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Metabolic programming in early life in humans

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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. Randomized trials of maternal nutritional interventions during pregnancy have so far had limited follow-up 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.

This article is part of the theme issue 'Developing differences: early-life effects and evolutionary medicine'.

1. Low birth weight, adult disease and the developmental origins of health and disease 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 diabetes [2]. Together, this evidence led to the concept that undernutrition 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 deficiencies [3]. Metabolic programming by fetal

undernutrition is therefore likely to be of greatest relevance in low- and middle-income countries.

2. 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-growth [4]. 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 diabetes [6] 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 controls [7]. As mothers become heavier in almost all populations, the incidence of diabetes in pregnancy is increasing [8], 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 range [9]. 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 children [10]. Other studies have shown linear increases in child adiposity with increasing maternal glucose concentrations [11] and/or insulin resistance [12] independent of maternal body-mass index (BMI). Further research is needed to determine optimal maternal glucose concentrations in pregnancy.

Like the diabetic mother, an obese mother has higher levels of circulating fuels [13]. Newborns of obese women are generally heavier, though they can be growth restricted owing to placental insufficiency. They have more body fat [14] and higher BMI in childhood than children of non-obese women [15,16]. Maternal obesity without diabetes is associated with an increased risk of metabolic syndrome in children and an increased risk of cardiovascular death in adult life [15,16]. 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 group [17], 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 weight [16]. Definitive evidence would be the demonstration that interventions to reduce maternal adiposity before or during pregnancy reduce obesity risk in the children.

3. Other pre-natal factors

(a) Glucocorticoids

It was proposed very early in the DOHaD story that fetal exposure to glucocorticoids could be a key programming factor [18]. The fetus is protected from maternal glucocorticoids by a placental enzyme (11β-hydroxysteroid dehydrogenase) which is partially nutritionally regulated [19]. In animals, fetal glucocorticoid exposure, 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 children [20]. 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 that increases newborn survival), showed no difference in adiposity, blood pressure, serum lipids or fasting plasma glucose compared with offspring of mothers in the placebo group [21]. However, the steroid-exposed offspring had higher 30 min insulin concentrations and lower 120 min 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 life [22]. Thus, glucocorticoids may be both programmed and agents of programming, and therefore a means by which programming could cross generations [20,23]. 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 pregnancy [24]. 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 experience [25].

(b) 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 children [26]. Based on data from more than 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 either had 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-smokers [27]. 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 children [28]. However, animal studies have shown that administration of nicotine to pregnant rats increases body fat in the pups [29]. 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 owing to effects on maternal or fetal vascular function.

There is an 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 defects [30,31]. 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 children [30,31]; this is an area of ongoing research.

4. 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 hypertension [32–38]. 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 s.d. 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, the children 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 undernutrition 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 undernutrition. 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 on the lower the birth weight [39] (and, vice versa, the adverse association of lower birth weight with disease risk is greater the more adult lifestyle risk factors are present), give support to this explanation.

5. 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 infants [40]. 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-fed [41]. Most of the evidence on long-term effects of breastfeeding 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 breastfeeding is protective against hypertension, diabetes or obesity [42].

6. 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 II [43]. 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 function [43,44]. 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 grow 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 of non-exposed women [48].

7. 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 randomized controlled trials (RCTs) of interventions in the mother during pregnancy.

(a) Nutritional interventions during pregnancy in under-nourished populations: protein–energy

The only trial with adult follow-up is the cluster-randomized INCAP trial in Guatemala, in which, during 1962–1977, 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 lipid [49] and glucose concentrations [50], but no effect on blood pressure [51]. This study had a small follow-up sample size, especially given the cluster design. In another cluster-randomized 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 with controls [52]. Again, there was no effect on blood pressure. By contrast, among adolescents whose mothers took part in a RCT 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 groups [53]. Plasma glucose was lower in offspring of mothers who received the protein–energy intervention, but the effect was very small (0.05 mmol l^{-1}).

(b) Nutritional interventions during pregnancy in under-nourished populations: micronutrients

Between 1999 and 2001, 4926 pregnant women in rural Nepal were cluster-randomized 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 three 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 concentrations [54]. 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 group [55]. 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 tablets [56]. 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 groups [57].

(c) Nutritional interventions during pregnancy: combined protein/energy and micronutrients

The Maternal and Infant Nutrition Interventions in Matlab (MINIMAT) trial in Bangladesh randomized pregnant women to supplementation with either iron and folic acid or multiple micronutrients combined in a factorial design with randomized 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 composition [58]. 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^{-1} (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)) [61] and *lower* HDL-cholesterol (−0.028 mmol l^{-1} (95% CI −0.053, −0.002)) [60] (changes in the 'wrong' direction) but lower plasma glucose concentrations (−0.099 mmol l^{-1} (95% CI −0.179, −0.019)) [60]. There were no effects on markers of inflammation or oxidative stress [60].

Overall, these trials in under-nourished populations provide little evidence of consistent long-term benefits from supplementing under-nourished 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 periconceptional 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 Project [61] and Pune Vitamin B12 Intervention Study in India (PRIYA) [62], the PRECONCEPT trial in Vietnam [63], a four-country trial of a lipid-based energy and multiple micronutrient supplement [64] and the HeLTI (Health Life Trajectories Initiative) family of studies in Canada, India, South Africa and China (http://www.cihr-irsc.gc.ca/e/50275.html, accessed 14 July 2018), in which multifaceted 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.

(d) 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 age [65]. Two other small trials, with follow-up of the children up to 10 years of age, have shown similar findings [66]. 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 pressure [67,68]. The UK UPBEAT study provided a complex behavioural intervention targeting maternal diet (glycaemic load and saturated fat intake) and physical activity in 1555 obese pregnant women. A follow-up of the infants at five months of age showed no difference in triceps skinfold thickness between the intervention and standard care groups (−0.14 s.d. (95% CI −0.38, 0.10)) but subscapular skinfold thickness was reduced in the intervention group (−0.26 s.d. (95% CI −0.49, −0.02)) [69]. 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 ongoing [70].

(e) 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 groups [28]. There is a need for more research in this area.

(f) Interventions to increase breastfeeding

It is not feasible to randomize breastfeeding, but two large studies in different settings have randomized 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 three months, and 8% versus less than 1% at six 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 and apolipoprotein A1 concentrations or prevalence of metabolic syndrome [71,72]. In the MINIMAT trial, half the women were randomized further during the last trimester of pregnancy, to receive either breastfeeding counseling or usual health messages. There were no differences in the children's body composition, assessed by anthropometry, at 5 years between these groups [73].

(g) Interventions to prevent or treat childhood obesity

Diet, physical activity and behaviour change interventions have proven effective for treating and preventing obesity in children [74–76]. The Cochrane review on preventing obesity concluded that programmes reduced mean BMI by on average -0.15 kg m^{-2}, which is a small effect and unlikely to benefit later outcomes. Programmes were 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 activities [76]. Although some of these programmes have shown improvements in cardio-metabolic disease risk markers during or immediately after the intervention, there do not appear to be data yet on long-term impact.

8. 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) owing 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 remains [77]. There is extensive evidence from animal studies of tissue remodelling in the heart, pancreas, liver and hypothalamus in response to fetal undernutrition.

Epigenetic effects (changes in DNA methylation, histone modifications and non-coding microRNAs) are thought to be one mechanism underlying this 'memory' [78]. 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 fertilized egg is demethylated between fertilization 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-fertilized 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 factors [79]. 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 conception [80]. 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 concentrations [79]. 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 season [81].

A recurring theme in these studies is the one-carbon cycle, which generates methyl groups for use in DNA methylation. Vitamins B6 and B12, folic acid, choline and betaine are required for normal functioning of the cycle [79]. 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 embryogenesis [82,83]. 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 offspring [84]. There is a need for more epigenetic studies within RCTs 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 grandfathers [85].

9. 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 optimizing 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 1000 days' (from conception to the age of 2 years post-natally). So far these initiatives have not been parallelled 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 a 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 an impact without their being embedded in health and education systems and rooted in national policies, and without making changes in increasingly obesogenic environments.

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References

1. Osmond C, Barker DJ. 2000 Fetal, infant, and childhood growth are predictors of coronary heart disease, diabetes, and hypertension in adult men and women. *Environ. Health Perspect.* **108**(Suppl. 3), 545–553.
2. Fernandez-Twinn DS, Ozanne SE. 2010 Early life nutrition and metabolic programming. *Ann. NY Acad. Sci.* **1212**, 78–96. (doi:10.1111/j.1749-6632.2010.05798)
3. Black RE *et al.* 2008 Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet* **371**, 243–260. (doi:10.1016/S0140-6736(07)61690-0)
4. Pedersen J. 1954 Weight and length at birth of infants of diabetic mothers. *Acta Endocrinol.* **16**, 330–342. (doi:10.1530/acta.0.0160330)
5. Freinkel N. 1980 Banting Lecture 1980. Of pregnancy and progeny. *Diabetes* **29**, 1023–1035. (doi:10.2337/diab.29.12.1023)
6. Dabelea D, Hanson RL, Lindsay RS, Pettitt DJ, Imperatore G, Gabir MM, Roumain J, Bennett PH, Knowler WC. 2000 Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. *Diabetes*

49, 2208–2211. (doi:10.2337/diabetes.49.12.2208)

7. Krishnaveni GV, Veena SR, Hill JC, Kehoe S, Karat SC, Fall CHD. 2010 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* **33**, 402–404. (doi:10.2337/dc09-1393)
8. International Diabetes Federation. 2017 *IDF Diabetes Atlas*, 8th edn. Brussels, Belgium: International Diabetes Federation. See http://www.diabetesatlas.org.
9. Metzger BE *et al.* 2009 Hyperglycaemia and adverse pregnancy outcome (HAPO); associations with neonatal anthropometrics. *Diabetes* **58**, 453–459. (doi:10.2337/db08-1112)
10. Hillier TA, Pedula KL, Schmidt MM, Mullen JA, Charles MA, Pettitt DJ. 2007 Childhood obesity and metabolic imprinting: the ongoing effects of maternal hyperglycemia. *Diabetes Care* **30**, 2287–2292. (doi:10.2337/dc06-2361)
11. Ehrlich SF, Rosas LG, Ferrara A, King JC, Abrams B, Harley KG, Hedderson MM, Eskenazi B. 2013 Pregnancy glycemia in Mexican-American women without diabetes or gestational diabetes and programming for childhood obesity. *Am. J. Epidemiol.* **177**, 768–775. (doi:10.1093/aje/kws312)
12. Hamilton JK, Odrobina E, Yin J, Hanley AJ, Zinman B, Retnakaran R. 2010 Maternal insulin sensitivity during pregnancy predicts infant weight gain and adiposity at 1 year of age. *Obesity (Silver Spring)* **18**, 340–346. (doi:10.1038/oby.2009.231)
13. Huda SS, Brodie LE, Sattar N. 2010 Obesity in pregnancy: prevalence and metabolic consequences. *Fetal Neonatal Med.* **15**, 70–76. (doi:10.1016/j.siny.2009.09.006)
14. Catalano PM, Presley L, Minium J, Hauguel-de Mouzon S. 2009 Fetuses of obese mothers develop insulin resistance in utero. *Diabetes Care* **32**, 1076–1080. (doi:10.2337/dc08-2077)
15. Gaillard R, Santos S, Duijts L, Felix JF. 2016 Childhood health consequences of maternal obesity during pregnancy. *Ann. Nutr. Metab.* **69**, 171–180. (doi:10.1159/000453077)
16. Godfrey KM, Reynolds RM, Prescott SL, Nyirenda M, Jaddoe VW, Eriksson JG, Broekman BF. 2017 Influence of maternal obesity on the long-term health of offspring. *Lancet Diabetes Endocrinol.* **5**, 53–64. (doi:10.1016/S2213-8587(16)30107-3)
17. Smith J *et al.* 2009 Effects of maternal surgical weight loss in mothers on intergenerational transmission of obesity. *J. Clin. Endocrinol. Metab.* **94**, 4275–4283. (doi:10.1210/jc.2009-0709)
18. Seckl JR. 2004 Prenatal glucocorticoids and long-term programming. *Eur. J. Endocrinol.* **151**, 49–62. (doi:10.1530/eje.0.151U049)
19. Langley-Evans SC, Phillips GJ, Benediktsson R, Gardner DS, Edwards CR, Jackson AA, Seckl JR. 1996 Protein intake in pregnancy, placental glucocorticoid metabolism and the programming of hypertension in the rat. *Placenta* **17**, 169–172. (doi:10.1016/S0143-4004(96)80010-5)
20. Reynolds RM. 2013 Programming effects of glucocorticoids. *Clin. Obstet. Gynecol.* **56**, 602–609. (doi:10.1097/GRF.0b013e31829939f7)
21. Dalziel SR, Walker NK, Parag V, Mantell C, Rea HH, Rodgers A, Harding JE. 2005 Cardiovascular risk factors after antenatal exposure to betamethasone: 30-year follow-up of a randomised controlled trial. *Lancet* **365**, 1856–1862. (doi:10.1016/S0140-6736(05)66617-2)
22. Phillips DI, Walker BR, Reynolds RM, Flanagan DE, Wood PJ, Osmond C, Barker DJ, Whorwood CB. 2000 Low birth weight predicts elevated plasma cortisol concentrations in adults from 3 populations. *Hypertension* **35**, 1301–1306. (doi:10.1161/01.HYP.35.6.1301)
23. Phillips DI, Matthews SG. 2011 Is perinatal neuroendocrine programming involved in the developmental origins of metabolic disorders? *World J. Diabetes* **2**, 211–216. (doi:10.4239/wjd.v2.i12.211)
24. Yehuda R, Engel SM, Brand SR, Seckl J, Marcus SM, Berkowitz GS. 2005 Transgenerational effects of post traumatic stress disorder in babies of mothers exposed to the World Trade Centre attacks during pregnancy. *J. Clin. Endocrinol. Metab.* **90**, 4115–4118. (doi:10.1210/jc.2005-0550)
25. Alastalo H, Raikokonen K, Pesonen AK, Osmond C, Barker DJP, Heinonen K, Kajantie E, Eriksson JG. 2013 Early life stress and blood pressure levels in late adulthood. *J. Hum. Hypertens.* **27**, 90–94. (doi:10.1371/journal.pone.0069011)
26. Rayfield S, Plugge E. 2017 Systematic review and meta-analysis of the association between maternal smoking in pregnancy and childhood overweight and obesity. *J. Epidemiol. Community Health* **71**, 162–173. (doi:10.1136/jech-2016-207376)
27. Mattsson K, Källén K, Longnecker MP, Rignell-Hydbom A, Rylander L. 2013 Maternal smoking during pregnancy and daughters' risk of gestational diabetes and obesity. *Diabetologia* **56**, 1689–1695. (doi:10.1007/s00125-013-2936-7)
28. Oken E, Levitan EB, Gillman MW. 2008 Maternal smoking during pregnancy and child overweight: systematic review and meta-analysis. *Int. J. Obes.* **32**, 201–210. (doi:10.1038/sj.ijo.0803760)
29. Behl M *et al.* 2013 Evaluation of the association between maternal smoking, childhood obesity, and metabolic disorders: a National Toxicology Program Workshop review. *Environ. Health Perspect.* **121**, 170–180. (doi:10.1289/ehp.1205404)
30. Philips EM, Jaddoe VWV, Trasande L. 2017 Effects of early exposure to phthalates and bisphenols on cardiometabolic outcomes in pregnancy and childhood. *Reprod. Toxicol.* **68**, 105–118. (doi:10.1016/j.reprotox.2016.08.015)
31. Heindel JJ *et al.* 2017 Metabolism disrupting chemicals and metabolic disorders. *Reprod. Toxicol.* **68**, 3–33. (doi:10.1016/j.reprotox.2016.10.001)
32. Fall CHD. 2011 Evidence for the intra-uterine programming of adiposity in later life. *Ann. Hum. Biol.* **38**, 410–428. (doi:10.3109/03014460.2011.592513)
33. Eriksson JG, Forsen T, Tuomilehto HJ, Barker DJP. 2001 Early growth and coronary heart disease in later life: longitudinal study. *Br. Med. J.* **322**, 949–953. (doi:10.1136/bmj.322.7292.949)
34. Law CM, Shiell AW, Newsome CA, Syddall HE, Shinebourne EA, Fayers PM, Martyn CN, de Swiet M. 2002 Fetal, infant, and childhood growth and adult blood pressure: a longitudinal study from birth to 22 years of age. *Circulation* **105**, 1088–1092. (doi:10.1161/hc0902.104677)
35. Fall CHD *et al.* 2008 Adult metabolic syndrome and impaired glucose tolerance are associated with different patterns of body mass index gain during infancy; data from the New Delhi birth cohort. *Diabetes Care* **31**, 2349–2356. (doi:10.2337/dc08-0911)
36. Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJP. 2003 Early adiposity rebound in childhood and risk of type 2 diabetes in adult life. *Diabetologia* **46**, 190–194. (doi:10.1007/s00125-002-1012-5)
37. Bhargava SK *et al.* 2004 Relation of serial changes in childhood body mass index to impaired glucose tolerance in young adulthood. *New Engl. J. Med.* **350**, 865–875. (doi:10.1056/NEJMoa035698)
38. Adair LS *et al.* 2013 Associations of linear growth and relative weight gain during early life with adult health and human capital in countries of low and middle income: findings from five birth cohort studies. *Lancet* **382**, 525–534. (doi:10.1016/S0140-6736(13)60103-8)
39. Li Y *et al.* 2015 Birth weight and later life adherence to unhealthy lifestyles in predicting type 2 diabetes: prospective cohort study. *Br. Med. J.* **351**, h3672. (doi:10.1136/bmj.h3672)
40. Owen CG, Whincup PH, Cook DG. 2011 Breast-feeding and cardiovascular risk factors and outcomes in later life: evidence from epidemiological studies. *Proc. Nutr. Soc.* **70**, 478–484. (doi:10.1017/S0029665111000590)
41. Horta BL, Loret de Mola C, Victora CG. 2015 Long-term consequences of breastfeeding on cholesterol, obesity, systolic blood pressure and type 2 diabetes: a systematic review and meta-analysis. *Acta Paediatr.* **104**, 30–37. (doi:10.1111/apa.13133)
42. Fall CHD *et al.* 2011 Infant-feeding patterns and cardiovascular risk factors in young adulthood: data from five cohorts in low- and middle-income countries. *Int. J. Epidemiol.* **40**, 47–62. (doi:10.1093/ije/dyq155)
43. Roseboom TJ, Painter RC, van Abeelen AF, Veenendaal MV, de Rooij SR. 2011 Hungry in the womb: what are the consequences? Lessons from the Dutch famine. *Maturitas* **70**, 141–145. (doi:10.1016/j.maturitas.2011.06.017)
44. Ravelli G-P, Stein ZA, Susser MW. 1976 Obesity in young men after famine exposure in utero and early infancy. *New Engl. J. Med.* **295**, 349–353. (doi:10.1056/NEJM197608122950701)
45. Hult M, Tornhammer P, Ueda P, Chima C, Edstedt Bonamy A, Ozumba B, Norman M. 2010 Hypertension, diabetes and overweight: looming

legacies of the Biafran famine. *PLoS ONE* **5**, e13582. (doi:10.1371/journal.pone.0013582)

46. Li Y, He Y, Qi L, Jaddoe VW, Feskens EJ, Yang X, Ma G, Hu FB. 2010 Exposure to the Chinese famine in early life and the risk of hyperglycemia and type 2 diabetes in adulthood. *Diabetes* **59**, 2400–2406. (doi:10.2337/db10-0385)
47. Li Y *et al.* 2011 Exposure to the Chinese famine in early life and the risk of hypertension in adulthood. *J. Hypertens.* **29**, 1085–1092. (doi:10.1097/HJH.0b013e328345d969)
48. Painter RC, Osmond C, Gluckman P, Hanson M, Phillips DI, Roseboom TJ. 2008 Transgenerational effects of prenatal exposure to the Dutch famine on neonatal adiposity and health in later life. *Br. J. Obstet. Gynaecol.* **115**, 1243–1249. (doi:10.1111/j.1471-0528.2008.01822.x)
49. Stein AD, Wang M, Ramirez-Zea M, Flores R, Grajeda R, Melgar P, Ramakrishnan U, Martorell R. 2006 Exposure to a nutrition supplementation intervention in early childhood and risk factors for cardiovascular disease in adulthood: evidence from Guatemala. *Am. J. Epidemiol.* **164**, 1160–1170. (doi:10.1093/aje/kwj328)
50. Conlisk AJ, Barnhart HX, Martorell R, Grajeda R, Stein AD. 2004 Maternal and child nutritional supplementation are inversely associated with fasting plasma glucose concentration in young Guatemalan adults. *J. Nutr.* **134**, 890–897. (doi:10.1093/jn/134.4.890)
51. Webb AL, Conlisk AJ, Barnhart HX, Martorell R, Grajeda R, Stein AD. 2005 Maternal and childhood nutrition and later blood pressure levels in young Guatemalan adults. *Int. J. Epidemiol.* **34**, 898–904. (doi:10.1093/ije/dyi097)
52. Kinra S, Sarma KVR, Ghafoorunissa MVVR, Ravikumar R, Mohan V, Wilkinson IB, Cockroft JR, Davey Smith G, Ben-Shlomo Y. 2008 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. *Br. Med. J.* **337**, a605. (doi:10.1136/bmj.a605)
53. Hawkesworth S, Walker CG, Sawo Y, Fulford AJ, Jarjou LM, Goldberg GR, Prentice A, Prentice AM, Moore SE. 2011 Nutritional supplementation during pregnancy and offspring cardiovascular disease risk in The Gambia. *Am. J. Clin. Nutr.* **94**, 1853S–1860S. (doi:10.3945/ajcn.110.000877)
54. Stewart CP, Christian P, Schulze KJ, Leclerq SC, West Jr KP, Khatry SK. 2009 Antenatal micronutrient supplementation reduces metabolic syndrome in 6- to 8-year-old children in rural Nepal. *J. Nutr.* **139**, 1575–1581. (doi:10.3945/jn.109.106666)
55. Stewart CP, Christian P, LeClerq SC, West Jr KP, Khatry SK. 2009 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.* **90**, 132–140. (doi:10.3945/ajcn.2008.27368)
56. Vaidya A, Saville N, Shrestha BP, Costello AM, Manandhar DS, Osrin D. 2008 Effects of a maternal multiple micronutrient supplement on children's weight and size at 2 years of age in Nepal; follow-up of a double blind randomised controlled trial. *Lancet* **371**, 452–454. (doi:10.1016/S0140-6736(08)60172-5)
57. Devakumar D, Chaube SS, Wells JC, Saville NM, Ayres JG, Manandhar DS, Costello A, Osrin D. 2014 Effect of antenatal multiple micronutrient supplementation on anthropometry and blood pressure in mid-childhood in Nepal: follow-up of a double-blind randomised controlled trial. *Lancet Glob. Health* **2**, e654–e663. (doi:10.1016/S2214-109X(14)70314-6)
58. Khan AI, Kabir I, Hawkesworth S, Ekström EC, Arifeen S, Frongillo EA, Persson LÅ. 2015 Early invitation to food and/or multiple micronutrient supplementation in pregnancy does not affect body composition in offspring at 54 months: follow-up of the MINIMat randomised trial, Bangladesh. *Matern. Child Nutr.* **11**, 385–397. (doi:10.1111/mcn.12021)
59. Hawkesworth S, Wagatsuma Y, Kahn AI, Hawlader MD, Fulford AJ, Arifeen SE, Persson LÅ, Moore SE. 2013 Combined food and micronutrient supplements during pregnancy have limited impact on child blood pressure and kidney function in rural Bangladesh. *J. Nutr.* **143**, 728–734. (doi:10.3945/jn.112.168518)
60. Ekström EC, Lindström E, Raqib R, El Arifeen S, Basu S, Brismar K, Selling K, Persson LÅ. 2016 Effects of prenatal micronutrient and early food supplementation on metabolic status of the offspring at 4.5 years of age. The MINIMat randomized trial in rural Bangladesh. *Int. J. Epidemiol.* **45**, 1656–1667. (doi:10.1093/ije/dyw199)
61. Potdar RD *et al.* 2014 Improving women's diet quality pre-conceptionally and during gestation: effects on birth weight and prevalence of LBW; a randomized controlled efficacy trial in India (Mumbai Maternal Nutrition Project). *Am. J. Clin. Nutr.* **100**, 1257–1268. (doi:10.3945/ajcn.114.084921)
62. Kumaran K *et al.* 2017 The Pune Rural Intervention in Young Adolescents (PRIYA) study: design and methods. *BMC Nutrition* **3**, 41. (doi:10.1186/s40795-017-0143-5)
63. Nguyen PH *et al.* 2017 Impact of preconceptional micronutrient supplementation on maternal mental health during pregnancy and postpartum: results from a randomized controlled trial in Vietnam. *BMC Womens Health* **17**, 44. (doi:10.1186/s12905-017-0401-3)
64. Hambidge KM *et al.* 2014 Preconception maternal nutrition: a multi-site randomized controlled trial. *BMC Pregnancy Childbirth* **14**, 111. (doi:10.1186/1471-2393-14-111)
65. Gillman MW, Oakley H, Baghurst PA, Volkmer RE, Robinson JS, Crowther CA. 2010 Effect of treatment of gestational diabetes mellitus on obesity in the next generation. *Diabetes Care* **33**, 964–968. (doi:10.2337/dc09-1810)
66. Guillemette L, Durksen A, Rabbani R, Zarychanski R, Abou-Setta AM, Duhamel TA, McGavock JM, Wicklow B. 2017 Intensive gestational glycemic management and childhood obesity: a systematic review and meta-analysis. *Int. J. Obes.* **41**, 999–1004. (doi:10.1038/ijo.2017.65)
67. Tanvig M, Vinter CA, Jørgensen JS, Wehberg S, Ovesen PG, Lamont RF, Beck-Nielsen H, Christesen HT, Jensen DM. 2014 Anthropometrics and body composition by dual energy X-ray in children of obese women: a follow-up of a randomized controlled trial (the Lifestyle in Pregnancy and Offspring [LiPO] study). *PLoS ONE* **9**, e89590. (doi:10.1371/journal.pone.0089590)
68. Tanvig M, Vinter CA, Jørgensen JS, Wehberg S, Ovesen PG, Beck-Nielsen H, Christesen HT, Jensen DM. 2015 Effects of lifestyle intervention in pregnancy and anthropometrics at birth on offspring metabolic profile at 2.8 years: results from the Lifestyle in Pregnancy and Offspring (LiPO) study. *J. Clin. Endocrinol. Metab.* **100**, 175–183. (doi:10.1210/jc.2014-2675)
69. Patel N *et al.* 2017 Infant adiposity following a randomised controlled trial of a behavioural intervention in obese pregnancy. *Int. J. Obes.* **41**, 1018–1026. (doi:10.1038/ijo.2017.44)
70. Blake-Lamb T, Locks LM, Perkins ME, Woo Baidal JA, Cheng ER, Taveras EM. 2016 Interventions for childhood obesity in the first 1,000 days. *Am. J. Prev. Med.* **50**, 780–789. (doi:10.1016/j.amepre.2015.11.010)
71. Fewtrell MS. 2011 Breast feeding and later risk of CVD and obesity: evidence from randomised trials. *Proc. Nutr. Soc.* **70**, 472–477. (doi:10.1017/S0029665111000589)
72. Martin RM *et al.* 2017 Effects of promoting long-term, exclusive breastfeeding on adolescent adiposity, blood pressure, and growth trajectories: a secondary analysis of a randomized clinical trial. *JAMA Pediatr.* **171**, e170698. (doi:10.1001/jamapediatrics.2017.0698)
73. Khan AI, Hawkesworth S, Ekström EC, Arifeen S, Moore SE, Frongillo EA, Yunus M, Persson LÅ, Kabir I. 2013 Effects of exclusive breastfeeding intervention on child growth and body composition: the MINIMat trial, Bangladesh. *Acta Paediatr.* **102**, 815–823. (doi:10.1111/apa.12282)
74. Al-Khudairy L *et al.* 2017 Diet, physical activity and behavioural interventions for the treatment of overweight or obese adolescents aged 12 to 17 years. *Cochrane Database Syst. Rev.* **6**, CD012691. (doi:10.1002/14651858.CD012691)
75. Mead E *et al.* 2017 Diet, physical activity and behavioural interventions for the treatment of overweight or obese children from the age of 6 to 11 years. *Cochrane Database Syst. Rev.* **6**, CD012651. (doi:10.1002/14651858.CD012651)
76. Waters E, de Silva-Sanigorski A, Burford BJ, Brown T, Campbell KJ, Gao Y, Armstrong R, Prosser L, Summerbell CD. 2011 Interventions for preventing obesity in children. *Cochrane Database Syst. Rev.* **12**, CD001871. (doi:10.1002/14651858.CD001871.pub3)
77. Luyckx VA, Bertram JF, Brenner BM, Fall CH, Hoy WE, Ozanne SE, Vikse BE. 2013 Effect of fetal

and child health on kidney development and long-term risk of hypertension and kidney disease. *Lancet* **382**, 273–283. (doi:10.1016/S0140-6736(13)60311-6)

78. Bansal A, Simmons RA. 2018 Epigenetics and developmental origins of diabetes: correlation or causation? *Am. J. Physiol. Endocrinol. Metab.* **315**, E15–E28. (doi:10.1152/ajpendo.00424.2017)
79. Lillycrop KA, Burdge GC. 2012 Epigenetic mechanisms linking early nutrition to long term health. *Best Pract. Res. Clin. Endocrinol. Metab.* **26**, 667–676. (doi:10.1016/j.beem.2012.03.009)
80. James P *et al.* 2018 Candidate genes linking maternal nutrient exposure to offspring health via DNA methylation: a review of existing evidence in humans with specific focus on one-carbon metabolism. *Int. J. Epidemiol.* **47**, 1910–1937. (doi:10.1093/ije/dyy153)
81. Kühnen P *et al.* 2016 Interindividual variation in DNA methylation at a putative POMC metastable epiallele is associated with obesity. *Cell Metab.* **24**, 502–509. (doi:10.1016/j.cmet.2016.08.001)
82. Oliver MH, Jaquiery AL, Bloomfield FH, Harding JE. 2007 The effects of maternal nutrition around the time of conception on the health of the offspring. *Soc. Reprod. Fertil. Suppl.* **64**, 397–410.
83. Fleming TP *et al.* 2018 Origins of lifetime health around the time of conception: causes and consequences. *Lancet* **391**, 1842–1852. (doi:10.1016/S0140-6736(18)30312-X)
84. McMullen S, Langley-Evans SC, Gambling L, Lang C, Swali A, McArdle HJ. 2012 A common cause for a common phenotype: the gatekeeper hypothesis in fetal programming. *Med. Hypotheses* **78**, 88–94. (doi:10.1016/j.mehy.2011.09.047)
85. Pembrey M *et al.* 2014 Human transgenerational responses to early-life experience: potential impact on development, health and biomedical research. *J. Med. Genet.* **51**, 563–572. (doi:10.1136/jmedgenet-2014-102577)