Metabolic programming in early life in humans; a review

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Summary

An association of low birth weight with an increased risk of adult cardiovascular disease and diabetes led to the developmental origins of health and disease (DOHaD) hypothesis, which proposes that undernutrition during early development permanently ‘programmes’ organ structure and metabolism, leading to vulnerability to later cardio-metabolic disease. High birth weight caused by maternal gestational diabetes is also associated with later diabetes, suggesting that fetal over-nutrition also has programming effects. Post-natal factors (excess weight gain/obesity, smoking, poor diets and physical inactivity) interact with fetal exposures to increase disease risk. Animal studies have shown permanent metabolic effects in offspring after alterations to maternal or early post-natal diets but evidence in humans is largely limited to observational and quasi-experimental situations such as maternal famine exposure. Randomised trials of maternal nutritional interventions during pregnancy have limited follow-up so far of the offspring. Moreover interventions usually started after the first trimester and therefore missed key peri-conceptional or early pregnancy events such as epigenetic changes, placentation and fetal organogenesis. Recent and ongoing trials, intervening pre-conceptionally and powered for long-term offspring follow-up will address these issues. While current preventive strategies for cardio-metabolic disease focus on high risk individuals in mid-life, DOHaD concepts offer a ‘primordial’ preventive strategy to reduce disease in future generations by improving fetal and infant development.

Low birth weight, adult disease and the DOHaD hypothesis

The developmental origins of health and disease (DOHaD) hypothesis arose initially out of human cohort studies showing that people of lower birth weight had a higher risk of adult cardiovascular disease, hypertension, type 2 diabetes, and metabolic syndrome (‘cardio-metabolic disease’)1. These findings were replicated in different populations and were found to be independent of potential confounders, such as low socio-economic status. Animal experiments showed that manipulating the diet of mothers during pregnancy, and other interventions that impair fetal nutrition, led to widespread and permanent changes in tissue structure, body composition, endocrine responses and metabolism in the offspring and a vulnerability to adult hypertension and diabetes2. Together, this evidence led to the concept that under-nutrition during critical periods of the early development of metabolic tissues and systems such as the pancreas, heart, kidney, liver, skeletal muscle, adipose tissue, and endocrine axes left permanent metabolic abnormalities, and a concomitant vulnerability to cardio-metabolic disease; this has been called ‘metabolic programming’. Fetal growth restriction is most common in populations with a high prevalence of maternal underweight, stunting and micronutrient deficiencies3. Metabolic programming by fetal undernutrition is therefore likely to be of greatest relevance in low- and middle-income countries.

**Gestational diabetes, maternal overweight and excess pregnancy weight gain**

There is now good evidence that in addition to fetal growth restriction fetal exposure to maternal gestational diabetes (GDM, often associated with high birth weight) programmes an increased risk of obesity and type 2 diabetes in later life. The fetus of a mother with GDM is exposed to increased concentrations of glucose, lipids and amino acids (fuels) which cross the placenta and hyper-stimulate the fetal pancreas, causing hyper-insulinaemia and fetal over-growth4. Freinkel suggested in 1980 that this could have long-term effects (‘fuel-mediated teratogenesis’)5, and this was confirmed when studies (initially among native American populations with a high prevalence of GDM) showed that children of diabetic mothers were themselves developing increased rates of obesity and early-onset type 2 diabetes6 compared with children of non-diabetic mothers or with their older siblings born before the mother developed diabetes. Indian children born to GDM mothers have greater adiposity throughout childhood, and higher glucose and insulin concentrations, compared with offspring of diabetic fathers or non-diabetic controls7. As mothers become heavier in almost all populations, the incidence of diabetes in pregnancy is increasing8, and this is likely to exacerbate the burden of obesity and diabetes in the next generation.

Maternal insulin resistance and plasma glucose concentrations are physiologically increased during pregnancy, as a normal process to facilitate fetal nutrition, but there is debate as to whether lesser degrees of maternal hyperglycaemia (in the non-diabetic range) can increase adiposity and diabetes risk in the children. Birth weight and newborn adiposity increase linearly with maternal glucose concentrations, even in the normal range9. In a US study of women routinely screened for GDM using oral glucose tolerance tests, there was a positive association, even in the non-diabetic group, between maternal glucose concentrations and prevalence of overweight in the children10. Other studies have shown linear increases in child adiposity with increasing maternal glucose concentrations11 and/or insulin resistance12 independent of maternal BMI. Further research is needed to determine optimal maternal glucose concentrations in pregnancy.

Like the diabetic mother, an obese mother has higher circulating fuels13. Newborns of obese women are generally heavier, though they can be growth restricted due to placental insufficiency. They have more body fat14 and higher BMI in childhood than children of non-obese women15,16. Maternal obesity without diabetes is associated with an increased risk of metabolic syndrome in children and an increased risk of cardiovascular death in adult life15,16. It is controversial whether or not these associations indicate programming of obesity by intra-uterine exposure to fetal over-nutrition. As with glucose intolerance in pregnancy, this would have huge implications for public health because of the potential for upward trends in maternal BMI to accelerate rates of obesity and cardio-metabolic disease across generations. Alternative explanations to fetal programming could be shared genes and/or shared post-natal diet and activity patterns. In support of an intra-uterine effect are studies of siblings born before and after maternal bariatric surgery in which a higher prevalence of obesity was found in the former group17 and studies showing that the children of women with greater weight gain during pregnancy have an increased risk of overweight/obesity independent of pre-pregnancy weight16. Definitive evidence would be the demonstration that interventions to reduce maternal adiposity before or during pregnancy reduce obesity risk in the children.

**Other pre-natal factors**

*Glucocorticoids:* It was proposed very early in the DOHaD story that fetal exposure to glucocorticoids could be a key programming factor18. The fetus is protected from maternal glucocorticoids by a placental enzyme (11β-hydroxysteroid dehydrogenase) which is partially nutritionally regulated19. In animals, fetal glucocorticoid exposure, either by direct administration, induction of maternal stress, or inhibition of the enzyme, leads to lower birth weight, and later hypertension and/or diabetes. In humans, elevated maternal cortisol concentrations in pregnancy are associated with higher blood pressure and insulin concentrations in the children20. A follow-up of young adults whose mothers participated in a trial of pre-natal steroids in the last trimester of pregnancy, to prevent respiratory distress syndrome in their pre-term babies (an intervention which increases newborn survival), showed no difference in adiposity, blood pressure, serum lipids, or fasting plasma glucose compared with offspring of mothers in the placebo group21. However, the steroid-exposed offspring had higher 30-minute insulin concentrations and lower 120-minute glucose concentrations, which may indicate insulin resistance and an increased risk of type 2 diabetes at older ages.

Lower birth weight is associated in humans with increased stress-induced cortisol concentrations in later life22. Thus glucocorticoids may be both programmed and agents of programming, and therefore a means by which programming could cross generations20,23. Studies of the long-term cardio-metabolic effects of stressful events in early life in humans are rare. However, reduced cortisol concentrations have been reported in infants of mothers who experienced the 9/11 attack on New York in 2001 during pregnancy24. Post-natal stress exposure may also be important. Finnish men and women who as children were evacuated and separated from their parents during World War II had higher systolic and diastolic blood pressures, and were more likely to be on medication for coronary heart disease than those who did not have this experience25.

*Environmental toxins:* There is increasing evidence that exposure to some environmental toxins during fetal development has long-term programming effects. The best studied in humans is tobacco smoke. Maternal smoking during pregnancy is associated with lower birth weight and an increased risk of obesity in the children26. Based on data from >200,000 children in 39 observational studies, mainly in high income countries, children whose mothers smoked have a 30-40% higher risk of overweight and 50-60% increased risk of obesity than children whose mothers had either never smoked or were former smokers who abstained during pregnancy. Studies of adult outcomes are few, but a large study from Sweden, with good ascertainment of maternal smoking, reported an increased risk of gestational diabetes in daughters of women who smoked during pregnancy compared with daughters of non-smokers27. These associations may not be causal and could reflect residual confounding: mothers who smoke differ from non-smokers in socio-economic status and other ways that could predict an increased obesity risk in the children28. However, animal studies have shown that administration of nicotine to pregnant rats increases body fat in the pups29. The mechanisms are unknown, but they could be direct effects of nicotine and/or other chemical constituents of tobacco smoke that cross the placenta, or result from altered fetal nutrition due to effects on maternal or fetal vascular function.

There is increasing interest in possible long-term programming effects of other environmental toxins, especially endocrine disrupting chemicals, compounds that influence hormonal and other cell-messaging systems, and which are common pollutants in the modern environment, often in small quantities insufficient to produce birth defects30,31. The evidence in humans for long term metabolic effects of fetal exposure is limited, but there are some data linking exposure in mothers to obesity in the children30,31; this is an area of ongoing research.

**Post-natal weight gain**

In contrast to lower birth weight, *greater* childhood and adult weight or BMI is consistently associated in cohort studies with an increased risk of later cardio-metabolic disease. In all populations, faster BMI gain (upward crossing of centiles, or rising Z-scores) from mid-childhood onwards is associated with increased adult adiposity, an increased risk of coronary heart disease, type 2 diabetes and hypertension32-38. The highest risk of disease in adults, and the most adverse levels of cardio-metabolic risk markers in children, are consistently found in those who started life with a low birth weight but became relatively heavy. Childhood or adult BMI sometimes interacts with birth weight in the prediction of adult disease, indicated by stronger adverse effects of BMI on disease risk in people of lower birth weight. Upward crossing of BMI centiles during childhood does not necessarily mean childhood obesity. For example, in the New Delhi birth cohort in India, children who later developed type 2 diabetes had a mean BMI throughout childhood that was low (between -0.5 and -1.0 SDs according to the WHO growth reference) and in the Helsinki birth cohort in Finland, children who later developed type 2 diabetes had a mean BMI close to the WHO median. In both cohorts they had a lower birth weight and infant BMI than the rest of their respective cohorts who did not become diabetic, but crossed within-cohort centiles upwards (becoming ‘obese relative to themselves’ but not necessarily obese in absolute terms) during mid-childhood and adolescence. The importance of this is that using obesity criteria to detect children at risk of future cardio-metabolic will miss many at-risk individuals.

There are several possible reasons why weight or BMI gain in childhood or adult life, on a background of fetal restriction, might be associated with disease. Given adequate nutrition, low birthweight babies tend to catch-up post-natally (compensatory growth), and the rapidity of post-natal growth may indicate the severity of growth restriction in relation to growth potential. Another explanation may be that intra-uterine under-nutrition programmes increased post-natal adiposity gain. There is some evidence for this in humans from famine studies (see below)32. Alternatively weight gain may be disadvantageous because it places excess demand on metabolic tissues that have impaired capacity to respond because of the earlier under-nutrition. Data from human studies showing that, in addition to higher adult body weight, other lifestyle risk factors for cardio-metabolic disease such as a lack of physical activity, unhealthy diets and smoking, also have a greater adverse effect the lower the birth weight39 (and, vice versa, the adverse association of lower birthweight with disease risk is greater the more adult lifestyle risk factors are present) gives support to this explanation.

**Other post-natal factors**

There is debate as to whether being breastfed protects against later obesity and cardio-metabolic disease. Lower rates of obesity, hypertension and type 2 diabetes and lower cholesterol concentrations have been reported in adults who were breastfed as infants40. In a recent meta-analysis, the pooled odds ratio from 11 studies was 0.87 (95% CI 0.76-0.99) for obesity, and 0.65 (95%CI 0.49-0.86) for type 2 diabetes, among adults who had been breastfed compared with those who were bottle fed41. Most of the evidence on long-term effects of breast feeding is from observational studies in high income countries, and because breastfeeding is strongly associated with higher maternal socio-economic status and education in these countries, residual confounding is a major issue. Data from five low- and middle-income countries, which have different confounding patterns, showed no evidence that breast feeding is protective against hypertension, diabetes or obesity42.

**Famine studies**

Several research groups have tested the DOHaD concept by following up people exposed in early life to severe nutritional deprivation. The best known are the Dutch Famine studies, which have investigated men and women born to pregnant mothers who experienced starvation during World War II43. The famine affected a previously well-nourished population for several months over an extreme winter, after which nutrition quickly returned to normal. This made it possible to explore the consequences of exposure during different stages of gestation. Famine exposure in late pregnancy reduced birth weight by 200-300 g, while early pregnancy exposure was associated with a normal mean birth weight. There was an increased risk of type 2 diabetes among men and women who had been exposed to famine during late gestation, but early pregnancy exposure was associated with a range of health problems including not only cardio-metabolic disorders such as obesity, dyslipidaemia, coronary heart disease, and type 2 diabetes but also greater stress responsiveness, poorer mental health and perceived general health, premature brain ageing and lower cognitive function43,44. The Dutch Famine findings have made the important point that transient pre-natal nutritional deprivation can have adverse long-term effects on health without necessarily altering birth weight.

Follow-up of young-to-middle-aged adults exposed in early life to the lengthy Biafran (1967-1970)45 and Chinese (1959-1961)46,47 famines have also shown increased hypertension, impaired glucose tolerance, diabetes and overweight/obesity among adults who were in utero when their mothers were exposed to famine, or exposed during infancy, compared with controls conceived after famine.

There are limitations to famine studies. Data collection systems often collapsed during famine leading to a lack of individual-level data on the severity of undernutrition, although maternal weight and birth weight were recorded in the Dutch Famine. There would have been variation in the intensity of famine exposure according to wealth and/or peoples’ ability to growth their own food. Mortality rates were often high during famine, and survivors are likely to have differed from non-survivors in ways that could influence their later disease risk. Only a small proportion of survivors were followed up. The choice of suitable controls is difficult; people exposed to famine at older ages may not be suitable if the ‘vulnerable’ window is wider than believed, as several recent studies suggest. Controls living in ‘unaffected’ adjacent areas may also be unsuitable because of the pervasive effects of war. Nevertheless, famine studies have been invaluable in providing support for the DOHaD hypothesis, and in showing that exposure can be related to later health outcomes independently of birth weight. Follow-up of one of the Dutch Famine cohorts has shown possible transgenerational effects of famine exposure; for example among the offspring of women exposed to famine in utero, newborn length was reduced and a higher percentage reported poor adult health than among offspring on non-exposed women48.

**Effect of interventions in early life on cardio-metabolic outcomes**

We are only just beginning to see DOHaD concepts tested definitively in humans by following up children born during randomised controlled trials of interventions in the mother during pregnancy.

*Nutritional interventions during pregnancy in under-nourished populations;* *protein-energy:* The only trial with adult follow-up is the cluster-randomised INCAP trial in Guatemala, in which, during 1962 to 1977, pregnant mothers and children up to the age of 7 years received either Atole (a high-energy, high-protein drink) or Fresco (lower energy, no protein) as a daily supplement. Both drinks contained multiple micronutrients. Follow-up studies have shown beneficial effects of pre-natal (maternal) supplementation with Atole on serum lipid49 and glucose concentrations50, but no effect on blood pressure51. This study had a small follow-up sample size, especially given the cluster design. In another cluster-randomised protein-energy trial in India, pregnant mothers in intervention villages received food-based energy and protein supplements as part of a package of public health interventions, while those in control villages received standard care. The offspring have been followed up into adolescence, when insulin resistance and arterial stiffness were reduced in the children of women in the intervention villages compared to controls52. Again, there was no effect on blood pressure. In contrast, among adolescents whose mothers took part in a randomised controlled trial of protein-energy supplementation during pregnancy in the Gambia, an intervention that had a large beneficial effect on birth weight and infant mortality, there were no differences in blood pressure, body composition, or serum cholesterol concentrations between intervention and control groups53. Plasma glucose was lower in offspring of mothers who received the protein-energy intervention, but the effect was very small (0.05 mmol/l).

*Nutritional interventions during pregnancy in under-nourished populations; micronutrients:* Between 1999 and 2001, 4926 pregnant women in rural Nepal were cluster-randomised to receive daily micronutrient supplements containing either vitamin A alone (control) or with added folic acid, folic acid+iron, folic acid+iron+zinc or multiple micronutrients, from early pregnancy until 3 months postpartum. The children were followed up at 6-8 years of age. None of the micronutrient combinations influenced the children’s blood pressure, or cholesterol, triglyceride, glucose or insulin concentrations54. There was a lower risk of microalbuminuria and a reduction in skinfold thickness in the folic acid+iron+zinc groups, and a reduced risk of microalbuminuria and metabolic syndrome in the folic acid group55. Follow-up data from another multiple micronutrient trial in pregnant women in Nepal, showed lower systolic blood pressure in the children (N=917) at 2 years (-2.5 mmHg, 95% CI –4.55 to –0.47) compared with children whose mothers received standard iron/folate tablets56. However, a further follow-up study of these children at 8 years showed no differences in body composition or blood pressure between intervention and control groups57.

*Nutritional interventions during pregnancy; combined protein/energy and micronutrients:* The Maternal and Infant Nutrition Interventions in Matlab (MINIMAT) trial in Bangladesh randomised pregnant women to supplementation with either iron and folic acid or multiple micronutrients combined in a factorial design with randomised food-based energy supplementation (600 kcal daily) starting at either 9 or 20 weeks gestation. Follow-up of the children at 4.5 years showed no effect of either multiple micronutrients or earlier energy supplementation on body composition58. Earlier compared with later energy supplementation was associated with lower diastolic blood pressure (-0.72 mm Hg [(95% CI: -1.28, -0.16])59 and lower LDL-cholesterol concentrations (-0.068 mmol/l [95% CI -0.126; -0.011])60. Multiple micronutrient supplementation was associated with *higher* diastolic blood pressure (0.87 mm Hg [95% CI: 0.18, 1.56])61and *lower* HDL-cholesterol (-0.028 mmol/l [95% CI -0.053, -0.002])60 (changes in the ‘wrong’ direction) but lower plasma glucose concentrations (-0.099 mmol/l [95% CI -0.179, -0.019])60. There were no effects on markers of inflammation or oxidative stress60.

Overall, these trials in under-nourished populations provide little evidence of consistent long-term benefits from supplementing undernourished mothers from early or mid-pregnancy for offspring cardio-metabolic disease risk. More evidence is needed, however, because there are limitations to these trials as tests of the DOHaD concept. For example, childhood or adolescence may be too early to detect benefits; risk of disease may be low in both intervention and control groups in populations with low post-natal weight gain; and single interventions may be inadequate to alter fetal development sufficiently in mothers with multiple deprivations. Based on what is known from animal models of fetal programming, it may be necessary to intervene earlier in pregnancy or even pre-conceptionally in order to influence processes such as placentation and organogenesis (which occur mainly in the first trimester) and peri-conceptional epigenetic changes. Pre-conceptional supplementation trials are challenging, but several are in the pipeline (either ongoing or completed for birth outcomes) including the Mumbai Maternal Nutrition Project61 and Pune Vitamin B12 Intervention Study in India (“PRIYA”)62, the PRECONCEPT trial in Vietnam63, a 4-country trial of a lipid based energy and multiple micronutrient supplement64 and the HeLTI (Health Life Trajectories Initiative) family of studies in Canada, India, South Africa and China65, in which multi-faceted interventions will be tested (nutrition, hygiene and sanitation, cleaner environment, avoidance of toxins, and programmes to reduce maternal stress, prevent depression and promote parenting skills) starting pre-conceptionally.

*Interventions in pregnancy to prevent or treat gestational diabetes, maternal obesity and excess pregnancy weight gain:* In an Australian trial, more intensive treatment of gestational diabetes reduced macrosomia and pregnancy complications but there was no reduction in BMI in the children at 4-5 years of age66. Two other small trials, with follow-up of the children up to 10 years of age, have shown similar findings67. There is a need for large well-designed RCTs to assess the benefits of interventions to prevent or treat gestational diabetes and the cardio-metabolic health of the offspring.

In the Danish LiPO (Lifestyle in Pregnancy and Offspring) trial obese pregnant women were offered dietary advice and support to increase their physical activity. No differences between the intervention and control groups were found at age 3 years in the children’s BMI, waist circumference, plasma glucose, insulin and lipid concentrations or blood pressure68,69. The UK UPBEAT study provided a complex behavioural intervention targeting maternal diet (glycaemic load and saturated fat intake) and physical activity in 1,555 obese pregnant women. A follow-up of the infants at 5 months of age showed no difference in triceps skinfold thickness between the intervention and standard care groups (-0.14 SD [95% CI -0.38, 0.10]) but subscapular skinfold thickness was reduced in the intervention group (-0.26 SD [95% CI -0.49, -0.02])70. Overall, there have been few trials targeting maternal overweight that have reported offspring cardio-metabolic outcomes, and where follow-up has occurred it has been in very young children. This is an area of great interest, however, and a large number of trials are ongoing71.

*Interventions to reduce or prevent maternal smoking in pregnancy:* There is currently very limited information from intervention studies in humans. Initial follow-up of small trials of smoking cessation programmes during pregnancy have found no differences in body weight between children of mothers in the intervention and control groups28. There is a need for more research in this area.

*Interventions to increase breastfeeding:* It is not feasible to randomise breastfeeding, but two large studies in different settings have randomised mothers to receive additional support to breastfeed and have follow-up data in the children. In the Promotion of Breastfeeding Intervention Trial (PROBIT) in Belarus exclusive breastfeeding was increased in the intervention group compared with controls (43% versus 6% exclusively breastfed at 3 months, and 8% versus <1% at 6 months). The children have been investigated at the ages of 6 and 11 years, and have shown no differences between groups in adiposity, blood pressure, plasma glucose, insulin, adiponectin, apolipoprotein A1 concentrations or prevalence of metabolic syndrome72,73. In the MINIMAT trial, half the women were randomized further during the last trimester of pregnancy, to receive either breast feeding counselling or usual health messages. There were no differences in the children’s body composition, assessed by anthropometry, at 5 years between these groups74.

*Interventions to prevent or treat childhood obesity:* Diet, physical activity and behaviour change interventions have proven effective for treating and preventing obesity in children75-77. The Cochrane review on preventing obesity concluded that programmes reduce mean BMI by an average -0.15 kg/m2, which is a small effect and unlikely to benefit later outcomes. Programmes are most effective among children aged 6-12 years, in school-based interventions that influenced the school curriculum, supported teachers and improved school food quality, and/or in interventions that involved parents and encouraged home activities77. Although some of these programmes have shown improvements in cardio-metabolic disease risk markers during or immediately after the intervention, there does not appear to be data yet on long-term impact.

**Mechanisms of programming and epigenetics**

The DOHaD concept relies on the existence of mechanisms by which a ‘memory’ of the early life environment is retained into later life. This could be a morphological memory, for example permanently altered structure of specific organs or tissues (‘tissue remodelling’) due to sub-optimal development during critical periods. This could be permanently reduced cell numbers, altered distribution of cell types within an organ or selection of more resilient alternative cell types. An example is the kidney; human nephrons develop only during fetal life, and if fewer develop during gestation a permanent deficit remains78. There is extensive evidence from animal studies of tissue re-modelling in the heart, pancreas, liver and hypothalamus in response to fetal under-nutrition.

Epigenetic effects (changes in DNA methylation, histone modifications and non-coding microRNAs) are thought to be one mechanism underlying this ‘memory’79. Among epigenetic marks, the most researched in humans has been DNA methylation. An individual’s methylome is laid down during pre-natal life and childhood, with the period of embryonic development being particularly important. With the exception of imprinted genes, a high proportion of the DNA in the fertilised egg is demethylated between fertilisation and implantation, after which methylation is built up again throughout the developmental period (including intra-uterine life, early childhood and puberty). Differential re-methylation is how the single cell fertilised egg gives rise to all the different cell types present in the fetus and their gene expression patterns. During early gestation re-methylation can be modified by the maternal diet and other environmental factors80. In humans, changes in DNA methylation have been shown in association with a variety of pre-natal nutritional exposures including maternal famine exposure during pregnancy, maternal micronutrient supplementation, and season of conception81. Differences in gene methylation acquired in utero have been related to later phenotypes relevant to cardio-metabolic health, including adiposity, blood pressure, insulin resistance, lipid profiles and leptin concentrations80. No studies in humans have demonstrated the full chain of events from an intervention affecting methylation at a specific locus, through gene expression, to a disease-related phenotype, supported by evidence of causality. The closest example is a study from The Gambia, where there are marked seasonal changes in nutritional status, creating natural variation in early life nutritional exposures. Children and adults conceived during the rainy (‘hungry’) season had higher methylation at the POMC locus, which plays a role in body weight regulation, as well as higher BMI and obesity risk, than those conceived during the dry season82.

A recurring theme in these studies is the 1-carbon cycle, which generates methyl groups for use in DNA methylation. Vitamins B6, B12, folic acid, choline and betaine are required for normal functioning of the cycle80. Nutritional effects on epigenetic characteristics could produce the ‘plasticity’ of phenotype in early life that is inherent to the concept of fetal programming. Furthermore, this type of plasticity means that the programming of long-term outcomes may not require major nutritional deficits during organogenesis and differentiation, but could result from short-lived and subtle changes in the nutritional environment at stages of development when nutrient demands for growth are still quite small, such as during the peri-conceptional period and early embryogenesis83,84. Epigenetic changes in a limited number of key metabolic genes could explain the striking phenomenon in animal models whereby widely differing nutritional interventions in the mother apparently result in the same ‘metabolic syndrome’ phenotype in the offspring85. There is a need for more epigenetic studies within randomised controlled trials of peri-conceptional and pregnancy interventions in humans, and for exploration in human studies of possible paternal influences on children’s health via epigenetic mechanisms. Paternal effects could explain intriguing associations between mortality in one generation and nutritional exposures experienced by their fathers and grandfathers86.

**Implications for Public Health**

Current strategies to prevent cardio-metabolic disease focus mainly on middle-aged individuals with existing risk factors (e.g. promoting weight reduction in overweight/obese individuals). These secondary prevention measures a) tend to have modest effects and b) do not address the impact on disease on future generations. The DOHaD findings have enormous public health implications because they suggest an alternative ‘primordial’ prevention strategy of optimising early nutrition and development to both control the rising burden of cardio-metabolic disease, and improve childhood growth, cognitive function, reproductive success and other aspects of ‘human capital’, breaking intergenerational cycles of deprivation and disease. The weight of evidence has led to a high level of acceptance that sub-optimal nutrition in utero and early childhood casts a long shadow on health. This has had a powerful effect in stimulating governments and international agencies in low- and middle-income countries to improve programmes to support maternal and infant nutrition and health during the ‘first 1,000 days’ (from conception to the age of 2 years post-natally). So far these initiatives have not been paralleled in high income countries, where public awareness about the harmful consequences of maternal obesity and diabetes during pregnancy is low, and where services to deal specifically with maternal obesity and other forms of sub-optimal maternal nutrition pre-conceptionally and in early pregnancy are largely lacking. Research evidence of effectiveness will be needed in order to drive such public health interventions. In all settings, initiatives to improve the health literacy and nutrition of adolescent boys and girls, couples planning pregnancy, and pregnant women, need to be developed and strengthened. High quality nutrition during infancy, including optimal breastfeeding and nutritious complementary (weaning) foods, is likely to be equally important. There is strong evidence that efforts should be made to control the inexorable global rise in adiposity and fall in physical activity, including that among children, for their own future health. While effective programmes to deal with obesity have been developed, usually as part of research projects, it is hard to see how most of the interventions could be sustained over a long enough time to have impact without being embedded in health and education systems, rooted in national policies, and making changes in increasingly obesogenic environments.

**Authors' Contributions**  
Both authors contributed to writing the manuscript.

**Competing Interests**

We have no competing interests.

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