

Fetal Programming and the Risk of Noncommunicable Disease

Caroline H. D. Fall

Received: 20 January 2012 / Accepted: 15 June 2012 / Published online: 25 July 2012
© Dr. K C Chaudhuri Foundation 2012

Abstract The “developmental origins of health and disease” (DOHaD) hypothesis proposes that environmental conditions during fetal and early post-natal development influence lifelong health and capacity through permanent effects on growth, structure and metabolism. This has been called ‘programming’. The hypothesis is supported by epidemiological evidence in humans linking newborn size, and infant growth and nutrition, to adult health outcomes, and by experiments in animals showing that maternal under- and over-nutrition and other interventions (*e.g.*, glucocorticoid exposure) during pregnancy lead to abnormal metabolism and body composition in the adult offspring. Early life programming is now thought to be important in the etiology of obesity, type 2 diabetes, and cardiovascular disease, opening up the possibility that these common diseases could be prevented by achieving optimal fetal and infant development. This is likely to have additional benefits for infant survival and human capital (*e.g.*, improved cognitive performance and physical work capacity). Fetal nutrition is influenced by the mother’s diet and body size and composition, but hard evidence that the nutrition of the human mother programmes chronic disease risk in her offspring is currently limited. Recent findings from follow-up of children born after randomised nutritional interventions in pregnancy are mixed, but show some evidence of beneficial effects on vascular function, lipid concentrations, glucose tolerance and insulin resistance. Work in experimental animals suggests that epigenetic phenomena, whereby gene expression is modified by DNA methylation, and which are sensitive

to the nutritional environment in early life, may be one mechanism underlying programming.

Keywords Fetal programming · Developmental origins of health and disease (DOHaD) · Birthweight · Childhood growth · Epidemiologic transition · Noncommunicable chronic disease

Abbreviations

CHD	Coronary Heart Disease
CVD	Cardiovascular Disease
GDM	Gestational Diabetes Mellitus
LMIC	Low and Middle Income Countries
PMNS	Pune Maternal Nutrition Study

Introduction - The Global Rise of Chronic Noncommunicable Disease

The 20th century witnessed large changes in the patterns of disease and mortality across the world, with reductions in infectious disease mortality, and a rise in chronic noncommunicable cardio-metabolic diseases such as cardiovascular disease (CVD) and type 2 diabetes [1]. This transition started in the most affluent nations, but is now well under way in low and middle income countries (LMICs) like India [2]. The number of cases of diabetes in the Indian sub-continent is predicted to rise by over 70 %, from around 46 million in 2007 to 80 million in 2025 [3]. Cardiovascular disease mortality has reached a plateau in high income countries, and is falling in many, but is still rising in LMICs and is now the commonest cause of death among Indian adults [2]. Although diabetes is increasing everywhere, the rate of rise is fastest in LMICs [3], and due to an earlier onset of disease and complications, and the high cost of treatment, this presents a serious threat to economic growth. Why should this be of concern to pediatricians?

C. H. D. Fall (✉)
MRC Lifecourse Epidemiology Unit, University of Southampton,
Southampton General Hospital,
Southampton, Hampshire SO16 6YD, UK
e-mail: chdf@mrc.soton.ac.uk

The Connection with Factors Acting in Early Life

It is well-known that CVD and type 2 diabetes are diseases of adult lifestyle. Smoking, high-energy and high-fat diets, and a lack of physical exercise, which lead to overweight, hypertension, dyslipidemia and other metabolic changes (e.g., increased pro-inflammatory cytokines), are risk factors for both diseases [3, 4]. However, research over the last 20 y, has shown that adult lifestyle is not the whole story. In 1977, Forsdahl discovered a geographical correlation within Norway between coronary heart disease (CHD) mortality in 1964–67 and infant mortality rates 70 y earlier (1896–1925) [5]. 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 by Barker and colleagues, a decade later, shifted the focus to *pre-natal* rather than childhood events. Differences between UK local authority areas in neonatal mortality (a marker for poverty and low birthweight) in 1921–25 predicted death rates from stroke and CHD in 1968–78 [6]. The subsequent discovery, in the UK country of Hertfordshire, of ledgers recording birthweights of men and women born during 1911–1930 made it possible to show that lower birthweight and weight at one year were associated with an increased risk of later death from CHD and stroke [7]. The effects were linear and graded across the range of birthweight, with no evidence

that they were limited only to low birthweight individuals. It has since been shown that lower birthweight is also associated with higher rates of adult hypertension, type 2 diabetes and metabolic syndrome [8].

The Fetal Programming Hypothesis

Based on these data, Barker suggested the roots of cardiovascular disease lay partly in the effects of poverty on *mothers*, resulting in undernutrition during critical periods of development during fetal and early post-natal life [9]. In the ‘fetal programming hypothesis’ (sometimes called the ‘Barker hypothesis’), he proposed that fetal under-nutrition could occur for a variety of reasons, including poor maternal diet and/or problems with the mobilisation and transfer of nutrients from mother to fetus (Fig. 1), an example of programming [10]. In the face of this threat to survival, the fetus makes adaptations to limit its growth, prioritise the development of essential tissues, and hasten maturation. For example, there is a reduction in the blood supply to the lower body and limbs to preserve brain blood flow, and with it the sacrifice of muscle deposition and the development of the liver, pancreas and kidneys. The secretion of and sensitivity to hormones that promote fetal growth (e.g., insulin and insulin-like growth factors) is reduced. The hypothalamo-pituitary-adrenal axis is up-regulated to advance fetal maturation. Barker

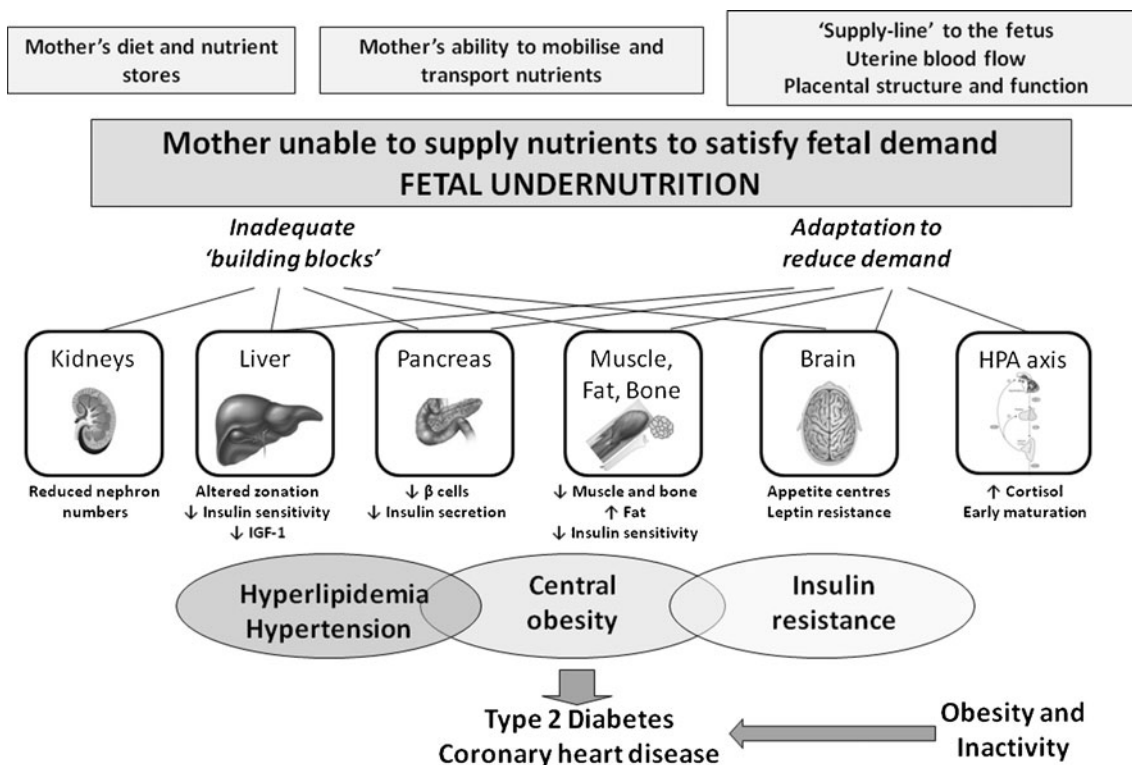


Fig. 1 The fetal programming hypothesis. Reproduced with permission from Fall C et al. Annals of Human Biology 2011

argued that these changes in the fetus or young infant became permanent, an example of the biological phenomenon known as ‘programming’ [11].

Small Becoming Big

The hypothesis suggested that the programmed fetus or young infant remained permanently vulnerable to later cardio-metabolic disease. This fitted well with findings in the early Hertfordshire studies, and confirmed elsewhere, that the highest risk of cardio-metabolic disease was in men and women who had evidence of early-life deprivation (lower birthweight or infant weight) and who had become overweight as adults (‘small becoming big’); those whose early development had been compromised and whose later lifestyles stressed the homeostatic systems most strongly [8]. It is important to make the point here that it would be a misconception to think that lower birthweight, in *itself*, causes later disease, but rather the early-life re-structuring of the body’s tissues, and re-setting of endocrine and metabolic axes. The associations with birthweight occur because the same insults that programme function often also reduce growth and lower birthweight. Studies have shown that programming can occur in the absence of changes in birthweight [11].

Over-nutrition as well as Under-nutrition

Maternal diabetes during pregnancy exposes the fetus to an excess of nutrients. Diabetic mothers are not only hyperglycemic, but also have elevated circulating lipids and amino acids. The fetal pancreas and liver are stimulated to secrete increased insulin and insulin-like growth factors, both of which are growth-promoting hormones in the fetus. This results in the well-described macrosomic infant of the diabetic mother. Freinkel suggested that this could cause obesity and diabetes in later life (“fuel mediated teratogenesis”) [12] and it is now established that gestational diabetes is a risk factor for later diabetes in the offspring [13]. There are therefore problems at both ends of the birthweight spectrum. In most populations, the prevalence of gestational diabetes is low, and the predominant pattern is the association of lower birthweight with higher diabetes risk, except in very large studies such as the US Nurses’ Study, in which a small upturn in risk is visible at the high end of the birthweight range [14] (Fig. 2). In populations with a very high prevalence of gestational diabetes, such as the Pima Indians, the curve becomes truly U-shaped (Fig. 2).

There is increasing interest in whether maternal obesity also programmes cardio-metabolic risk in the children. Like the diabetic mother, an obese mother has increased circulating

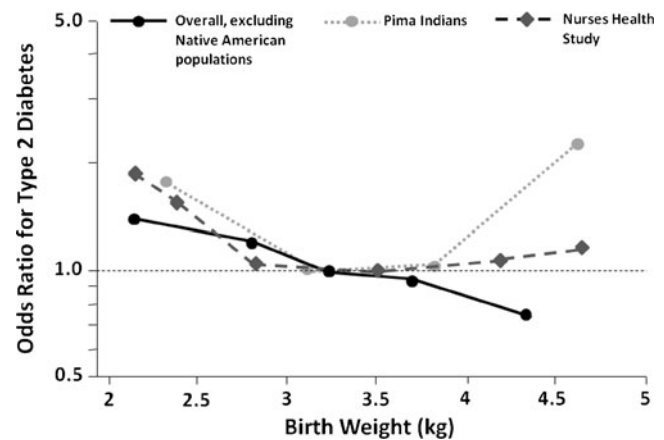


Fig. 2 Odds ratios for type 2 diabetes in relation to birthweight in all studies (excluding Native American populations), the US Nurses’ Health Study, and Pima Indians (adapted from reference 14)

glucose, insulin, lipids and pro-inflammatory factors [15] and potentially exposes the fetus to ‘fuel-mediated teratogenesis’. Newborn adiposity increases with maternal glucose concentrations even in the sub-diabetic range [16]. There is mounting evidence linking maternal obesity during pregnancy to obesity and the metabolic syndrome in the children [17], though better evidence of a causal link is awaited.

Programming by Fetal Nutrition - Proof of Principle in Animal Models

Work in animals has shown that fetal undernutrition, achieved either by under-nourishing the mother during pregnancy or by impairing the fetal nutritional supply line (uterine artery ligation or placental reduction) produces hypertension and diabetes in later life [18–20]. For *e.g.*, feeding rat mothers a moderately protein restricted diet or a severe ‘globally’ restricted diet from conception until the end of pregnancy or lactation leads to cardio-metabolic changes (increased adiposity, insulin resistance, glucose intolerance, dyslipidemia, endothelial dysfunction and hypertension) in the adult offspring. In these animal experiments, the development of diabetes in the offspring is associated with permanent changes at tissue level (*e.g.*, reduced pancreatic beta cell mass), cellular level (*e.g.*, altered mitochondrial numbers) and molecular level (*e.g.*, altered expression of genes regulating the insulin signalling pathway). In addition, animal studies have shown that over-nutrition, achieved by feeding mothers high-energy diets, or making the mother obese, or diabetic, causes insulin resistance and diabetes in the offspring [18–20]. This work provides proof of principle of nutritional programming of chronic disease in later life and has led to the rapidly growing field of science known as the Developmental Origins of Health and Disease (DOHaD).

Inter-generational Effects

Early-life programming is one mechanism whereby there is inter-generational (mother-offspring) transmission of disease risk (Fig. 3). If maternal under-nutrition and poor fetal development recur across generations (left-hand circle), the children are at risk of developing adult cardio-metabolic disease, especially if they become overweight or obese post-natally ('small becoming big'). If the child is a female, she is at risk of becoming diabetic in pregnancy, leading to fuel-mediated teratogenesis, and exposing the fetus to another route to later cardio-metabolic risk (right-hand circle).

Mechanisms of Programming

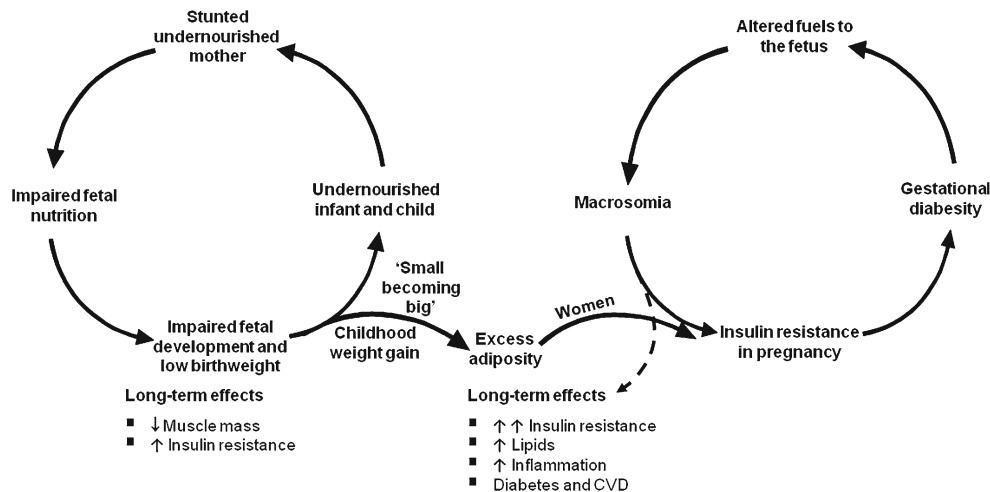
The structural and physiological changes that occur in response to fetal nutrition may result simply from inadequate nutrients or 'building blocks' for the growth of specific tissues. It is likely, however, that they also occur as orchestrated adaptations to reduce fetal demand and enable fetal survival (Fig. 1). Waterland has described the ways in which these changes could then become permanent: alterations in cell number, or clonal selection of particular types of cells, in tissues with finite periods of growth and differentiation; or by altered patterns of gene expression ('metabolic differentiation') [21]. Gene expression is regulated by modifiable 'epigenetic marks' on DNA, including methyl groups and histones. These marks differ between tissues, enabling cells with the same genetic code to have a variety of functional phenotypes. Patterns of DNA methylation are largely established during embryogenesis, fetal development and early postnatal life, and are sensitive to the nutritional environment [22]. For *e.g.*, maternal protein restriction during pregnancy, which causes hypertension in the offspring, appears to act, at least partially, through altered methylation and expression of specific genes. Both the altered methylation

and the metabolic abnormalities can be prevented by supplementing the maternal diet with folic acid, an important component of the biochemical pathways involved in the generation of methyl groups [23]. Other experimental animal models have shown effects of methyl-donor nutrients in the mother, like folic acid and vitamin B12, on gene methylation and the development of obesity, insulin resistance and diabetes in the offspring [24, 25]. The science of epigenetics is in its infancy, and there are few data from humans. However, epigenetic changes have been shown in the offspring of women exposed to the Dutch famine [26] and epigenetic variation has been related to childhood adiposity [27]. Epigenetic phenomena are exciting because of their potential to explain the link between the pre-natal environment and metabolic disease in later life. Epigenetic patterns can be inherited from one generation to the next and could therefore also explain inter-generational effects [28].

Evidence for Early-life Programming in India

Indian researchers have been active in the field of DOHaD since its inception and have studied populations at different stages of the epidemiologic transition, including rural subsistence farmers, urban slum-dwellers and urban middle class. Initial studies were, as in Hertfordshire, based on historical birth records, from which children and adults were traced and investigated. The first was a study among children in Pune, and showed higher blood pressure, insulin resistance and serum lipids in children of lower birthweight, especially if they were currently relatively heavy [29] (Fig. 4a). This study showed that changes in insulin concentrations were detectable in young children, an important step for DOHaD research as it showed that individuals need not necessarily be followed up into late middle age to detect cardio-metabolic programming. Other birth cohort studies in Mysore (children, insulin resistance) and New Delhi (adults, glucose tolerance), this time

Fig. 3 Inter-generational pathways of fetal programming



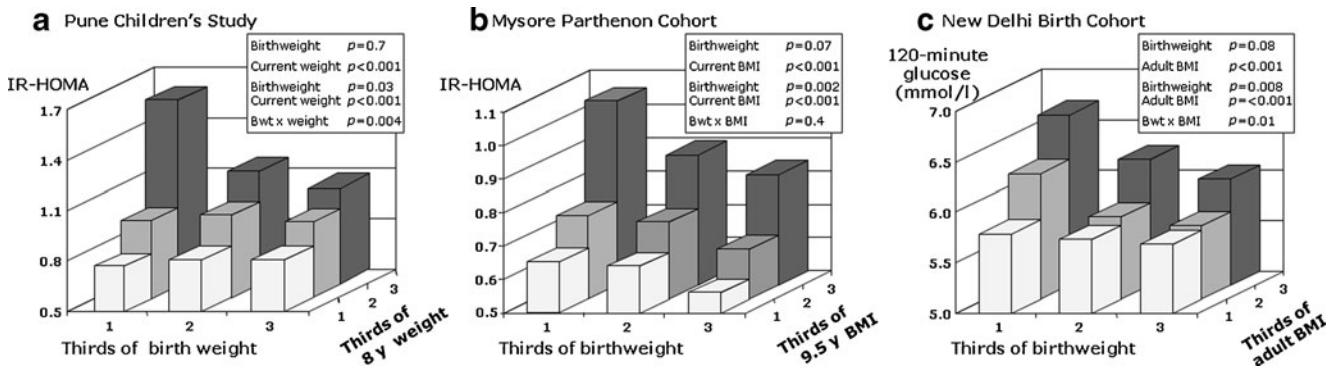


Fig. 4 Cohort studies, including these three from India, consistently show that lower birth weight followed by the development of above average weight or BMI in childhood or adulthood is associated with

increased insulin resistance, and in adulthood by impaired glucose tolerance (adapted from references 29, 30 and 31)

using prospective cohort designs following the mothers from pregnancy and the offspring at numerous ages post-natally, have replicated this pattern [30, 31] (Fig. 4, b and c).

The New Delhi birth Cohort Study (NDBC), which was set up in 1969, has been followed up by one of its founders, Santosh Bhargava, almost continuously to the present day [31]. The participants are now aged 40–42 y, an age at which non-communicable chronic disease is likely to start emerging clinically. The cohort illustrates the transition experienced in urban Indian populations; in childhood less than 1 % of the cohort was obese, indeed many were undernourished. However, as adults aged 29 y, 10 % were obese ($>30 \text{ kg/m}^2$) and 4 % were already diabetic. At age 36 y, the prevalence of obesity and diabetes had doubled to 23 % and 10 %, respectively [32]. The cohort members had weight and height measured frequently during their growing years. This enabled detailed analysis of the growth patterns associated with adult disease. Figure 5 shows (heavy line) the mean BMI Z-score throughout childhood for the ~200 individuals out of ~1400 studied, who developed type 2 diabetes or pre-diabetes (impaired glucose tolerance) by the age of 29 y, compared to the rest of the cohort (shown as the horizontal zero line) [31]. They were thinner than the rest of the cohort at birth, and became relatively even thinner during infancy. However from the age of around 3–4 y, their BMI began to rise, crossing the cohort mean at about 10 y of age, and continuing upwards to reach an adult BMI much higher than the rest of the cohort. This suggests that the process of becoming obese starts very early in life, and that tackling it only in adult life may be too late. The graph also shows that, in this cohort, because of their small size at birth and during infancy, the at-risk children were not recognisably obese as children, and were actually below average BMI until about 10 y. They were, however, on an upward BMI path, at increased risk because of their low early (birth and infant) weights. A similar pattern of childhood growth was related to diabetes risk in a mixed rural–urban birth cohort in South India (Vellore) [33].

Research in India has also confirmed the increased diabetes risk associated with being the infant of a diabetic mother. Krishnaveni and colleagues followed up women enrolled in the ante-natal clinic of the Holdsworth Memorial Hospital in Mysore and found that 6 % developed gestational diabetes (GDM) [34]. The children have been followed up to the age of

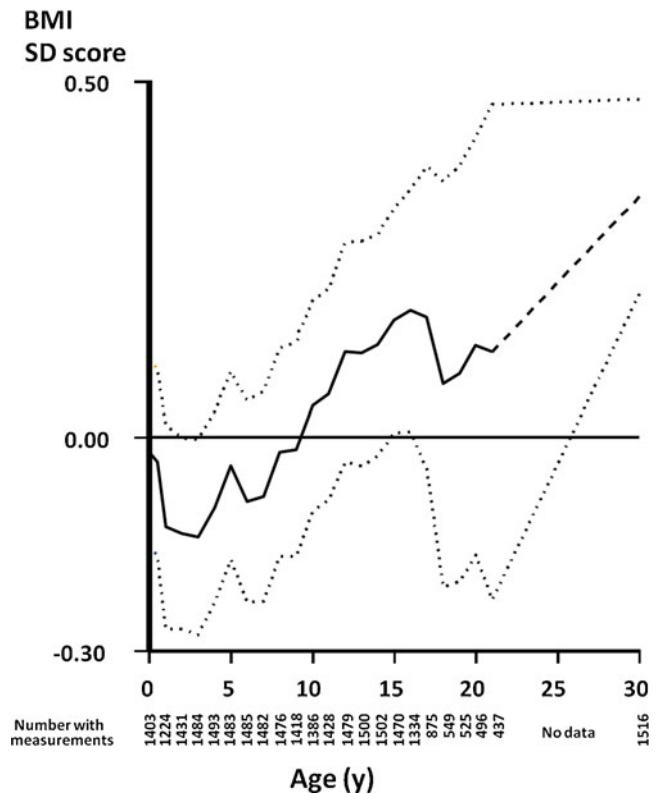


Fig. 5 Body mass index during childhood and adult life among members of the New Delhi Birth Cohort who developed pre-diabetes or diabetes (heavy line), compared with the rest of the cohort (represented by the zero line). The dashed line represents years in which no data were collected (between the ages of 21 and 28 y). The dotted lines represent 95 % confidence intervals. Adapted with permission from reference 31

9.5 y, when those born to GDM mothers were more adipose and had significantly higher plasma insulin concentrations than the rest of the cohort.

The Thin-fat Indian Newborn

In the first study in India specifically designed to examine associations of maternal diet and nutritional status in pregnancy with long-term cardio-metabolic outcomes, Yajnik et al. set up the Pune Maternal Nutrition Study (PMNS) in an agricultural community in rural Maharashtra [35, 36]. An important finding was that the Pune newborns were lighter than white caucasian UK newborns, but while having markedly reduced abdominal and mid-arm circumferences (interpreted to indicate low muscle and visceral mass) they had skinfolds that were similar to UK neonates, suggesting relatively preserved body fat [36]. Newborn MRI scans have shown increased intra-abdominal fat depots at birth in Indian newborns compared with UK white caucasian babies [37]. This 'thin-fat' newborn phenotype resembles the adult Indian phenotype (low muscle mass, central adiposity) that is thought to partly explain the high diabetes risk of Indians.

The PMNS showed associations of maternal diet and nutritional status with newborn size; while there were no associations with energy and protein intakes, mothers who ate green leafy vegetables, fruit and milk more frequently had heavier and larger newborns, suggesting the possible importance for fetal growth of maternal micronutrient nutrition [35]. These associations were seen even after adjusting for social and biological factors known to influence newborn size, such as maternal body size, education, socio-economic status and physical workload. Maternal folate concentrations in pregnancy also positively predicted birth measurements, while higher homocysteine concentrations predicted an increased risk of a small for gestational age birth, indicating a possible role for disordered methyl group metabolism in fetal growth restriction in this population [38]. Several research groups in India are now taking these findings forward into nutritional intervention studies before and during pregnancy, to define any effects on fetal growth, newborn body composition and longer term health and capacity.

Nutritional Intervention Studies in Human Pregnancy

Nutritional intervention studies in animal models have already been mentioned. Obviously it is a slower and more difficult process to accumulate evidence from nutritional interventions in human pregnancy. Studies of men and women who were exposed *in utero* to an 'intervention of history', the Dutch Hunger Winter of 1944–45, have shown

that they are at increased risk of adult obesity, type 2 diabetes, dyslipidemia and coronary heart disease [11]. Recently, several follow-up studies of children born to under-nourished mothers who took part in randomised trials of nutritional interventions in pregnancy have been published [39–45]. If maternal under-nutrition during pregnancy is a cause of cardio-metabolic disease in the offspring, we might expect 'better' body composition, and lower levels of CVD and its risk factors, among offspring of mothers in the intervention groups. The published trials include a variety of interventions but fall into two groups (mainly protein-energy supplementation [39–41] or mainly multiple micronutrient supplementation [42–45]). So far, all started in pregnancy, usually in the second or third trimester. The findings have been mixed. In Guatemala, villages were randomised to either a protein-energy drink (Atole) or a low-energy drink (Fresco) which were supplied daily to pregnant women and children <7 y of age. This is the only trial with adult follow-up data; it showed lower triglyceride and higher HDL cholesterol concentrations in men and women who received Atole before the age of 36 mo (either given to the mother in pregnancy or to them post-natally) [39]. In the Gambia, women received a daily high energy biscuit, from 20 wk of pregnancy (intervention group) or during lactation only (controls). The intervention influenced fetal nutrition, increasing birthweight by 136 g and halving perinatal mortality. In the children at 11–17 y of age, there was a small but significant reduction in plasma glucose concentrations, but no differences in adiposity or blood pressure [40]. Among adolescents in India whose pregnant mothers received food-based energy and protein supplements as part of a package of public health interventions, insulin resistance and arterial stiffness were reduced compared to controls [41]. Two multiple micronutrient trials (both from Nepal) showed an increase in birth weight in the intervention group [42, 43]. Vaidya et al. followed up children whose mothers received either multiple micronutrient supplements (intervention group) or routine iron and folic acid tablets (controls) during pregnancy [42]. Children of women in the intervention group had lower systolic blood pressure (2.5 mm Hg [0.5–4.6]) at 2 y. In the other trial, children whose mothers received vitamin A, iron, folic acid and zinc were taller and less adipose than children of control mothers (vitamin A alone) [43]. In a trial in Peru, infants of mothers who were supplemented with iron, folic acid and zinc were heavier and had larger calf muscle area than those of women who received iron and folic acid without zinc [44].

These studies provide some early evidence that altering the micronutrient intake of under-nourished human mothers during pregnancy can affect body composition and cardio-metabolic risk in the children. It is noteworthy that all these trials took place in under-nourished populations in LMICs, where levels of CVD risk factors, though rising, are relatively

low and where the opportunity for ‘becoming big’ post-natally is low compared with high-income settings. This would tend to reduce any differences between children from intervention and control groups. Also, these trials started supplementation after the diagnosis of pregnancy, and usually during the second trimester. If early pregnancy is a critical time for nutritional programming of adiposity, as suggested by animal studies [45] and the Dutch Famine data, effects may be limited. However, longer follow-up of these trials would be helpful, while data are required from studies in other populations and of other interventions, including pre-conceptional trials.

Other Exposures

In addition to maternal and/or fetal under-nutrition, other exposures during fetal life, including maternal exposure to stress or glucocorticoids, and to nicotine or other toxins, programmes long-term metabolism and disease risk in animal models [18–20]. In humans, maternal smoking has been linked to an increased risk of obesity in the children [46]. This is an important area of future research.

Conclusions

There is growing burden of cardiovascular disease and type 2 diabetes in developing countries like India. This can be directly attributed to the changes in diet and lifestyle that accompany economic growth and urbanisation, but risk is also strongly influenced by strengths and vulnerabilities set up by nutrition and other modifiable factors that determine the quality of fetal and post-natal development. Data from India and elsewhere suggest that there are opportunities to reduce the burden of adult chronic disease by putting more emphasis on achieving optimal development in early life, by improving the health and nutrition of girls and young women and the nutrition of infants.

Acknowledgements The author would like to thank the Indian scientists with whom she work, including those at the KEM Hospital, Pune; Holdsworth Memorial Hospital, Mysore; New Delhi Birth Cohort Study, New Delhi; Christian Medical College, Vellore; and Centre for the Study of Social Change, Mumbai; and also the Indian society for research into the developmental origins of health and disease, Sneha-India. The research described is funded by the Indian Council of Medical Research; Medical Research Council, UK; Wellcome Trust, UK; Parthenon Trust, Switzerland; and ICICI Foundation, India. The manuscript was produced with the assistance of Jane Pearce.

Conflict of Interest None.

Role of Funding Source The work was funded by the Medical Research Council, UK, the Wellcome Trust, UK and the Parthenon Trust (Switzerland). The funders played no role in the data analysis and interpretation.

References

1. Barker DJP. Rise and fall of Western diseases. *Nature*. 1989;338: 371–2.
2. Patel V, Chatterji S, Chisholm D, et al. Chronic diseases and injuries in India. *Lancet*. 2011;377:413–28.
3. International Diabetes Federation. *Diabetes Atlas*. 3rd ed. Belgium: Brussels; 2006.
4. Yusuf S, Hawken S, Ounpuu S, et al; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the Interheart Study): a case control study. *Lancet*. 2004;364:937–52.
5. Forsdahl A. Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic disease? *Br J Prev Soc Med*. 1977;31:91–5.
6. Barker DJP, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet*. 1986; i:1077–81.
7. Osmond C, Barker DJP, Winter PD, Fall CHD, Simmonds SJ. Early growth and death from cardiovascular disease in women. *Br Med J*. 1993;307:1519–24.
8. Fall CHD. Fetal and maternal nutrition. In: Stanner S, ed. *Cardiovascular disease: diet, nutrition and emerging risk factors*. British Nutrition Foundation Task Force. Oxford, UK: Blackwell Publishing; 2005.
9. Barker DJP. *Mothers, babies and health in later life*. London: Churchill Livingstone; 1998.
10. Lucas A. Programming by early nutrition in man. In: Bock GR, Whelan J, eds. *Ciba Foundation Symposium 156-The childhood environment and adult disease*. Chichester, UK: John Wiley & Sons, Ltd.; 1991. pp. 38–55.
11. Roseboom TJ, van der Meulen J, Ravelli ACJ, Osmond C, Barker DJP, Bleker OP. Effects of prenatal exposure to the Dutch famine on adult disease in later life: an overview. *Mol Cell Endocrinol*. 2001;185:93–8.
12. Freinkel N. Of pregnancy and progeny. *Diabetes*. 1980;29:1023–35.
13. Dabelea D, Hanson RL, Lindsay RS, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. *Diabetes*. 2000;49:2208–11.
14. Whincup PH, Kaye SJ, Owen CG, et al. Birthweight and risk of type 2 diabetes: a systematic review. *JAMA*. 2008;300:2886–97.
15. Huda SS, Brodie LE, Sattar N. Obesity in pregnancy: prevalence and metabolic consequences. *Semin Fetal Neonatal Med*. 2010;15:70–6.
16. Metzger BE, the HAPO Study Co-operative Research Group. Hyperglycaemia and adverse pregnancy outcome (HAPO); associations with neonatal anthropometrics. *Diabetes*. 2009;58:453–9.
17. Oken E. Maternal and child obesity: the causal link. *Obstet Gyn Clin N Am*. 2009;36:361–77.
18. Gardner DS, Jackson AA, Langley-Evans SC. The effect of prenatal diet and glucocorticoids on growth and systolic blood pressure in the rat. *Proc Nutr Soc*. 1998;57:235–40.
19. Warner MJ, Ozanne SE. Mechanisms involved in the developmental programming of adult disease. *Biochem J*. 2010;427:333–47.
20. Vickers MH, Krecowec SO, Breier BH. Is later obesity programmed in utero? *Curr Drug Targets*. 2007;8:923–34.
21. Waterland RA, Garza C. Potential mechanisms of metabolic imprinting that lead to chronic disease. *Am J Clin Nutr*. 1999;69: 179–97.
22. Burdge GC, Hanson MA, Slater-Jefferies JL, Lillycrop KA. Epigenetic regulation of transcription: a mechanism for inducing variations in phenotype (fetal programming) by differences in nutrition during early life? *Br J Nutr*. 2007;97:1036–46.
23. Lillycrop KA, Phillips ES, Jackson AA, Hanson MA, Burdge GC. Dietary protein restriction of pregnant rats induces and folic acid

- supplementation prevents epigenetic modification of hepatic gene expression in the offspring. *J Nutr*. 2005;135:1382–6.
24. Sinclair K, Allegrucci C, Singh R, Gardner D, Sebastian S, Bispham J. DNA methylation, insulin resistance, and blood pressure in offspring determined by maternal periconceptional B vitamin and methionine status. *Proc Nat Acad Sci USA*. 2007;104:19351–6.
 25. Waterland RA, Jirtle RL. Transposable elements: targets for early nutritional effects on epigenetic gene regulation. *Mol Cell Biol*. 2003;23:5293–300.
 26. Heijmans B, Tobi E, Stein A, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proc Natl Acad Sci USA*. 2008;105:17046–9.
 27. Godfrey KM, Gluckman PD, Hanson MA. Developmental origins of metabolic disease: life course and intergenerational perspectives. *Trends Endocrinol Metab*. 2010;21:199–205.
 28. Drake AJ, Walker BR. The intergenerational effects of fetal programming: non-genomic mechanisms for the inheritance of low birth weight and cardiovascular risk. *J Endocrinol*. 2004;180:1–16.
 29. Bavdekar A, Yajnik CS, Fall CHD, et al. The insulin resistance syndrome (IRS) in eight-year-old Indian children: small at birth, big at 8 years or both? *Diabetes*. 1999;48:2422–9.
 30. Krishnaveni GV, Veena SR, Wills AK, Hill JC, Karat SC, Fall CHD. Adiposity, insulin resistance and cardiovascular risk factors in 9–10 year old Indian children: relationships with birth size and postnatal growth. *J Dev Orig Hlth Dis*. 2010;1:403–11.
 31. Bhargava SK, Sachdev HPS, Fall CHD, et al. Relation of serial changes in childhood body mass index to impaired glucose tolerance in young adulthood. *N Engl J Med*. 2004;350:865–75.
 32. Huffman MD, Prabhakaran D, Osmond C, et al. Incidence of cardiovascular risk factors in an Indian urban cohort: results from the New Delhi birth cohort. *J Am Coll Cardiol*. 2011;57:1765–74.
 33. Raghupathy P, Antonisamy B, Geethanjali FS, et al. Glucose tolerance, insulin resistance and insulin secretion in young south Indian adults; relationships to parental size, neonatal size and childhood body mass index. *Diabetes Res Clin Pract*. 2010;87:283–92.
 34. Krishnaveni GV, Veena SR, Hill JC, Kehoe S, Karat SC, Fall CHD. Intra-uterine exposure to maternal diabetes is associated with higher adiposity and insulin resistance and clustering of cardiovascular risk markers in Indian children. *Diabetes Care*. 2010;33:402–4.
 35. Rao S, Yajnik CS, Kanade A, et al. Intake of micronutrient-rich foods in rural Indian mothers is associated with the size of their babies at birth; the Pune Maternal Nutrition Study. *J Nutr*. 2001;131:1217–24.
 36. Yajnik CS, Fall CHD, Coyaji KJ, et al. Neonatal anthropometry: the thin-fat Indian baby; the Pune Maternal Nutrition Study. *Int J Obes*. 2003;27:173–80.
 37. Modi N, Thamma EL, Uthaya SN, Umranikar S, Bell JD, Yajnik CS. Whole body magnetic resonance imaging of healthy newborn infants demonstrates increased central adiposity in Asian Indians. *Ped Res*. 2009;65:584–7.
 38. Yajnik CS, Deshpande SS, Panchanadikar AV, et al. Maternal total homocysteine concentration and neonatal size in India. *Asia Pacific J Clin Nutr*. 2005;14:179–81.
 39. Stein AD, Wang M, Ramirez-Zea M, et al. Exposure to a nutrition supplement intervention in early childhood and risk factors for cardiovascular disease in adulthood; evidence from Guatemala. *Am J Epidemiol*. 2006;164:1160–70.
 40. Hawkesworth S, Walker CG, Sawo Y, et al. Nutritional supplementation during pregnancy and offspring cardiovascular risk in the Gambia. *Am J Clin Nutr*. 2011;94:1853S–60S.
 41. Kinra S, Rameshwar Sarma KV, Ghafoorunnisa, et al. Effect of integration of supplemental nutrition with public health programmes in pregnancy and early childhood on cardiovascular risk in rural Indian adolescents: long term follow-up of Hyderabad nutrition trial. *BMJ*. 2008;337:a605.
 42. Vaidya A, Saville N, Shreshta BP, Costello AM, Manandhar DS, Osrin D. Effects of antenatal multiple micronutrient supplementation on children's weight and size at 2 years of age in Nepal: follow-up of a double-blind randomised controlled trial. *Lancet*. 2008;371:492–9.
 43. Stewart CP, Christian P, LeClerq SC, West KP, Khatri SK. Antenatal supplementation with folic acid+iron+zinc improves linear growth and reduces peripheral adiposity in school-age children in rural Nepal. *Am J Clin Nutr*. 2009;90:132–40.
 44. Iannotti LL, Zavaleta N, Leon Z, Shankar AH, Caulfield LE. Maternal zinc supplementation and growth in Peruvian infants. *Am J Clin Nutr*. 2008;88:154–60.
 45. Watkins AJ, Fleming TP. Blastocyst environment and its influence on offspring cardiovascular health; the heart of the matter. *J Anat*. 2009;215:52–9.
 46. Oken E, Levitan EB, Gillman MW. Maternal smoking during pregnancy and child overweight: systematic review and meta-analysis. *Int J Obes*. 2008;32:201–10.