1.4 (0.4-4.6)	1.6 (0.5-4.7)	1.3 (0.4-4.0)

[†]Odds ratios adjusted for sex and year of birth. *Hazard ratios adjusted for sex and year of birth. Reproduced from Barker DJF et al. Fetal origins of adult disease: Strength of effects and biological basis. *Internat J Epidemiol* 2002; 31:1235-1239, by permission of Oxford University Press.

Famine Studies

In 1944-45 part of the Netherlands suffered a period of famine when rations fell to <800 calories a day (the Dutch Hunger Winter). The population was well-nourished prior to the famine and food supplies were restored after 5 months. Pregnant mothers experienced extreme undernutrition for sharply delineated periods of gestation. Birthweights were normal among women exposed to famine in early gestation, but reduced by 350 g in those exposed in late gestation.¹³³ An early follow-up study showed increased obesity in young men whose mothers experienced famine in early gestation.¹³⁴ Cardiovascular disease risk factors were recently measured in 700 men and women born before, during and after the famine. Late gestation exposure was associated with glucose intolerance, increased insulin resistance, and an increase in type 2 diabetes, compared with subjects conceived after the famine.¹³⁵ Early gestation exposure was associated with higher LDL/HDL cholesterol concentrations¹³⁶ and (in women) higher BMI and waist circumference. Famine exposure was associated with increased infant mortality, but there were no effects on adult mortality (so far assessed only up to the age of 50 years).¹³⁷

Stanner compared men and women exposed to famine during the 1941-42 Siege of Leningrad with subjects born outside the siege area.¹³⁸ The famine lasted longer and was less acute in onset and termination than the Dutch famine, and birthweights were not recorded. Those exposed to famine in utero and/or in infancy showed increased subscapular/triceps skinfold ratios, diastolic blood pressure, ischaemic changes on ECG, and PAI activity and antigen, but lower factor VII concentrations than unexposed subjects. Unlike the Dutch study, there were no effects on glucose and insulin measurements. Men and women exposed in infancy were more likely to complain of angina than the in utero exposed group.

In rural Gambia, there is an annual cycle of adequate nutrition (harvest season) alternating with severe undernutrition during the rains (hungry season). Moore et al studied CVD risk factors in young adults for whom month of birth and infant anthropometric records were available.¹³⁹ There were no differences between season of birth groups (hungry vs. harvest) in blood pressure, fasting plasma glucose, insulin, lipid, fibrinogen or cortisol concentrations, or post-load glucose and insulin concentrations in an oral glucose tolerance test. Risk factors were not related to the subjects' weight-for-age in infancy and childhood.

Follow-Up of Diet and Nutrition Surveys and Trials

Three studies suggest that the balance of maternal protein and carbohydrate intakes during pregnancy is related to blood pressure in the offspring. During 1948-54 pregnant women attending Aberdeen Maternity Hospital recorded 7-day food diaries in late gestation. The offspring were traced and studied at the age of 40 years.^{140,141} Blood pressure was not directly related to maternal intakes of energy, protein, fat, carbohydrate, calcium, or a range of vitamins. At low maternal protein intakes (<50 g/day) a higher percentage calorie intake from protein was associated with lower offspring blood pressure. The reverse was true at high protein intakes.¹⁴⁰ In an attempt to replicate these findings, Shiell et al studied young men and women born in Motherwell, Scotland 1952-76, where mothers were advised to eat a high-meat low carbohydrate diet to prevent preeclampsia.¹⁴² Dietary intakes of 10 foods were recorded by trained staff. Protein intakes were higher than in Aberdeen (88g v 73 g). High intakes of meat and fish were associated with higher blood pressure. The highest blood pressures were found in men and women whose mothers had high meat/fish intakes but low intakes of green vegetables (Table 3). In a study in the Philippines, maternal intakes of protein, fat and energy were measured in late gestation and the children followed up in adolescence.¹⁴³ In boys, a higher percentage of maternal energy derived from protein, and in girls a higher percentage derived from fat, were associated with lower blood pressures. Mean protein intakes were not reported but are likely to have been low in this population.

Cardiovascular risk factors were recently measured in men and women whose mothers took part in the Oxford Nutrition Survey during 1942-1944, in which blood samples were taken in the third trimester to measure maternal vitamin A, C, B1 and phosphatase status.¹⁴⁴ No associations were found between these indices of maternal nutrition and offspring blood pressure, glucose and insulin or lipid concentrations.

These studies have many limitations, namely crude measures of diet and nutrition and large losses to follow-up. It is difficult to make much sense of their combined results. The data suggest that the balance rather than absolute intakes of protein and carbohydrate may influence blood pressure in the offspring, and that both low and high protein intakes may have adverse effects. They also suggest there may be maternal diet effects not mediated by reductions in birthweight. So far, there is no strong evidence that normal variations in dietary intakes during pregnancy have important effects on CVD risk in the offspring, but this has not been sufficiently studied. A number of prospective studies of maternal diet in pregnancy, specifically designed to investigate long-term outcomes in the offspring, are due to report outcomes in the children in the next few years.¹⁴⁵⁻¹⁴⁷

Table 3. Mean systolic blood pressure of men and women, adjusted for gender, body mass index, alcohol consumption, and cuff size according to their mother's consumption of meat, fish, and green vegetables in late pregnancy¹⁴²

Green Vegetables (portions/wk)	≤11	Meat and Fish (portions/wk)			All	Regression Coefficient (mm Hg/portion/wk)		
		-15	-21	>21		β	95% CI for β	p
<7	120 (131)	120 (93)	123 (54)	124 (41)	121 (319)	0.26	0.03-0.50	0.03
≥7	118 (58)	120 (94)	120 (74)	121 (81)	120 (307)	0.16	-0.06-0.38	0.16
All	119 (189)	120 (187)	121 (128)	122 (122)	120* (626)	0.19	0.04-0.35	0.02

Number of subjects given in parentheses. Overall SD = 11.5 mm Hg. Adapted from Shiell et al. Hypertension 2001; 38:1282-8.

In the only follow up study so far of a randomised controlled trial of a nutritional intervention in pregnancy, Belizan studied children born during a trial of maternal calcium supplementation in Argentina. Supplementation was associated with lower blood pressure.¹⁴⁸

Maternal Diabetes and Fetal Macrosomia

Although the main focus of this chapter is fetal growth restriction, recent data show that maternal gestational diabetes, which results in fetal overgrowth (macrosomia) also has adverse long-term effects. Offspring of diabetic mothers have an increased risk of obesity and type 2 diabetes compared with offspring of nondiabetic mothers or women who became diabetic after the pregnancy (Fig. 12).^{149,150} Gestational diabetes produces a U-shaped relationship between birthweight and adult type 2 diabetes.¹⁵¹⁻¹⁵³ With increasing obesity worldwide, gestational diabetes is also increasing¹⁵⁴ and may make an important contribution to the rising incidence of type 2 diabetes.

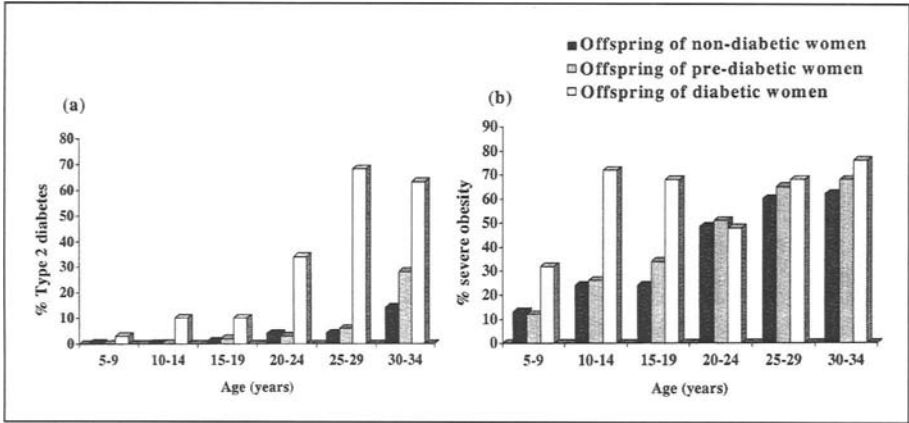


Figure 12. Prevalence of (a) type 2 diabetes and (b) obesity in offspring of nondiabetic, prediabetic and diabetic women (Pima Indians).¹⁴⁹ Reproduced from Dabelea et al. Effect of diabetes in pregnancy on offspring: Follow-up research in Pima Indians. J Mat Fet Med 2000; 9:83-88 with permission from Taylor & Francis Ltd (<http://www.tandf.co.uk/journals>).

Conclusions: Public Health Implications and Future Research

The 'developmental origins' hypothesis is attractive because it suggests that common degenerative diseases could be prevented by improving maternal health and fetal, infant and childhood development. Although it is not clear what optimal growth is and how it can be achieved, it may be more attainable than persuading middle-aged adults to return to 'primitive' lifestyles, and more positive than concluding that large numbers of people have genes incompatible with modern life. Data from experimental animals provide powerful evidence that a mother's nutrition programmes the metabolism of her offspring. However, there is currently insufficient evidence that maternal nutrition underlies CVD in humans. Future research should focus on the determinants of fetal growth, including maternal diet, and incorporate follow-up of the children for CVD-related outcomes. More research is needed into the long-term effects of weight gain in infancy. However, there is ample evidence to support efforts to prevent excessive BMI gain in childhood and this should be a public health priority. Current data suggest that the greatest benefit in terms of future risk-reduction will be in low birthweight individuals. Epidemiological research should go hand in hand with studies of the genes known to influence fetal growth, those associated with cardiovascular disease, and gene-environment interactions.

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