Winter 12-1-2017

Developmental origins of health and disease: current knowledge and potential mechanisms

Daniel J. Hoffman
Rutgers University - New Brunswick/Piscataway, dhoffman@aesop.rutgers.oup.com

Rebecca M. Reynolds
The University of Edinburgh

Daniel B. Hardy
Physiology and Pharmacology, daniel.hardy@schulich.uwo.ca

Feature Article

Developmental origins of health and disease: current knowledge and potential mechanisms

Daniel J. Hoffman, Rebecca M. Reynolds, and Daniel B. Hardy

Epidemiologic and clinical research has provided a large body of evidence supporting the developmental origins of health and disease (DOHaD), but there has been a relative dearth of mechanistic studies in humans due to the complexity of working with large, longitudinal cohorts. Nonetheless, animal models of undernutrition have provided substantial evidence for the potential epigenetic, metabolic, and endocrine mechanisms behind DOHaD. Furthermore, recent research has explored the interaction between the environment and the gastrointestinal system by investigating how the gut microbial ecology may impact the capacity for nutrient processing and absorption in a manner that may limit growth. This review presents a summary of current research that supports the concept of DOHaD, as well as potential mechanisms and interactions that explain how nutrition in utero and during early childhood influences lifelong health.

INTRODUCTION

Human health, often defined as the absence of disease, is determined by a number of factors related to diet, environment, and economics, as well as country of residence and educational attainment. The confluence of these areas highlights the interplay of both biological and socioeconomic factors that ultimately allow for normal developmental processes to occur and optimal health during the life of a human. Over the past 30 years, substantial attention has been given to the influence of nutrition in utero and during critical periods of growth on health in adulthood, an area termed the "fetal origins hypothesis" or "fetal programming"; it was later modified to the "developmental origins of health and disease" (DOHaD) to better reflect both the gestational and postnatal periods. Beginning with the work of Barker and Osmond in 1986,[1] it was documented that chronic diseases commonly associated with higher income had become more prevalent in lower-income regions of England and Wales. Thereafter, a number of studies were conducted using the Hertfordshire birth cohort, which included more than 15 000 babies for whom birth weight and early feeding practices were documented in the early part of the 20th century.[2] From this cohort, it was shown that children born small are at a higher risk for developing type 2 diabetes (T2D), hypertension, and coronary heart disease.[2–4] Similar results have been published using birth cohorts from South Africa, Finland, the United States, Brazil, and China, among others.[5–9] However, a consistent challenge to human cohort studies has been the elucidation of clear physiological or environmental mechanisms behind the findings.

Early epidemiological research of DOHaD used data from several well-documented famines and historical cohorts (Table 1[1–4,6–18]). Among these, the most

Affiliation: *D.J. Hoffman* is with the Department of Nutritional Sciences, Program in International Nutrition, and the New Jersey Institute for Food, Nutrition, and Health, Center for Childhood Nutrition Education and Research, Rutgers University, New Brunswick, New Jersey, USA. *R.M. Reynolds* is with the University/British Heart Foundation Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, United Kingdom. *D.B. Hardy* is with the Department of Obstetrics & Gynecology and the Department of Physiology & Pharmacology, The Children's Health Research Institute and the Lawson Health Research Institute, University of Western Ontario, London, Ontario, Canada.

Correspondence: *D.J. Hoffman*, Department of Nutritional Sciences, School of Environmental and Biological Sciences, Rutgers University, 61 Dudley Rd, New Brunswick, NJ 08901. E-mail: dhoffman@aesop.rutgers.edu.

Key words: developmental origins, disease, epigenetics, fetal origins, glucocorticoids, health, obesity.

doi: 10.1093/nutrit/nux053

Table 1 **Summary of cohort studies on early nutrition and adult health and disease**

Reference	Country/region	Study design	Sample size	Independent variable	Outcome variable	Conclusion
Barker and Osmond (1986)[1]	England and Wales	Ecological	291 082 infants; 649 817 adults	Infant death in 1921–1925	Death by coronary heart disease	Positive association
Hales et al. (1991)[2]	England	Birth cohort	468 men	Fetal growth, infant growth	Glucose tolerance	Positive association
Osmond et al. (1993)[3]	England	Birth cohort	5585 women; 10141 men	Growth	Coronary heart disease	Negative association
Fall et al. (1995)[4]	England	Birth cohort	290 men	Birth weight	Coronary heart disease	Negative association
Musa et al. (2016)[6]	South Africa	Birth cohort	1935 men and women	Birth length, weight gain	Coronary heart disease	Positive association
Perng et al. (2016)[7]	USA	Birth cohort	963 boys and girls	Body mass index Z score, Weight gain	Obesity	Positive association No clear association
Kannisto et al. (1997)[8]	Finland	Ecological	816 997 men and women	Famine exposure	Mortality and life expectancy	Positive association
Victora et al. (2003)[9]	Brazil	Birth cohort	5914 men	Birth weight	Blood pressure	Negative association
Ravelli et al. (1998)[10]	Netherlands	Retrospective	702 men and women	Famine exposure	Glucose tolerance	Inverse association
Stein et al. (2006)[11]	Netherlands	Retrospective	299 men and women	Famine exposure	Blood pressure	Positive association
Wang et al. (2016)[12]	China	Retrospctive	781 men and women	Famine exposure	Type 2 diabetes	Positive association
Huang et al. (2010)[13]	China	Retrospective	35 025 women	Famine exposure	Blood pressure	Positive association
Finer et al. (2016)[14]	Bangladesh	Retrospective	190	Famine exposure	Glucose tolerance DNA methylation	Positive association Positive association
Hanson and Smith (2013)[15]	USA	Retrospective	715 men and677 women	Famine exposure	Mortality risk	Positive association
St Clair (2005)[16]	Netherlands	Retrospective	1 600 000 men and women	Famine exposure	Schizophrenia	Positive association
Crookston et al. (2011)[17]	Peru, Ethiopia, India, and Vietnam	Retrospective	12 000 boys and girls	Stunting	Cognition	Negative relationship
Walker et al. (2005)[18]	Jamaica	Intervention	103 boys and girls	Stunting	Cognition	Negative relationship

well known is the Dutch famine cohort, which included men and women born before, during, and after the Nazi-imposed famine of 1944–1945.[10] Adults who were exposed to the famine during mid or late gestation were reported to have lower glucose tolerance compared with those exposed early in gestation or never exposed to the famine.[10] Additionally, adults who had been exposed to famine during any 10-week period of gestation were almost 3 times more likely to have hypertension than unexposed adults.[11] In China, adults who were exposed in utero to the Chinese famine of 1958 had a 50% increased risk for T2D compared with those not exposed to famine.[12] It was also reported that adults exposed to the famine in utero were almost 4 times more likely to have hypertension than those who had postnatal exposure to the famine.[13] Consistent with these studies, adults who experienced gestational exposure to famine in Bangladesh and remained underweight as adults were more likely to be hyperglycemic compared with unexposed adults.[14] Finally, in terms of mortality, Utah pioneers whose mothers were pregnant during periods of severe food shortages in the mid-19th century were found to have had a higher risk for mortality compared with those whose mothers were not exposed, but the effect was most consistent for men.[15] Although there are certainly methodological differences among various studies of famine exposure and later health, the basic aspects of such studies are relatively consistent and allow for broad conclusions based on their findings.

In addition to the association between nutritional deprivation early in life and risk for nutrition-related chronic diseases, a number of studies have found a link between poor nutrition early in life and mental health and cognitive development. For example, prenatal exposure to the Chinese famine from 1959 to 1961 nearly doubled the risk of schizophrenia for those in the 1960 exposure group compared with those born after the famine[16]; these results are strikingly similar to the relative risk of 2.7 for schizophrenia found in the Dutch famine cohort.[19] Studies from different countries have also found that poor nutrition in childhood has a negative impact on cognition. In Peru, stunted children (defined as height-for-age Z score [HAZ] < -2.0) scored significantly lower ($P < 0.05$) on a series of cognitive tests compared with taller children.[17] Children who experienced catch-up growth (indicating a positive change in HAZ) had cognitive scores similar to those of children who remained stunted.[20] However, a study on growth and cognitive performance that included more than 8000 children from 4 developing countries found that children who recovered height from age 1 year to age 8 years performed poorly compared with children who were never stunted but scored better than children who remained stunted[21]; this suggests that timing of nutritional interventions is vital to improving human capital. The point is made even more clear by a study of stunted children in Jamaica who received psychosocial stimulation and scored markedly higher on IQ, verbal, and reading tests compared with stunted children who did not receive such stimulation.[18] Recently, as some of the children from this cohort are now parents, it was reported that offspring of stunted parents scored lower on a battery of cognition tests, independent of birth weight and height-for-age,[22] but it is not clear if the effects are related to social or biological factors. Furthermore, stunted children in India who received nutritional supplementation for 6 months had cognitive test scores similar to those of children who remained stunted, as well as those who recovered height.[23] Although the degree of stunting at age 2 years has been shown to be related to consistent and long-term cognitive deficits, such deficits in a cohort from Cebu, Philippines, declined by age 11 years.[24] The studies reviewed herein indicate that the timing of interventions is clearly critical to the overall impact of nutrition on brain development during gestation and childhood, an area of research that warrants much greater attention to improve human capital throughout the world, but especially in lower-income countries.

In summary, a large number of studies provide evidence that supports the concept of DOHaD. Most studies that used data from famine and longitudinal cohorts have found that poor nutrition and/or growth during the "first 1000 days" are risk factors for a number of chronic diseases later in life. Exactly how and when different tissue and organ systems are influenced by nutrient deprivation remain major research questions, but new studies are providing intriguing insights into potential mechanisms behind DOHaD. It is important to consider how conflicting studies can inform the research community in a way that shapes future research designs and agendas. To facilitate such considerations, this review explores recent research on early nutrition and body composition with links to chronic diseases, how maternal undernutrition influences adipose tissue depots and dyslipidemia, the role of glucocorticoid exposure in utero and in adult health, and potential mechanisms that explain how poor nutrition in utero and during childhood influences disease risk in adulthood.

OBESITY AND BODY COMPOSITION

Nutritional deficits from conception through early childhood that result in individuals being born small for gestational age (SGA) or growth retarded are associated with adult obesity.[25–30] This has been covered thoroughly in a review of studies with similar and conflicting conclusions by Yu et al,[31] and results from such studies are summarized in Table 2.[5,26,32–34,36–38,40–44] Briefly, one of

Table 2 **Summary of cohort studies on early nutrition and obesity and body composition**

Reference	Country/region	Study design	Sample size	Independent variable	Outcome variable	Conclusion
Yang et al. (2008)[5]	China	Retrospective		Famine exposure	BMI	U-shaped relationship
Stein et al. (2004)[26]	Netherlands	Retrospective	1826	Famine exposure	Birth weight; crown-to-heel length; head circumference	Negative association
Ravelli et al. (1976)[32]	Netherlands	Retrospective	300 000	Famine exposure	Body mass index	Positive association
Eriksson et al. (2001)[33]	Finland	Birth cohort	5210	Size at birth	Body mass index	U-shaped relationship
Newby et al. (2005)[34]	Sweden	Birth cohort	18 000	Birth weight	Body mass index	U-shaped relationship
Painter et al. (2008)[35]	Netherlands	Transgenerational	1496	Maternal famine exposure	Ponderal index	Positive association
Dolan (2007)[27]	USA	Retrospective		Birth weight	Truncal fat mass	Inverse relationship
Ylihärsilä (2007)[28]	Finland	Birth cohort	2003	Birth weight	Body mass index	Inverse relationship
					Lean body mass	Positive association
Kensara (2005)[39]	England	Case-control	32	Birth weight	Percentage body fat mass	Inverse association
					Truncal fat mass	Inverse association
Te Velda (2003)[29]	Netherlands	Retrospective	229	Size at birth	Fat mass Trunk fat/limb fat ratio	Positive association
						Positive association
Gunnarsdottir (2004)[30]	Iceland	Birth cohort	3707	Size at birth	Body mass index	Positive relationship
					Truncal fat mass	Inverse relationship
Salgin et al. (2015)[36]	South Africa	Birth cohort	2352	Gain of weight and length	Skinfold thickness	Positive association
Crowther et al. (2008)[37]	South Africa	Birth cohort	152	Growth rate	Insulin resistance	Positive association
Vidulich et al. (2007)[38]	South Africa	Birth cohort	476	Size at birth	Bone mineral content	Inverse relationship

the first studies of gestational famine exposure and obesity showed that men from the Dutch famine cohort who were exposed to famine during the first 2 trimesters of gestation were more likely to be obese than those exposed during late gestation and early infancy.[32] Similarly, the prevalence of obesity was greater for women who were exposed to the Chinese famine in utero than for those who were not exposed to the famine.[5] Eriksson et al.[33] reported a U-shaped relationship between birth weight and body mass index (BMI) such that adults born weighing < 2500 g or > 3500 g were more likely to be classified as obese than those born weighing between 2500 g and 3500 g. In a study of 18 000 Swedish women, those born small or large (< 2500 g or ≥ 4000 g) had a higher BMI than women born with a "normal" weight.[34] There may even be transgenerational effects of famine exposure on obesity and health as offspring of women from the Dutch famine cohort were born with a higher ponderal index and were almost twice as likely as offspring of women unexposed to the famine to report "poor health" as adults.[35] It is important to view the totality of these results in light of the fact that BMI was often used as the index for adiposity. It is well known that BMI is an imperfect tool outside of screening for obesity, and clinical studies that assess body composition and body fat distribution are often more helpful in elucidating the effect of early nutrition on adult body composition.

It is also well recognized that birth size reflects only 1 dimension of growth and the postnatal period may play an equal, if not greater, role in overall growth and adult health such that the rate of growth, assessed as change in BMI *Z* score (BMIZ), or rate of weight gain is predictive of adult BMI or body composition.[36] Perhaps the most novel study developed to address growth patterns, as well as social and biological factors influencing growth and development, is the Birth to 20 (Bt20) cohort study.[6] Briefly, 3200 babies were recruited at birth in Soweto, Johannesburg, South Africa in the early 1990s and underwent measures of body composition, growth, and socioeconomic indicators. Postnatal growth patterns (rate of weight or length gain) were used to differentiate between size at birth and/or growth as a risk factor for outcomes studied. In the Bt20 cohort, birth weight and weight gain were not associated with negative lipid profiles when adjusted for linear growth from birth to 4 years.[6] However, rapid gain of height and weight from birth were associated with being overweight in adolescence.[40] Furthermore, rapid weight gain early in life was associated not only with increased adult adiposity but also early menarche, a known risk factor for metabolic disorders and some forms of cancer.[41,42] In contrast, a study of children from the United States with intrauterine growth retardation were found

to have a higher waist circumference and greater insulin resistance than children born with normal birth weight, independent of changes in BMIZ from birth to age 10 years.[43] However, a separate study showed that children who experienced greater childhood weight gain had greater fat mass, independent of birth weight, than children who had a slower rate of weight gain.[44]

The interaction between birth weight and weight gain in early childhood is highlighted in the Project Viva study of US children, in which gain in BMIZ after 1 year was associated with greater adiposity, independent of birth size.[7] For all children, regardless of birth weight, a rapid change in BMIZ from 6 months to 1 year postnatal was associated with increased insulin resistance.[7] In a separate analysis, a gain in BMIZ in the first 6 postnatal months was associated with higher systolic blood pressure in childhood.[7] Although excess body fat alone is not pathogenic, it is related to disease risk, and, indeed, children who were born small and then grew faster than peers were more likely to be insulin resistant than those born larger or those with a slower postnatal growth rate.[37] In addition to body fatness, it has been reported that birth size and postnatal growth exert independent effects on skeletal development, depending on the timing of growth. For example, being born small and remaining small through the first year of life was associated with both smaller bones and bones with lower mineral content in the femoral neck.[38] Nutrition during gestation clearly has profound and lasting effects on body size and body fat distribution, as well as on development of metabolically active tissue, contributing to metabolic disorders. However, different methods of measuring body composition were used in these studies, as were different statistical analyses, which underscores the need forfuture studies to normalize methods so esults are more comparable with existing studies.

With regard to postnatal nutrition insults, a number of studies have found that stunting is a risk factor for obesity and central adiposity. In the mid-1990s, a study conducted in 4 countries undergoing the nutrition transition found that stunting in adolescence was a risk for obesity in adulthood.[45] Many, but not all, clinical studies of stunting and risk for obesity support this initial finding. For example, in Senegal, adolescent girls who were stunted before the age of 2 years were more likely to accumulate subcutaneous fat in the trunk and arms than nonstunted girls, even when analyses were adjusted for BMI.[46] In Guatemala, children who were stunted had a BMI above the median for US children of the same age but their level of extremity fat was low, as assessed using skinfold measurements.[47] Data from the same cohort showed that adults who were severely stunted as children had greater central fat, independent of total fat mass and other confounding factors, than those who were moderately or never stunted.[48] Stunted children in Brazil who were studied for 4 years gained more fat in the truncal region than children from the same shantytowns who were not stunted.[49] However, other studies have found different relationships. For example, longitudinal analyses of the Bt20 cohort found that stunting at age 2 years was not associated with a high BMI or central adiposity.[50] Also, a study of indigenous children in Bolivia showed that stunting was associated with lower BMIZ and body fatness assessed using skinfold measurements.[51] At the same time, in a Brazilian cohort, stunting was not associated with higher BMI or fat mass compared with children who were of normal height.[52] Although differing from other cohort studies, results from the Brazilian cohort, which had a relatively low prevalence of undernutrition (< 10%), showed that poor growth early in life resulted in shortness later in life; while this was a predictor of poor health outcomes and other factors associated with poverty, it was not a predictor of excess adiposity or obesity. What is important to consider when these complementary and conflicting results are presented is that each study, although perhaps similar in participant characteristics or inclusion criteria, may differ in terms of outcome measurements, sample size, and the socioeconomic environment in which the study sample has grown and developed. Although investigators attempt to control for all possible confounding factors, the interactions among a large number of factors are bound to influence associations, thus preventing consensus on the question being studied.

An abundance of clinical research has provided solid evidence that poor nutrition in the "first 1000 days" has a negative impact on body composition and body fat distribution in ways that may increase the risk for metabolic disorders and other chronic diseases. Although these studies provide some insight into physiological consequences of poor nutrition during critical periods of growth and development, they still do not provide sufficient insight into precise mechanisms that explain why poor growth increases the risk of various chronic diseases. What follows is a detailed discussion of potential metabolic and hormonal mechanisms that support these clinical studies.

DYSLIPIDEMIA AND IMPAIRED METABOLIC OUTCOMES

The liver and adipose are critical for proper lipid and glucose metabolism in mammals, and impaired development and functioning of either of these tissues results in dyslipidemia, leading to obesity and insulin resistance and culminating in the metabolic syndrome.[53,54] Given the role of the liver in cholesterol, fatty acid, and

glucose homeostasis, it is not surprising that hepatic dysfunction underlies several of the symptoms that characterize the metabolic syndrome.[53,54] Because adipose tissue is critical to the proper storage of dietary and de novo hepatic lipids, compromised adipose function can also contribute toward the dysregulation of both lipid homeostasis and insulin sensitivity.[55] In addition to the metabolic syndrome, dyslipidemia can also lead to liver fibrosis (and the end stage, cirrhosis), a disease that contributes to almost 45% of all deaths in the developed world.[56,57]

Clinical evidence linking maternal undernutrition and dyslipidemia

The work of David Barker and others has now clearly established that adverse in utero events can permanently alter physiological processes, leading to dyslipidemia and the metabolic syndrome.[58] The early evidence that an impairment of liver size and/or function was involved with dysmetabolism came from the strong correlation between reduced abdominal circumference at birth and elevated total and low-density lipoprotein cholesterol later in life.[59] Second, intrauterine growth restriction (IUGR), caused by either placental insufficiency or maternal malnutrition, often results in asymmetric organ development, whereby there is a reduction in the growth of less essential organs, including the liver, lungs, and kidneys.[60,61] Third, there is a strong inverse relationship between birth weight and obesity or glucose intolerance, which are both under the regulation of the liver.[2,32,62,63] Altered adipose function in humans can also contribute to dyslipidemia, given that low-birth-weight offspring exhibit defects in the expression of critical genes (eg, *Cyclin T2* and *HNFα*) involved with leptin secretion and insulin sensitivity.[64,65]

The major factor influencing the inverse relationship between low-birth-weight offspring and metabolic disease in postpartum life is nutrition-induced accelerated growth, which culminates with an earlier onset of the symptoms of dyslipidemia and the metabolic syndrome, compared with offspring without catch-up growth.[66–69] Given that liver development is highly compromised in IUGR pregnancies, babies born from these pregnancies undergo the greatest catch-up growth during postnatal life.[60,61] Postpartum recovery in hepatic growth is evident in SGA children who undergo hypersomatotropism as early as day 4 of postnatal life due to increased hepatic and circulating insulin growth factor 1 (IGF-1).[70] This is detrimental in the long term given that low-birth-weight infants with rapid postnatal growth exhibit a higher low-density lipoprotein/high-density lipoprotein ratio, likely attributed to impaired cholesterol homeostasis in the liver.[71] Although future noninvasive imaging studies are warranted to track liver and adipose development in these IUGR infants from fetal life to adulthood, to date, animal models of maternal undernutrition have shed great light into the molecular (ie, epigenetic) mechanisms underlying the fetal programming of dyslipidemia.

Animal models linking maternal undernutrition and dyslipidemia

Idiopathic IUGR due to placental insufficiency occurs in approximately 8% of all pregnancies.[72,73] Moreover, maternal undernutrition in pregnancy can also lead to IUGR depending upon the timing (pre- vs postconception) and severity of the insult.[66,74–77] To date, the use of various nutritional models of IUGR (eg, uterine ligation, maternal nutrient restriction, and maternal protein restriction) has expanded knowledge of the distinct contributions of both the mother and fetus toward long-term metabolic deficits. Uterine ligation or ablation in rodent pregnancy is an excellent model of idiopathic IUGR given that placental insufficiency leads to decreases in both oxygenation and substrate availability for the fetus alone.[78–80] This model leads to impaired birth weight and lower liver-to–body weight ratios, followed by dyslipidemia and T2D, which are carried into the F2 generation.[81–85] These metabolic deficits exist, in part, due to altered glucose transporter expression, impairment of fatty-acid metabolism, increased glucocorticoid activity, augmented glucose production, and blunted insulin suppression, all within the liver.[81,83,86–88] It is noteworthy that these rat offspring also exhibit decreased hepatic and circulating insulin-like growth factor-1 (Igf-1), which is critical for insulin function, glucose metabolism, and growth.[89] In the guinea pig, uterine ablation manifests in hepatic perisinusoidal or periportal fibrosis in postnatal life concomitant with increased expression of profibrogenic markers, including *Smad4*, *Tgfβ1*, and *Mmp2*.[90]

Maternal nutrient restriction (MNR) or materal protein restriction (MPR) models provide insight into the contribution of maternal malnutrition alone on long-term hepatic function and dyslipidemia. Similar to offspring in the uterine ligation model, MNR offspring are compromised at birth, then experience rapid postnatal catch-up growth.[75,91,92] However, in this model, the impact of a decrease in both maternal and placental weight during pregnancy must be taken into consideration.[75,93] Sheep and rat studies have demonstrated that MNR leads to higher hepatic lipid and glycogen content in the offspring, manifesting in glucose intolerance and insulin insensitivity.[91,94] The impaired glucose tolerance in MNR sheep offspring is also attributed, in part, to increased circulating cortisol and augmented hepatic *Pepck* expression.[94] In contrast with uterine-ligated offspring,

MNR offspring with catch-up growth exhibit increases in Igf-1, which has been associated with decreased longevity but not necessarily metabolic disease.[91] Overall, although maternal nutrient status may directly alter the expression of the these hepatic genes via epigenetic mechanisms, this may also occur indirectly, given that maternal undernutrition increases hypoxia in fetal metabolic (ie, liver, kidney) organs.[91,93,95]

Finally, maternal low-protein diets and/or placental insufficiency often lead to fetal deficiencies in amino acids, which are critical for growth.[96,97] Therefore, the MPR model is a very distinct and relevant model to examine how reduced amino acids lead to asymmetric IUGR, without any impact on maternal physiology (eg, weight gain or food intake).[62,98] Depending on the timing of protein restoration, MPR offspring display glucose intolerance, visceral obesity, hypercholesterolemia, and hypertension despite no differences in postnatal food intake.[98–104] The hypercholesterolemia exhibited in MPR male offspring following catch-up growth was attributed to silencing of *Cyp7a1*, the critical enzyme in cholesterol metabolism.[99] Interestingly, the expression and activity of hepatic Cyp3a and Cyp2c11 was augmented in these MPR offspring, implying that long-term drug metabolism (ie, statins) could be influenced by compromised fetal development.[105] Because testosterone is a major substrate for Cyp3a and Cyp2c11 enzymes, this may also explain the lower circulating testosterone levels in MPR male offspring and, consequentially, the long-term sexual dimorphism that exists in this model.[104] Similar to uterine-ligated offspring, MPR offspring with catch-up growth have lower hepatic Igf-1 expression; however, this decrease is mainly attributed to the effects of protein restriction during lactation.[98] Collectively, the MPR model truly highlights the main tenet of Barker's "predictive adaptive response," which suggests that when there is no nutritional mismatch in postnatal life, MPR offspring do not exhibit any alterations to cholesterol catabolism, insulin sensitivity, or drug metabolism later in life.[99,100,105]

Although human and animal studies have certainly established strong links between maternal malnutrition and metabolic deficits in the offspring, the origin of IUGR and long-term dysmetabolism are not only linked with a poor nutritional environment in utero. Certainly, any disturbances in the maternal–fetal hormonal milieu during pregnancy could influence the etiology of IUGR and, more important, the long-term programming of endocrine function, growth, and cardiovascular health.

GLUCOCORTICOID EXPOSURE AND ADULT HEALTH

Cortisol, the principal circulating glucocorticoid hormone in humans, is essential for normal fetal development and tissue maturation. One of the major hypotheses to explain DOHaD is fetal glucocorticoid overexposure.[106] This hypothesis is supported by substantial experimental data (in rodents and other species) where manipulations that increase fetal glucocorticoid exposure cause lower offspring birth weight and associated cardiovascular risk factors, including higher blood pressure and insulin resistance, as well as mental health and cognitive problems, in later life.[107] Indeed, early studies suggested that the effects of maternal undernutrition are partly mediated by glucocorticoids. For example, the hypertension induced in the offspring by a maternal low-protein diet is prevented by pharmacological blockade of glucocorticoid biosynthesis and can be reintroduced by replacement of corticosterone.[108] Thus, it is important to review recent data that may implicate the influence of cortisol on specific pathways that may mediate disease risk, such as altered maternal cortisol due to maternal stress and/or obesity.

In humans, available data also suggest that glucocorticoid programming occurs. Maternal treatment with synthetic steroids in pregnancy is associated with lower birth weight and insulin resistance in young adulthood.[109] Higher endogenous maternal cortisol levels measured in blood, saliva, urine, or amniotic fluid have been linked to offspring lower birth weight or shorter gestation at delivery.[110] The differences in cortisol are modest but have major influences on pregnancy outcomes. In 1 study, a 2.6% greater salivary cortisol level at wakening was associated with a 1-week shortening of pregnancy duration.[111] However, the findings may be confounded by timing of sample collection, gestational age at time of sample collection, and maternal characteristics and are dependent on whether total cortisol or free (bioavailable) cortisol is measured. For example, in a large study of 2810 women, the association between higher maternal serum cortisol measured in the early second trimester and lower birth weight was only observed among women with morning cortisol measurements, and the relationship attenuated after adjustment for confounding factors.[112] Regardless, it is clear that maternal cortisol levels do exert some influence on fetal growth and pregnancy.

There is also increasing evidence that the adverse effects of fetal glucocorticoid exposure extend well beyond fetal growth. Comparisons of siblings show that those who were exposed to high cortisol in utero have lower IQ levels at age 7 years and complete 1 fewer year of schooling.[113,114] Such within-sibship comparisons are less likely to be confounded by shared familial characteristics, such as background socioeconomic characteristics, than more standard observational epidemiology studies. Additionally, both endogenous maternal cortisol levels in pregnancy and use of exogenous antenatal

steroids have been linked to changes in childhood brain development and behavior.[115,116] Prenatal exposure to elevated maternal cortisol levels has also been linked with increased cardiovascular risk factors in the offspring at age 42 years.[117] The adult daughters of mothers with the highest free cortisol tertile during the third trimester of pregnancy versus daughters of mothers with the lowest cortisol tertile had a 36.7% (95% confidence interval [CI], 8.4%–72.5%) greater mean 10-year coronary heart disease risk score, calculated using the Framingham risk algorithm incorporating diabetes, systolic and diastolic blood pressure, total and high-density lipoprotein cholesterol, smoking, age, and sex. One possible mechanism explaining maternal glucocorticoid levels and birth outcomes may be a perturbation of the hypothalamic-pituitary-adrenal (HPA) axis.

The regulation of the maternal HPA axis undergoes dramatic changes during pregnancy, with circulating cortisol levels rising markedly to approximately 3-fold nonpregnant levels by the third trimester.[118] The fetus is protected from high maternal glucocorticoid levels by the placental barrier enzyme 11ß-hydroxysteroid dehydrogenase type 2 (HSD2), which converts active cortisol to inactive cortisone. In animal models, manipulations that reduce HSD2 activity (either pharmacological inhibition, maternal low-protein diet, or genetic modification to knock down HSD2) increase fetal exposure to glucocorticoids, which results in lower birth weight.[107] Placental HSD2 also appears to be a key player in human developmental origins of health and disease. Children homozygous for mutations in *hsd11b2* encoding HSD2 have lower birth weight than their unaffected or heterozygous siblings.[119] Lower placental HSD2 activity correlates with reduced birth weight in some (but not all) human studies and higher blood pressure in 3-year-olds who had a normal birth weight.[120,121] Observational studies show that women who consume large amounts of liquorice (which contains glycyrrhizin, an HSD2 inhibitor) during pregnancy have a shorter gestation.[122] Intriguingly their children have increased odds of attention-deficit-hyperactivity disorder behaviors, score lower on tests of IQ, and have poorer memory, and the girls enter puberty earlier.[123] Direct placental perfusion studies done immediately postpartum show that liquorice derivatives allow substantially increased passage of active cortisol from the maternal circulation to the fetal circulation, suggesting fetal glucocorticoid exposure as a mechanism underlying the adverse offspring consequences of maternal liquorice consumption in pregnancy.[124] Importantly, placental HSD2 is downregulated by other programming influences, including maternal malnutrition, inflammation, or stress in rodent models and maternal stress in humans, suggesting placental HSD2 activity may be a key mechanistic pathway underpinning programming.[107,125] Studies using HSD2$^{-/-}$ mice fed a maternal low-protein diet tested whether reduced placental HSD2 activity was a crucial link between the maternal environment (undernutrition) and adverse programming outcomes. The HSD2$^{-/-}$ fetuses of mice fed a low-protein diet had reduced fetal weight compared with fetuses of mice fed a control diet, indicating that the growth-restricting effects of the maternal low-protein diet act in addition to any reduction in HSD2 activity, thereby refuting this as the sole mechanistic pathway.[126]

Although the focus of this review has been on maternal undernutrition and adverse fetal and infant outcomes, the challenge facing the DOHaD field is maternal obesity, with 1 in 5 women in Western societies obese during the antenatal period. Epidemiological studies show that offspring born to obese mothers have an increased risk of premature death from cardiovascular events, increased cardiometabolic risk factors, and a host of other health issues, including poorer neuropsychiatric and neurocognitive development and increased susceptibility to asthma.[127–130] No studies have investigated whether this may be mediated by altered maternal cortisol and/or placental HSD2 activity in obese pregnant women. Observational studies show maternal cortisol levels are lower in obese pregnant women and that obese pregnant women have decreased HPA axis activity, as evidenced by lower corticotrophin-releasing hormone (CRH) levels compared with normal-weight women.[112,131,132] Preliminary data suggest this may impact on outcomes. For example, in 1 study, CRH levels at 28 weeks were an independent predictor of gestation at delivery in analyses adjusting for confounding factors (a mean decrease in CRH of −0.25 pmol/L [95%CI, −0.45 to −0.043 pmol/L] for every 1-day increase in gestational age at delivery).[131] This observation suggests that adverse pregnancy outcomes may result not only from high maternal cortisol levels and increased HPA axis activity (as previously found in the animal studies and existing human studies) but also from lower maternal cortisol levels and decreased HPA axis activity (as observed in obese pregnant women). This suggests there is an optimal glucocorticoid exposure for normal fetal growth and gestation length: fetal glucocorticoid overexposure associates with lower birth weight and preterm delivery, whereas underexposure associates with higher birth weight and longer gestation at delivery. Both fetal glucocorticoid over- and underexposure are associated with adverse consequences for offspring health. Further studies are needed to test his hypothesis.

Based on the studies reviewed, the available evidence supports altered glucocorticoid action, sensitivity and/or transfer to the fetus as a major endocrine pathway linking fetal growth to later life disease.

Dysregulation of this pathway occurs in both maternal undernutrition and overnutrition impacting on fetal glucocorticoid exposure and subsequent growth. The molecular mechanisms underpinning altered glucocorticoid exposure to fetal growth remain poorly understood, but candidate processes are discussed in the next section.

UNDERLYING MECHANISMS

To date, emerging animal and clinical studies are beginning to elucidate how poor nutrition in utero or during the first 2 years of life influences disease risk later in life. These include epigenetic and transcriptional mechanisms, cellular stresses, metabolic adaptations, alterations to the microbiome, and/or social determinants. Some of these mechanisms (ie, epigentetic) are instigated at the time of the perinatal insult, whereas other mechanisms (ie, endoplasmic reticulum stress) play a greater role to influence metabolic disease during postpartum life (ie, during catch-up growth).[99,100] Epigenetic mechanisms elucidate many of the long-term effects of these perinatal insults given that they can quickly influence gene expression in a tissue- and gene-specific manner to adapt to suboptimal (eg, undernutrition) windows of developmental plasticity. However, these epigenetic changes can have long-lasting implications on gene expression in postnatal life, resulting in metabolic disease. Mechanisms of epigenetic action include DNA methylation, post-translational histone modifications, and microRNA-mediated repression. IUGR offspring resulting from various degrees of maternal malnutrition and/or placental insufficiency may exhibit different or similar metabolic deficits due to global, tissue, or site-directed epigenetic modifications.

DNA methylation

The chromatin environment can be altered during perinatal life due to direct DNA methylation whereby methyl groups are added to CpG sites on DNA by members of the DNA methyltransferase family. Given that the essential amino acid methionine provides a critical donor to DNA methylation, it is not surprising that alterations in dietary folate/folic acid (involved in methionine metabolism and required for methylation reactions) during perinatal life have a profound effect on DNA methylation profiles and long-term gene expression.[133] In humans, adipose-derived stem cells (ADSCs) from low-birth-weight adult men display increased DNA methylation surrounding the promoter of *CYCLIN T2*, which is attributed to impaired leptin secretion.[64] Moreover, IUGR infants exhibit hypermethylation of the *HNF4α* gene, a nuclear receptor, which, when impaired, leads to T2D.[65,134] Lillycrop et al[135,136] found that MPR in rats leads to decreased hepatic expression of DNA methyltransferase-1 and lower DNA methylation surrounding the promoter of the glucocorticoid receptor (*Gr*), culminating in higher expression of *Gr* in the offspring. Conversely, high levels of methyl vitamins (eg, folate, vitamins B_{12} and B_6) in rodent pregnancy promotes DNA methylation of the leptin promoter, contributing to obesity and insulin resistance in the offspring.[133] It should be noted that undernutrition does not always result in increased DNA methylation. In sheep, a maternal diet lower in amino acids led to decreased DNA methylation surrounding the promoter *of* insulin growth factor 2 receptor (*Igf2r*) in fetal white adipose tissue.[137] In primate studies, baboon MNR offspring exhibit decreased methylation of the promoter of *PCK1* concomitant with augmented *PEPCK* expression, which is implicated in hyperglycemia and T2D.[93,138,139]

Maternal undernutrition leading to altered DNA methylation can also have transgenerational consequences. For example, uterine ligation in pregnancy culminated in offspring with higher DNA methylation in the promoter of hepatic *Igf-1*, which persists into the F2 generation even if the F1 IUGR offspring are completely nourished.[84,140] Interestingly, supplementing the diet of the F1 IUGR offspring with folic acid, choline, betaine, vitamin B_{12}, and other essential nutrients prevented the hypermethylation of the *Igf-1* promoter in the F2 generation, alleviating the symptoms of the metabolic syndrome.[84]

Post-translational histone modifications

Post-translational histone modification, a second major epigenetic mechanism involved in fetal programming, influences the chromatin environment via methylation, acetylation, phosphorylation, ubiquitination, and/or ADP-ribosylation of histones.[141] In general, euchromatin is associated with histones, which are acetylated on specific residues (eg, K9 and K14 of histone H3), whereas heterochromatin contains predominately hypoacetylated and/or methylated histones.[142] These histone modifications occur and can be sustained by a diverse range of histone-modifying enzymes whose expression levels may also be influenced by external environmental insults (eg, low nutrients) during critical perinatal windows of development.[142]

Rat models have demonstrated that uterine ligation, maternal hypoxia, and MPR lead to post-translational histone modifications and altered hepatic and pancreatic function in the offspring.[99,103,143,144] As previously mentioned, MPR-induced IUGR rat male offspring exhibit hypercholesterolemia concomitant with a

decrease in postnatal Cyp7a1 expression, in both the short and long term.[99] This was associated with enhanced trimethylation of histone H3 (lysine 9) and suppressed acetylation of histone H3 (Lysine 9, 14), all markers of chromatin silencing, within the LXRE region of the *Cyp7a1* promoter from 3 weeks to 4 months of postnatal life.[99] In contrast, 4-month-old MPR female offspring did not exhibit changes in histone modifications or altered cholesterol levels.[99] The trigger of these histone modifications in fetal life are due, in part, to MPR-mediated decreases in lysine demethylases involved in removing trimethyl groups of histone H3 (lysine 9). Maternal protein restriction has also led to silencing of the promoter of liver X receptor (*Lxrα*) in the liver at 4 months of age due to decreased histone H3 acetylation (lysine 9, 14), resulting in increased hepatic gluconeogenesis.[103] In a model of maternal hypoxia (eg, 12% oxygen) in rodent pregnancy leading to decreased maternal food intake and IUGR, the 12-month-old IUGR male offspring displayed hypoglycemia concomitant with increased histone H3 trimethylation (lysine 9) of the hepatic *G6Pase* promoter.[144]

MicroRNAs

MicroRNAs (miRNAs) can also play a key role in the fetal programming of metabolic disease. MicroRNAs are short, noncoding RNA molecules 20–25 nucleotides in length that regulate gene expression via degradation of mRNA species and/or repression of translation.[145,146] Because they can bind to 3'-UTR with partial sequence homology to induce cleavage or repression of productive translation, it is well established that a single miRNA may have numerous targets in the genome.[147] Conversely, given the nature of miRNA targeting, a single mRNA transcript can theoretically be targeted by several miRNAs.[147]

In low-birth-weight humans and the offspring of undernourished rats, higher adipose miR-483–3p levels have been associated with decreased growth differentiation factor-3 (*gdf3*), leading to enhanced lipotoxicity, decreased lipid storage, and higher insulin resistance.[148] Moreover, MPR during pregnancy and lactation has been demonstrated to increase the hepatic expression of the entire miR-29 family in postnatal life, which silences the expression of *Igf-1*, which is believed to contribute to decreased growth.[98] Interestingly, restoration of maternal dietary proteins in MPR offspring at birth prevented miR-29 repression of *Igf-1*.[98] In the guinea pig uterine ligation model, undernutrition in utero suppressed miR-146a expression in 5-month-old offspring, concomitant with an increase in miR-146a's target profibrotic gene, *smad4*.[90] Elegant rodent studies have demonstrated that individual changes in maternal dietary lipids (ie, soybean, olive oil, fish oil, linseed, or palm oil) can have differential effects on programming the long-term expression of miRNAs in metabolic tissues.[149] Moreover, the dietary lipid modifications that led to alterations in the long-term expression of these miRNAs were pregnancy- and tissue-specific (eg, the liver).[149]

Indirect effect of postnatal catch-up growth in mediating long-term metabolic dysfunction

In addition to changes in the epigenome initiated by insults during perinatal life, postnatal catch-up growth in undernourished offspring also plays a major role in exacerbating the metabolic outcomes in low-birth-weight children.[66–69] Given that the undernourished neonatal liver undergoes major postnatal catch-up growth, it is very likely that the stress of active hepatocyte replication and growth during this period may lead to greater detrimental metabolic deficits, which only arise after this window of nutrient recovery. A major mechanism likely involved in this rapid growth–triggered process is endoplasmic reticulum (ER) stress. Endoplasmic reticulum stress ensues when ER homeostasis is compromised, leading to luminal accumulation of misfolded or unfolded proteins.[100] Endoplasmic reticulum stress can be triggered by alterations in amino acids, hypoxia, increase in lipid load, impaired disulfide bond formation, compromised Ca^{2+} homeostasis, decreased N-linked glycosylation, and oxidative stress. In response to ER stress, the unfolded protein response tries to alleviate the ER by increasing the expression of chaperone proteins involved in refolding misfolded proteins and/or attenuating protein translation. However, if ER stress persists, apoptosis is initiated, leading to alterations in gene expression and cell function. In 5-month-old MPR offspring with postnatal catch-up growth (due to restoration of proteins at weaning), there is augmented hepatic ER stress attributed to impaired insulin sensitivity.[100]

In contrast, hepatic ER stress concomitant with impaired insulin signaling is not evident in fetal life or in 5-month-old MPR offspring that do not undergo catch-up growth.[100] This would suggest that the low-protein diet itself does not play a direct role in instigating ER stress, but rather, the ER stress is caused by the catch-up growth that results from the nutritional mismatch after weaning. In a rat model of perinatal nicotine exposure that led to IUGR offspring and long-term dyslipidemia, ER stress was also evident in the adipose tissue after postnatal catch-up growth.[150,151] Higher oxidative stress, lipid overload, and/or impaired disulfide bond formation likely triggers the cascade that leads to chronic ER stress when there is a nutritional mismatch in postnatal life.[83,85] Endoplasmic reticulum stress in

these IUGR offspring with catch-up growth could also alter epigenetic events, such as alterations in microRNAs. For example, activation of ER stress can induce miR-29a.[152] It is noteworthy that miR-29a is increased in MPR offspring with both catch-up growth and ER stress, concomitant with suppression of both of its target genes, *Igf-1* and *pAkt-1* (Ser473).[98,100]

Metabolic adaptations following growth retardation

Studies of potential metabolic mechanisms to explain the link between in utero or postnatal undernutrition and adult health have focused on specific components of energy expenditure, such as resting metabolic rate (RMR) or substrate oxidation, because certain metabolic adaptations may increase the risk for adiposity later in life. Two studies found no differences in RMR in stunted children compared with normal-height children.[153–155] However, others found a lower rate of energy expenditure in growth-retarded children compared with normal-height children.[156,157] As noted previously, differences in the results of studies of body composition or energy metabolism can often be attributed to differences in methodologies or statistical analyses. For example, the 2 cited studies that show metabolic differences used ratios for energy metabolism per unit of body composition rather than linear regression analysis, which would be the more appropriate statistical approach.

Studies of substrate oxidation are more consistent than those of energy expenditure in that a number of studies have found metabolic adaptations associated with poor growth in utero or during early childhood. One of the first studies of metabolic adaptations and poor growth studied a cohort of children in Brazil and found that stunted children oxidized fat at a lower rate than normal-height children from the same shantytowns of São Paulo, Brazil.[158] Adult men from the Hertfordshire cohort who were born small compared with others from the cohort born with a higher birth weight had a lower rate of daily fat oxidation.[159] Additionally, adults from the Buryat communities in southern Siberia who experienced growth retardation following the fall of the Soviet Union and were shorter than their peers had a lower rate of fat oxidation.[160] Finally, North Korean children who were either stunted or short for age had a significantly lower rate of fat oxidation ($P < 0.05$) than North Korean children who were not growth retarded.[161] These consistent findings across cultural and genetic differences suggest that poor growth, either in utero or during childhood, results in a metabolic adaptation that favors fat storage and promotes excess adiposity under the right environmental conditions. There are a number of potential explanations for these results, but they remain difficult to confirm given the ethical aspects of studying poor growth as it occurs. However, studies of large mammals may provide evidence for potential mechanisms.

With regard to metabolism of large mammals exposed to energy restriction, 1 study involved pigs born with low (L) or normal (N) birth weight that were subsequently fed either ad libitum or exposed to further energy restriction (R) following weaning and found that the L pigs had significantly lower fat oxidation ($P = 0.005$) than the N pigs.[162] Moreover, the rate of fat oxidation was 50% lower in the LR pigs than in the NR pigs. Mechanisms of metabolic adaptions following energy restriction based on results from both pig and human studies may be supported by a study in protein-restricted pigs, in which those pigs fed a 14% protein diet increased expression of lipogenic genes (eg, *FAS*, *PPARγ*, and *FABP4*) compared with pigs fed a 20% protein diet.[163] Additionally, the pigs on the low-protein diet had a lower expression of lipolytic genes than those on the normal-protein diet. Still, studies of sheep suggest that energy restriction alters substrate metabolism in a tissue-specific manner and may favor carbohydrate metabolism.[164,165] Nonetheless, given that the research cited above showed that poor growth is associated with less lean body mass[166] and poor bone development,[38] body composition compartments that are metabolically active, such adaptations that favor carbohydrate metabolism seem logical. At the same time, recent research discussed below suggests that changes in the microbiome or specific nutrient deficiencies (B vitamins) may also alter nutrient delivery or availability in ways that alter or interfere with normal metabolic pathways and could result in changes in substrate oxidation.

Role of the microbiome as a mediator between poor growth and chronic disease

Recently, the microbiome has been shown to differ between humans who are normal weight and those who are obese,[167] an observation that has generated novel hypotheses related to the role of the microbiome and factors that influence gut health in the growth and development of children. A great proportion of undernourished children live in communities with poor sanitation where the risk of intestinal infections is high and access to adequate nutrition is limited.[168] Persistent diarrhea is known to cause alterations in intestinal integrity, decrease the absorption of nutrients, cause inflammation, and increase the risk for other enteropathic conditions that promote undernutrition.[169] Growth faltering is sure to occur if repeated intestinal infections occur and poor nutrition prevents complete recovery of intestinal changes due to diarrhea, both of which may alter the gut

microbiome. What is not well known is whether changes in the microbiome are a result of undernutrition and/or what role the microbiome may have on the development of pathogenic phenotypes, such as obesity or metabolic adaptations to undernutrition.

Undernourished children have a less diverse gut microbiota than healthy children.[170] More importantly, it was recently reported that children suffering from subacute malnutrition had an "immature" microbiota compared with a standard curve developed from healthy children living in the same part of Bangladesh.[171] An important study of growth and microbiome found that microbiota transplanted from healthy or undernourished children to healthy mice resulted in normal or impaired growth, respectively.[172] Recently, an interesting analysis of common bacteria found in the human microbiome was presented in relation to the biosynthesis of B vitamins, and it was reported that riboflavin and niacin are among the vitamins most commonly synthesized by the human microbiota.[173] This finding is of particular importance because alterations in the bacterial milieu can plausibly alter the availability of key micronutrients involved in the tricarboxylic acid cycle and ATP synthesis, potentially altering energy metabolism. Although clinical studies to address this question are lacking, 1 study of maternal vitamin status and offspring adiposity showed that children born to women with low vitamin B_{12} status had greater adiposity and insulin resistance compared with those born to women with normal B_{12} status.[174] Thus, maternal B vitamin deficiencies may play a central role in adult body composition and chronic disease risk of offspring, as discussed in a review by Finer et al.[175] Moreover, the authors outline the impact that B vitamin deficiencies in utero have on 1-carbon metabolism, which could have downstream effects on metabolic processes, including carbohydrate and lipid metabolism, as well as methylation patterns of key genes involved in energy metabolism. Therefore, it is conceivable that microbiome disruptions or alterations may contribute to, or perpetuate, metabolic adaptations as discussed above, lending support to the notion that environmental conditions play a leading or complementary role in growth and the development of adult disease.

Social and economic determinants of growth and role in developmental origins of health and disease

Clearly a number of physiological mechanisms plausibly link poor growth early in life to chronic disease development in adulthood. At the same time, an area that often receives limited attention is the socioeconomic and environmental conditions in which children with poor growth develop. These areas are important to consider given that various social and environmental factors, such as education, income, access to food, and sanitation, play direct roles in fetal growth, nutrient availability, and maternal health. Data on the interaction between biological and social factors that influence growth and health are important to consider given the broader goal of improving health in all parts of the world.

Studying biological processes within the context of economic changes reveals subtle influences that may precede poor nutrition or impede adequate dietary intake, both of which influence subsequent growth and development. From the Bt20 cohort, improving socioeconomic status was determined to be protective against higher systolic blood pressure, independent of size at birth.[20] In addition, higher levels of social support and income were both found to be predictors of bone mineral content, even after adjusting for body composition and pubertal development.[21] Exposure to the Chinese famine and living in higher-income areas were independently associated with an increased risk of T2D, suggesting that prosperity may exacerbate the risk for chronic disease formerly thought to be only attributable to famine exposure.[176] Such interactions are most apparent in a study by Li et al[177] in which in utero famine exposure increased the risk of T2D, yet those adults exposed to the famine who ate a Western diet were even more likely to have T2D compared with those who ate a traditional diet, clearly illustrating the intricate interaction between in utero and environmental exposures in regards to chronic disease development.

Although these studies focus on birth weight, a number of studies of postnatal growth retardation have shown the impact of socioeconomic status on risk and/or recovery from stunting as well as long-term effects of stunting on human capital. In South Africa, a higher birth weight was protective against stunting in boys and girls, but higher maternal education was protective in girls, whereas higher socioeconomic status was protective for boys.[23] As discussed earlier, even children who recover from stunting by age 5 years face considerable cognitive challenges compared with children of normal height, including challenges as severe as children with stunting remaining stunted.[23] A multicountry study of growth and human capital found that children who are born with a higher birth weight or have greater gain in height by age 2 years attained a higher level of schooling, an amount estimated to increase adult income by 5%.[2] This result is even more pronounced when the same data were used to evaluate broad aspects of human capital, including economic productivity, and found that height-for-age at 2 years was the best predictor of overall human capital.

Although the focus of this review has been on potential physiological mechanisms that explain how early growth influences adult health and disease, it remains

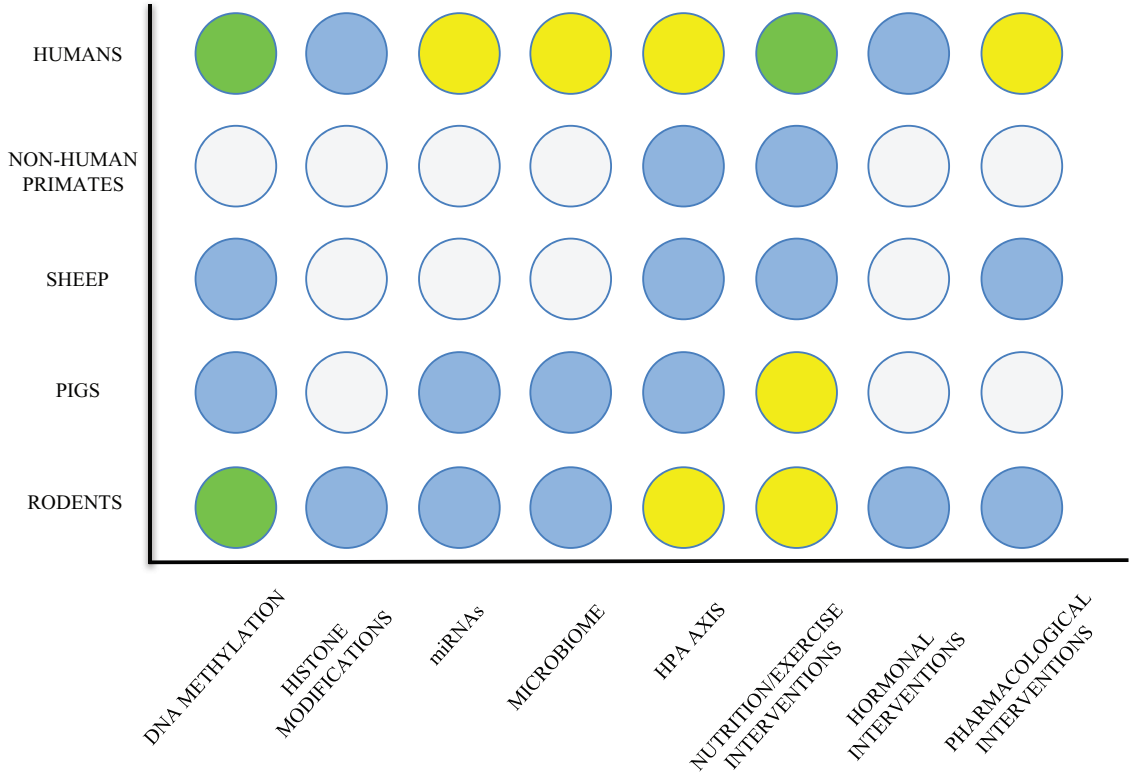

Figure 1 **Research density map of areas where abundant or limited resarch on developmental origins of health and disease have been conducted and published.** The *x* and *y* axes depict species and areas of research, respectively, with density of publications depicted by colored circles. Green indicates 50–100 publications, blue indicates 20–49 publications, yellow indicates 1–19 publications, and white indicates no publications. *Abbreviations:* HPA, hypothalamic-pituitary-adrenal; miRNA, microRNA.

important for investigators to appreciate and encourage multidisciplinary research of DOHaD. Given that poor growth has a considerable impact on both economic and human conditions in many countries, but mostly in lower-income countries where the prevalence of undernutrition is still high, the social cost of this research is as important as the scientific discoveries.

INTEGRATION OF MECHANISMS AND FUTURE DIRECTIONS

The mechanisms discussed in this review highlight the complexity of studying DOHaD in the context of determining how poor nutrition during critical periods of development may increase the risk of chronic disease later in life. A PubMed search of research related to DOHaD, ranging from epigenetic studies in rodents to human interventions, revealed areas where abundant or limited research has been published, including animal models, species, nutritional exposure, outcome, or intervention. This search was not performed as part of a critical meta-analysis of the topic, but it does identify areas where more research needs to be focused (see Figure 1). A file with the specific numbers of publications by area is provided (see DOHaD Publication Frequency Summary in the Supporting Information online), and access to search terms and results is available from the authors.

However, although not all potential mechanisms were discussed in the present review, the collective results from rodent, large animal, nonhuman primate, and human studies reveal potential integrated mechanisms that underlie DOHaD. For example, changes in fetal cortisol metabolism following maternal exposure to glucocorticoids may impact body composition, as found in several studies of growth retardation and adult fat distribution.[39,178–180] Likewise, the epigenetic effects caused by undernutrition (ie, MPR) very likely influence lipid metabolism in an indirect manner by altering the expression of PPARγ and its downstream lipogenic targets in adipose and hepatic tissue.[88,181] Studies also strongly demonstrate how postnatal catch-up growth might exacerbate IUGR-induced metabolic deficits via the integration of several mechanisms. Indeed, catch-up growth of undernourished IUGR rodents leads to long-term hepatic ER stress and alterations in miRNAs, culminating in impaired endocrine signaling (ie, Igf-1, pAkt1 [Ser473]),[98,100] which is noteworthy because activation of ER stress increases the expression of miRNAs.[152,182] Of course, such extrapolations are open

to debate, and such debates are encouraged to inform research and policy agendas. What remains at the crux of these discussions is the differential and sometimes competing impact of various forms of undernutrition during different windows of tissue and organismal development.

As is often reported, the survivors of the Dutch famine winter developed different chronic diseases primarily based on when their mothers experienced the famine—specifically whether it occurred during early, middle, or late pregnancy.[32,183–186] Moreover, Sohi et al.[98,100,103,105] have published a number of studies on the differential effects of long-term hepatic cholesterol, gluconeogenesis, Igf-1, and drug metabolism in relation to the specific type of energy/nutrient restriction and timing of undernutrition. Regardless of the precise epigenetic, biochemical, or physiological outcomes found by the thousands of studies on DOHaD, there is still a general lack of consensus on how these mechanisms integrate with the original tenet of Barker's predictive adaptive response hypothesis: that a thrifty phenotype occurs when there is a mismatch in the predictive environment between perinatal and postnatal life.[187] Such consensus may remain elusive given the challenges noted. Moving forward, it is imperative that gaps in research be highlighted to facilitate the proposal of more general mechanisms. Even more important is the potential for existing hypotheses to be used to formulate safe interventions that can prevent or ameliorate chronic diseases related to perinatal undernutrition.

Moving forward—the efficacy of early life interventions

Over the last few decades, clinical studies and animal models have established strong links between an undernourished in utero environment and long-term metabolic disease, but additional studies are warranted to identify safe and efficacious interventions in early life to ameliorate or prevent these metabolic deficits in low birth-weight offspring. Regardless of the species, the developing organism is subject to windows of tissue plasticity during pregnancy and in early life, and this plasticity can be modified by external environmental cues. These cues can consist of alterations in nutrition, the microbiome, and/or the hormonal milieu.

From a nutrition standpoint, several studies have investigated the ability of vitamins, folic acid, lipids, and proteins to ameliorate the adverse effects of undernutrition on metabolic disease. In a maternal diabetes model of IUGR in rodents, supplementation with vitamins C and E in pregnancy prevented decreases in fetal liver weight and hepatic lipid peroxidation.[188] Given its role as a methyl donor for DNA methylation, folic acid shows promise in reversing some of the epigenetic mechanisms associated with undernutrition. Lillycrop et al[135,189] demonstrated that administration of folic acid (5 μg/g diet) during MPR pregnancy prevented decreases in DNA methylation to the promoters of hepatic *PPARα* and *GR* and subsequently diminished their expression in early life with widespread, long-term effects in the adult liver. The timing and dose of folic acid appear to be critical given that the periconceptional intake of folic acid (400 μg/d) led to an increase in DNA methylation of hepatic *Igf-2* and, subsequently, low birth weight.[190] As mentioned previously, alterations in maternal dietary lipids can have differential effects on the long-term expression of miRs and ultimately insulin sensitivity in adipose and liver tissue.[149,191] Furthermore, the addition of multiple nutrients (ie, folic acid, vitamin B_{12}) to the diet of undernourished offspring can exert multigenerational effects, as shown by the lack of impairments in hepatic and lipid homeostasis in an F2 generation given supplements compared with F2 offspring who were not given nutrient supplementation.[84] With regard to protein supplementation in IUGR offspring, the beneficial effects appears to be very promoter- and time-specific. In rats, full restoration of maternal proteins at birth prevents long-term decreases in hepatic cholesterol metabolism (eg, Cyp7a1) and Igf-1 but leads to greater expression of genes involved in gluconeogenesis (eg, G6Pase and 11β-HSD1).[98,99,103] Moreover, administration of meat-sourced amino acids (eg, 2.5% taurine) during gestation and the first weeks of neonatal life led to restoration of β cell mass in MPR offspring, which was attributed to normalization of DNA synthesis, apoptosis, and fetal islet vasculogenesis.[192,193] These studies illustrate the complexity of the relationship between the timing of nutritional interventions and the plasticity of organ-specific development, factors that are pertinent to designing interventions in human pregnancy. A systematic review of studies examining the long-term health benefits in children exposed to maternal antenatal multiple micronutrient supplementation found no evidence that, compared with iron and folic acid supplementation, routine maternal antenatal multiple micronutrient supplementation improved childhood survival, growth, body composition, blood pressure, respiratory, or cognitive outcomes.[194] The authors concluded: "We recommend follow-up studies in more of the multiple micronutrient trials. Further research into biological mechanisms by which an early advantage could be attenuated will help in our understanding of the intervention and in designing future trials" (p 181).[194]

As a complement to nutritional interventions, altering the hormonal milieu could also be very promising for reversing the adverse effects of undernutrition

during pregnancy on metabolism in postnatal life. One of the best examples is with the use of the glucagon-like peptide-1 (Glp-1) analog, Exendin-4 (Ex-4). Neonatal administration of Ex-4 to uterine-ligated IUGR rodent offspring prevented the long-term development of hepatic oxidative stress and insulin resistance.[83] Moreover, it exerted beneficial effects to pancreatic β cell function through increases in the expression of Pdx-1.[195] However, in sheep, neonatal Ex-4 administration in IUGR offspring did not improve insulin sensitivity, likely because of greater tissue (eg, pancreas) maturity at birth in this species.[196,197] Translation of such studies into human interventions is challenging because the Glp-1 class of drugs is not licensed for use during pregnancy. However, as an alternative approach to improve insulin sensitivity, therapy with metformin (a drug that is widely used in pregnancy and approved for use by the United Kingdom National Institute for Health and Care Excellence for treatment of women with gestational diabetes) in early life has also been efficacious in low-birth-weight individuals. In low-birth-weight prepubertal girls, treatment with metformin for 4 years reduced insulin resistance, dyslipidemia, and hyperandrogenism compared with controls.[198] Other clinical studies have demonstrated that only the combination of exercise and metformin in obese adolescents, regardless of birth weight, decreases BMI and percentage body fat.[199,200] In IUGR rats, postnatal treatment with metformin diminishes the upregulation of hepatic *Gr* normally associated with obesity and glucose intolerance in these offspring.[201] Two randomized controlled trials that tested an intervention with metformin to improve insulin sensitivity in obese pregnant women demonstrated no impact on infant birth weight, although infant ponderal index tended to be improved, suggesting a potential beneficial effect of the intervention.[202,203] The late timing of the intervention in the second trimester when the fetal growth trajectory is already established may have impacted on the outcomes, but follow-up of the children is warranted, particularly to establish whether there are any potential benefits of metformin intervention in pregnancy on infant body composition, as proposed in the MIG-TOFU study.[204]

Targeting nuclear receptors may have a more sustained impact, given their widespread roles in influencing endocrine and metabolic function. Female IUGR offspring treated with agonists to the lipid-sensing nuclear receptor PPARγ showed long-term insulin-sensitizing effects, although hypoglycemia was also exhibited.[181] Given the role of the liver X receptor (LXRα) in regulating cholesterol, glucose, and fatty-acid homeostasis, altering LXR activity in early life could impair several symptoms of the metabolic syndrome. A pilot study using the LXR agonist (GW3695) during neonatal life (postnatal day 5–15) in MPR offspring led to decreased total cholesterol levels concomitant with increased LXRα and Cyp7a1 by 3 weeks of age, but the long-term effects remain unclear.[205]

Finally, the use of prebiotics and probiotics to combat undernutrition and promote healthy growth is continuing to gain substantial research and policy attention, such that a number of systematic reviews on the topic have been published.[206–208] Briefly, in 1 study of undernourished children in India, providing probiotic- and prebiotic-fortified milk resulted in a 13–g/year greater gain in weight compared with the control children.[209] Saran et al[210] reported that stunted children who received probiotic treatment for 6 months gained nearly 1.5 cm more in length during treatment and had fewer reported cases of diarrhea compared with children who received standard isocaloric dietary treatments. Infants in China who were undernourished and received probiotic treatments using yogurt gained almost 0.5 kg more in weight over 9 months compared with control children.[211] In addition, the children in the treatment group had a greater increase in HAZ by the end of the 9-month treatment (0.123 vs 0.077; $P < 0.01$). What is not well understood is precisely how such treatments improve growth, be it through increased nutrient availability, reduced intestinal infections, or reduced gastric permeability. Also, it is unclear whether specific strains of bacteria or whether fermented foods that may contain other strains or nutrients are most effective in supporting growth in undernourished children. Thus, improving research in this area should focus on integrated and comprehensive assessment of metabolic parameters as well as markers of gastrointestinal health to better understand the mechanisms through which probiotics support growth and health in undernourished children.[212] Figure 2 summarizes the known neonatal interventions.

Regardless of the success of particular intervention strategies in animal models, caution must be approached in assessing their overall efficacy. The efficacy of the intervention is influenced by its duration with respect to organ (prenatal vs postnatal) development in a species-specific manner. Moreover, the impact of the intervention on epigenetic processes must also be considered to determine its long-term sustainability (i.e., from neonatal life to adulthood, and/or transgenerational) and specificity (i.e., global vs promoter specific). For the time being, the safest approach may be to focus on general dietary interventions to reduce the rate of catch-up growth in IUGR offspring and the indirect burden it exerts on organ development and long-term function.

CONCLUSION

The concept of DOHaD was initially met with a great deal of skepticism, but as studies began to show findings

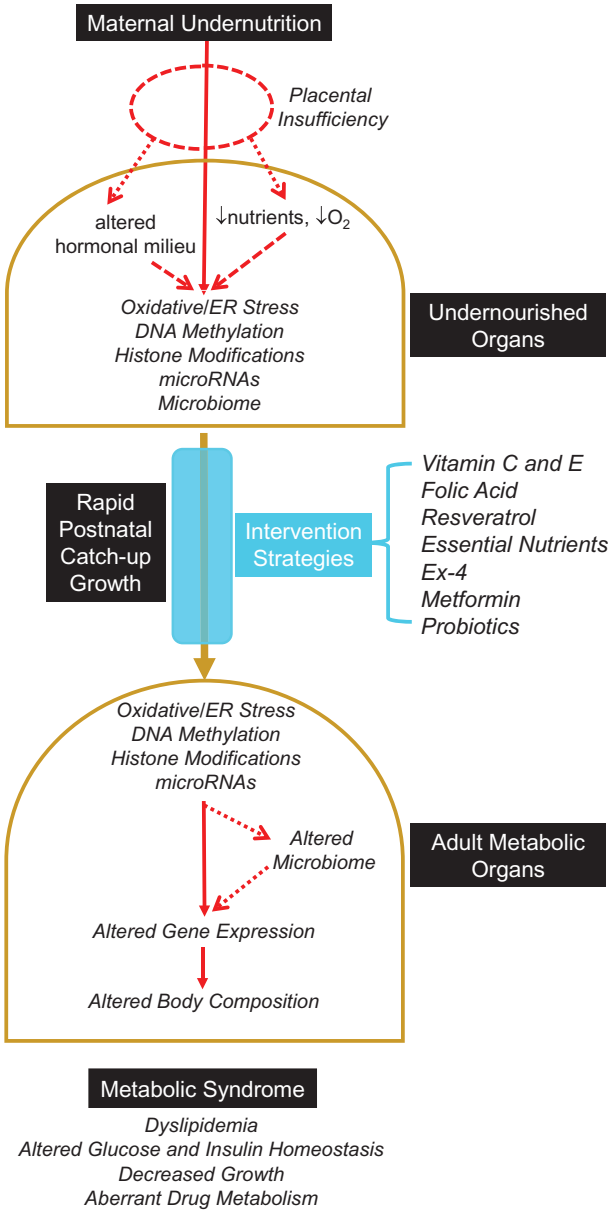

Figure 2 **Overview of the direct and indirect mechanisms underlying how undernutrition in utero impairs organ function, leading to the metabolic syndrome.** Direct pathways altered by maternal undernutrition are indicated by red solid arrows, whereas indirect pathways are indicated by red dashed arrows. Neonatal intervention strategies are illustrated by cyan arrows. *Abbreviation*: ER, endoplasmic reticulum.

similar to those of the Dutch famine and Hertfordshire cohorts, attention began to shift from epidemiological associations toward physiological mechanisms. With the advent of epigenetics, new and exciting possible mechanisms are being explored and new clinical and cohort studies are being developed to determine potential endocrine responses to undernutrition. As reviewed, particular adaptations following exposure to undernutrition vary according to the timing of the undernutrition, degree of maternal stress, and a number of social or economic factors. Clearly, the study design and sample, be it rodent, large mammal, or human, limit the implications of outcomes studied, whether it is response in the HPA axis, metabolic profiles, microbiome, or miRNAs. The challenge for the future of DOHaD research will be to develop cohort studies that use new technologies to test hypotheses based on mechanisms proposed by animal studies. It will also remain important to improve the overall understanding of how to moderate disease risk in populations with a high prevalence of undernutrition. Above all, research agendas and policies must support lower-income countries that continue to face economic and nutrition challenges and are most at risk for both the health and economic implications of DOHaD.

Acknowledgments

The authors would like to acknowledge the support of their institutions in the preparation of this article. They also extend their gratitude to Assenka Oksiloff for editorial guidance, Alessandro Bigoni for the preparation of the summary tables included in this review, and Adriana Carrieri for the literature search and preparation of the supplementary files.

Author contributions. DJH conceived of and contributed to the writing and editing of the manuscript, RMR contributed to the writing of the manuscript, and DBH contributed to writing of the manuscript and managed references. All authors gave final approval to the submitted and final version of the manuscript.

Funding. DJH is funded by the United States Agency for International Development (USAID EPA-A-00-09-00004) and the Busch Biomdeical Foundation. RMR is funded by the British Heart Foundation and Tommy's. DBH is funded by Canadian Institutes for Health Research (CIHR MOP 111001).

Declaration of interest. The authors have no relevant interests to declare.

Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

Appendix S1 **DOHaD publication frequency summary**

REFERENCES

1. Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet. 1986;327:1077–1081.

2. Hales CN, Barker DJ, Clark PM. Fetal and infant growth and impaired glucose tolerance at age 64. BMJ. 1991;303:1019–1022.
3. Osmond C, Barker DJ, Winter PD, et al. Early growth and death from cardiovascular disease in women. BMJ. 1993;307:1519–1524.
4. Fall CH, Vijayakumar M, Barker DJ, et al. Weight in infancy and prevalence of coronary heart disease in adult life. BMJ. 1995;310:17–19.
5. Yang Z, Zhao W, Zhang X, et al. Impact of famine during pregnancy and infancy on health in adulthood. Obes Rev. 2008;9(suppl 1):95–99.
6. Musa MG, Kagura J, Pisa PT, et al. Relationship between early growth and CVD risk factors in adolescents. J Dev Orig Health Dis. 2016;7:132–143.
7. Perng W, Hajj H, Belfort MB, et al. Birth size, early life weight gain, and midchildhood cardiometabolic health. J Pediatr. 2016;173:122–130.e1.
8. Kannisto V, Christensen K, Vaupel JW. No increased mortality in later life for cohorts born during famine. Am J Epidemiol. 1997;145:987–994.
9. Victora CG, Barros FC, Lima RC, et al. The Pelotas birth cohort study, Rio Grande do Sul, Brazil, 1982–2001. Cad Saúde Pública. 2003;19:1241–1256.
10. Ravelli AC, van der Meulen JH, Michels RP, et al. Glucose tolerance in adults after prenatal exposure to famine. Lancet. 1998;351:173–177.
11. Stein AD, Zybert PA, van der Pal-de Bruin K, et al. Exposure to famine during gestation, size at birth, and blood pressure at age 59 y: evidence from the Dutch Famine. Eur J Epidemiol. 2006;21:759–765.
12. Wang J, Li Y, Han X, et al. Exposure to the Chinese famine in childhood increases type 2 diabetes risk in adults. J Nutr. 2016;146:2289–2295.
13. Huang C, Li Z, Wang M, et al. Early life exposure to the 1959–1961 Chinese famine has long-term health consequences. J Nutr. 2010;140:1874–1878.
14. Finer S, Iqbal MS, Lowe R, et al. Is famine exposure during developmental life in rural Bangladesh associated with a metabolic and epigenetic signature in young adulthood? A historical cohort study. BMJ Open. 2016;6:e011768.
15. Hanson HA, Smith KR. Early origins of longevity: prenatal exposures to food shortage among early Utah pioneers. J Dev Orig Health Dis. 2013;4:170–181.
16. St Clair D. Rates of adult schizophrenia following prenatal exposure to the Chinese famine of 1959–1961. JAMA. 2005;294:557–562.
17. Crookston BT, Dearden KA, Alder SC, et al. Impact of early and concurrent stunting on cognition. Matern Child Nutr. 2011;7:397–409.
18. Walker SP, Chang SM, Powell CA, et al. Effects of early childhood psychosocial stimulation and nutritional supplementation on cognition and education in growth-stunted Jamaican children: prospective cohort study. Lancet. 2005;366:1804–1807.
19. Hoek HW, Brown AS, Susser E. The Dutch famine and schizophrenia spectrum disorders. Soc Psychiatry Psychiatr Epidemiol. 1998;33:373–379.
20. Crookston BT, et al. Children who recover from early stunting and children who are not stunted demonstrate similar levels of cognition. J Nutr. 2010;140:1996–2001.
21. Crookston BT, Schott W, Cueto S, et al. Postinfancy growth, schooling, and cognitive achievement: young lives. Am J Clin Nutr. 2013;98:1555–1563.
22. Walker SP, Chang SM, Wright A, et al. Early childhood stunting is associated with lower developmental levels in the subsequent generation of children. J Nutr. 2015;145:823–828.
23. Sokolovic N, Selvam S, Srinivasan K, et al. Catch-up growth does not associate with cognitive development in Indian school-age children. Eur J Clin Nutr. 2014;68:14–18.
24. Mendez MA, Adair LS. Severity and timing of stunting in the first two years of life affect performance on cognitive tests in late childhood. J Nutr. 1999;129:1555–1562.
25. Lucas A, Fewtrell MS, Cole TJ. Fetal origins of adult disease-the hypothesis revisited. BMJ. 1999;319:245–249.
26. Stein AD, Zybert PA, van de Bor M, et al. Intrauterine famine exposure and body proportions at birth: the Dutch Hunger Winter. Int J Epidemiol. 2004;33:831–836.
27. Dolan MS, Sorkin JD, Hoffman DJ. Birth weight is inversely associated with central adipose tissue in healthy children and adolescents. Obesity. 2007;15:1600–1608.
28. Ylihärsilä H, Kajantie E, Osmond C, et al. Birth size, adult body composition and muscle strength in later life. Int J Obes. 2007;31:1392–1399.
29. Te Velde SJ, Twisk JW, Van Mechelen W, et al. Birth weight, adult body composition, and subcutaneous fat distribution. Obes Res. 2003;11:202–208.
30. Gunnarsdottir I, Birgisdottir BE, Benediktsson R, et al. Association between size at birth, truncal fat and obesity in adult life and its contribution to blood pressure and coronary heart disease; study in a high birth weight population. Eur J Clin Nutr. 2004;58:812–818.
31. Yu ZB, Han SP, Zhu GZ, et al. Birth weight and subsequent risk of obesity: a systematic review and meta-analysis. Obes Rev. 2011;12:525–542.
32. Ravelli GP, Stein ZA, Susser MW. Obesity in young men after famine exposure in utero and early infancy. N Engl J Med. 1976;295:349–353.
33. Eriksson J, Forsén T, Tuomilehto J, et al. Size at birth, childhood growth and obesity in adult life. Int J Obes Relat Metab Disord. 2001;25:735–740.
34. Newby PK, Dickman PW, Adami H-O, et al. Early anthropometric measures and reproductive factors as predictors of body mass index and obesity among older women. Int J Obes Relat Metab Disord. 2005;29:1084–1092.
35. Painter RC, Osmond C, Gluckman P, et al. Transgenerational effects of prenatal exposure to the Dutch famine on neonatal adiposity and health in later life. BJOG. 2008;115:1243–1249.
36. Salgin B, Norris SA, Prentice P, et al. Even transient rapid infancy weight gain is associated with higher BMI in young adults and earlier menarche. Int J Obes (London). 2015;39:939–944.
37. Crowther NJ, Cameron N, Trusler J, et al. Influence of catch-up growth on glucose tolerance and beta-cell function in 7-year-old children: results from the Birth to Twenty study. Pediatrics. 2008;121:e1715–e1722.
38. Vidulich L, Norris SA, Cameron N, et al. Infant programming of bone size and bone mass in 10-year-old black and white South African children. Paediatr Perinat Epidemiol. 2007;21:354–362.
39. Kensara OA, Wootton SA, Phillips DI, et al. Fetal programming of body composition: relation between birth weight and body composition measured with dual-energy X-ray absorptiometry and anthropometric methods in older Englishmen. Am J Clin Nutr. 2005;82:980–987.
40. Chirwa ED, Griffiths P, Maleta K, et al. Postnatal growth velocity and overweight in early adolescents: a comparison of rural and urban African boys and girls. Am J Hum Biol. 2014;26:643–651.
41. Charalampopoulos D, McLoughlin A, Elks CE, et al. Age at menarche and risks of all-cause and cardiovascular death: a systematic review and meta-analysis. Am J Epidemiol. 2014;180:29–40.
42. Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. Lancet Oncol. 2012; 13:1141–1151.
43. Crume TL, Scherzinger A, Stamm E, et al. The long-term impact of intrauterine growth restriction in a diverse U.S. cohort of children: the EPOCH study. Obesity (Silver Spring). 2014;22:608–615.
44. Leunissen RWJ, Stijnen T, Hokken-Koelega ACS. Influence of birth size on body composition in early adulthood: the programming factors for growth and metabolism (PROGRAM) study. Clin Endocrinol. 2009;70:245–251.
45. Popkin BM, Richards MK, Montiero CA. Stunting is associated with overweight in children of four nations that are undergoing the nutrition transition. J Nutr. 1996;126:3009–3016.
46. Bénéfice E, Garnier D, Simondon KB, et al. Relationship between stunting in infancy and growth and fat distribution during adolescence in Senegalese girls. Eur J Clin Nutr. 2001;55:50–58.
47. Schroeder DG, Martorell R. Fatness and body mass index from birth to young adulthood in a rural Guatemalan population. Am J Clin Nutr. 1999;70:137S–144S.
48. Schroeder DG, Martorell R, Flores R. Infant and child growth and fatness and fat distribution in Guatemalan adults. Am J Epidemiol. 1999;149:177–185.
49. Hoffman DJ, Martins PA, Roberts SB, et al. Body fat distribution in stunted compared with normal-height children from the shantytowns of São Paulo, Brazil. Nutr. 2007;23:640–646.
50. Cameron N, Wright MM, Griffiths PL, et al. Stunting at 2 years in relation to body composition at 9 years in African urban children. Obes Res. 2005;13:131–136.
51. Tanner S, Leonard WR, Reyes-García V; TAPS Bolivia Study Team. The consequences of linear growth stunting: influence on body composition among youth in the Bolivian Amazon. Am J Phys Anthropol. 2014;153:92–102.
52. Gigante DP, Victora CG, Horta BL, et al. Undernutrition in early life and body composition of adolescent males from a birth cohorot study. Br J Nutr. 2007;97:949–954.
53. Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97:1837–1847.
54. Mathieu P, Pibarot P, Despres JP. Metabolic syndrome: the danger signal in atherosclerosis. Vasc Health Risk Manag. 2006;2:285–302.
55. Abate N. Adipocyte maturation arrest: a determinant of systemic insulin resistance to glucose disposal. J Clin Endocrinol Metab. 2012;97:760–763.
56. Mehal WZ, Iredale J, Friedman SL. Scraping fibrosis: expressway to the core of fibrosis. Nat Med. 2011;17:552–553.
57. Henderson NC, Iredale JP. Liver fibrosis: cellular mechanisms of progression and resolution. Clin Sci. 2007;112:265–280.
58. Barker DJ. The fetal and infant origins of adult disease. BMJ. 1990;301:1111.
59. Barker DJ, Martyn CN, Osmond C, et al. Growth in utero and serum cholesterol concentrations in adult life. BMJ. 1993;307:1524–1527.
60. Valsamakis G, Kanaka-Gantenbein C, Malamitsi-Puchner A, et al. Causes of intrauterine growth restriction and the postnatal development of the metabolic syndrome. Ann N Y Acad Sci. 2006;1092:138–147.
61. Neerhof MG. Causes of intrauterine growth restriction. Clin Perinatol. 1995;22:375–385.
62. Desai M, Hales CN. Role of fetal and infant growth in programming metabolism in later life. Biol Rev Camb Philos Soc. 1997;72:329–348.
63. McCance DR, Pettitt DJ, Hanson RL, et al. Birth weight and non-insulin dependent diabetes: thrifty genotype, thrifty phenotype, or surviving small baby genotype?. BMJ. 1994;308:942–945.
64. Broholm C, Olsson AH, Perfilyev A, et al. Epigenetic programming of adipose-derived stem cells in low birthweight individuals. Diabetologia. 2016;59:2664–2673.

65. Einstein F, Thompson RF, Bhagat TD, et al. Cytosine methylation dysregulation in neonates following intrauterine growth restriction. PloS One. 2010;5:e8887.
66. Yajnik C. Interactions of perturbations in intrauterine growth and growth during childhood on the risk of adult-onset disease. Proc Nutr Soc. 2000;59:257–265.
67. Eriksson JG. Early growth, and coronary heart disease and type 2 diabetes: experiences from the Helsinki Birth Cohort Studies. Int J Obes Relat Metab Disord. 2006;30:S18–S22.
68. Finken MJJ, Inderson A, Van Montfoort N, et al. Lipid profile and carotid intima-media thickness in a prospective cohort of very preterm subjects at age 19 years: effects of early growth and current body composition. Pediatr Res. 2006;59:604–609.
69. Martin RM, McCarthy A, Smith GD, et al. Infant nutrition and blood pressure in early adulthood: the Barry Caerphilly Growth study. Am J Clin Nutr. 2003;77:1489–1497.
70. Deiber M, Chatelain P, Naville D, et al. Functional hypersomatotropism in small for gestational age (SGA) newborn infants. J Clin Endocrinol Metab. 1989;68:232–234.
71. Singhal A, Cole TJ, Fewtrell M, et al. Breastmilk feeding and lipoprotein profile in adolescents born preterm: follow-up of a prospective randomised study. Lancet. 2004;363:1571–1578.
72. Jaquet D, Gaboriau A, Czernichow P, et al. Insulin resistance early in adulthood in subjects born with intrauterine growth retardation. J Clin Endocrinol Metab. 2000;85:1401–1406.
73. Ross MG, Beall MH. Prediction of preterm birth: nonsonographic cervical methods. Semin Perinatol. 2009;33:312–316.
74. Yudkin JS, Stanner S. Prenatal exposure to famine and health in later life. Lancet. 1998;351:1361–1362.
75. Elias AA, Ghaly A, Matushewski B, et al. Maternal nutrient restriction in guinea pigs as an animal model for inducing fetal growth restriction. Reprod Sci. 2016;23:219–227.
76. Lunney LH. Compensatory placental growth after restricted maternal nutrition in early pregnancy. Placenta. 1998;19:105–111.
77. Sohlström A, Katsman A, Kind KL, et al. Food restriction alters pregnancy-associated changes in IGF and IGFBP in the guinea pig. Am J Physiol. 1998;274:E410–E416.
78. Murotsuki J, Challis JR, Han VK, et al. Chronic fetal placental embolization and hypoxemia cause hypertension and myocardial hypertrophy in fetal sheep. Am J Physiol. 1997;272:R201–R207.
79. Ogata ES, Bussey ME, Finley S. Altered gas exchange, limited glucose and branched chain amino acids, and hypoinsulinism retard fetal growth in the rat. Metabolism. 1986;35:970–977.
80. Simmons RA, Gounis AS, Bangalore SA, et al. Intrauterine growth retardation: fetal glucose transport is diminished in lung but spared in brain. Pediatr Res. 1992;31:59–63.
81. Lane RH, Kelley DE, Gruetzmacher EM, et al. Uteroplacental insufficiency alters hepatic fatty acid-metabolizing enzymes in juvenile and adult rats. Am J Physiol Regul Integr Comp Physiol. 2001;280:R183–R190.
82. Simmons RA, Templeton LJ, Gertz SJ. Intrauterine growth retardation leads to the development of type 2 diabetes in the rat. Diabetes. 2001;50:2279–2286.
83. Raab EL, Vuguin PM, Stoffers DA, et al. Neonatal exendin-4 treatment reduces oxidative stress and prevents hepatic insulin resistance in intrauterine growth-retarded rats. Am J Physiol Regul Integr Comp Physiol. 2009;297:R1785–R1794.
84. Goodspeed D, Seferovic MD, Holland W, et al. Essential nutrient supplementation prevents heritable metabolic disease in multigenerational intrauterine growth-restricted rats. FASEB J. 2015;29:807–819.
85. Peterside IE, Selak MA, Simmons RA. Impaired oxidative phosphorylation in hepatic mitochondria in growth-retarded rats. Am J Physiol Endocrinol Metab. 2003;285:E1258–E1266.
86. Baserga M. Uteroplacental insufficiency alters hepatic expression, phosphorylation, and activity of the glucocorticoid receptor in fetal IUGR rats. Am J Physiol Regul Integr Comp Physiol. 2005;289:R1348–R1353.
87. Lane RH, Crawford SE, Flozak AS, et al. Localization and quantification of glucose transporters in liver of growth-retarded fetal and neonatal rats. Am J Physiol. 1999;276:E135–E142.
88. Lane RH, MacLennan NK, Hsu JL, et al. Increased hepatic peroxisome proliferator-activated receptor-gamma coactivator-1 gene expression in a rat model of intrauterine growth retardation and subsequent insulin resistance. Endocrinology. 2002;143:2486–2490.
89. Fu Q, Yu X, Callaway CW, et al. Epigenetics: intrauterine growth retardation (IUGR) modifies the histone code along the rat hepatic IGF-1 gene. FASEB J. 2009;23:2438–2449.
90. Sarr O, Blake A, Thompson JA, et al. The differential effects of low birth weight and Western diet consumption upon early life hepatic fibrosis development in guinea pig. J Physiol (London). 2016;594:1753–1772.
91. Tosh DN, Fu Q, Callaway CW, et al. Epigenetics of programmed obesity: alteration in IUGR rat hepatic IGF1 mRNA expression and histone structure in rapid vs. delayed postnatal catch-up growth. Am J Physiol Gastrointest Liver Physiol. 2010;299:G1023–G1029.
92. Elias AA, Ghaly A, Matushewski B, Regnault TR, Richardson BS. Maternal nutrient restriction (MNR) in guinea pigs leads to fetal growth restricted (FGR) offspring with differential rates of organ catch-up growth. Reprod Sci. 2016;23:149A.
93. Nijland MJ, Mitsuya K, Li C, et al. Epigenetic modification of fetal baboon hepatic phosphoenolpyruvate carboxykinase following exposure to moderately reduced nutrient availability. J Physiol. 2010;588:1349–1359.
94. George LA, Zhang L, Tuersunjiang N, et al. Early maternal undernutrition programs increased feed intake, altered glucose metabolism and insulin secretion, and liver function in aged female offspring. Am J Physiol Regul Integr Comp Physiol. 2012;302:R795–R804.
95. Elias AA, Maki Y, Matushewski B, et al. Maternal nutrient restriction in guinea pigs leads to fetal growth restriction with evidence for chronic hypoxia. Pediatr Res 2017;82:141–147.
96. Petry CJ, Ozanne SE, Hales CN. Programming of intermediary metabolism. Mol Cell Endocrinol. 2001;185:81–91.
97. Crosby WM. Studies in fetal malnutrition. Am J Dis Child. 1991;145:871–876.
98. Sohi G, Revesz A, Ramkumar J, et al. Higher hepatic miR-29 expression in undernourished male rats during the postnatal period targets the long-term repression of IGF-1. Endocrinology. 2015;156:3069–3076.
99. Sohi G, Marchand K, Revesz A, et al. Maternal protein restriction elevates cholesterol in adult rat offspring due to repressive changes in histone modifications at the cholesterol 7alpha-hydroxylase promoter. Mol Endocrinol. 2011;25:785–798.
100. Sohi G, Revesz A, Hardy DB. Nutritional mismatch in postnatal life of low birth weight rat offspring leads to increased phosphorylation of hepatic eukaryotic initiation factor 2 α in adulthood. Metabolism. 2013;62:1367–1374.
101. Guan H, Arany E, van Beek JP, et al. Adipose tissue gene expression profiling reveals distinct molecular pathways that define visceral adiposity in offspring of maternal protein-restricted rats. Am J Physiol Metab. 2005;288:E663–E673.
102. Petrik J, Reusens B, Arany E, et al. A low protein diet alters the balance of islet cell replication and apoptosis in the fetal and neonatal rat and is associated with a reduced pancreatic expression of insulin-like growth factor-II. Endocrinology. 1999;140:4861–4873.
103. Vo TX, Revesz A, Sohi G, et al. Maternal protein restriction leads to enhanced hepatic gluconeogenic gene expression in adult male rat offspring due to impaired expression of the liver X receptor. J Endocrinol. 2013;218:85–97.
104. Chamson-Reig A, Thyssen SM, Hill DJ, et al. Exposure of the pregnant rat to low protein diet causes impaired glucose homeostasis in the young adult offspring by different mechanisms in males and females. Exp Biol Med (Maywood). 2009;234:1425–1436.
105. Sohi G, Barry EJ, Velenosi TJ, et al. Protein restoration in low-birth-weight rat offspring derived from maternal low-protein diet leads to elevated hepatic CYP3A and CYP2C11 activity in adulthood. Drug Metab Dispos Biol Fate Chem. 2014;42:221–228.
106. Reynolds RM. Glucocorticoid excess and the developmental origins of disease: two decades of testing the hypothesis—2012 Curt Richter Award Winner. Psychoneuroendocrinol. 2013;38:1–11.
107. Cottrell EC, Seckl JR. Prenatal stress, glucocorticoids and the programming of adult disease. Front Behav Neurosci. 2009;3:19.
108. Langley-Evans SC. Hypertension induced by foetal exposure to a maternal low-protein diet, in the rat, is prevented by pharmacological blockade of maternal glucocorticoid synthesis. J Hypertens. 1997;15:537–544.
109. Dalziel SR, Walker NK, Paraq V, et al. Cardiovascular risk factors after antenatal exposure to betamethasone: 30-year follow-up of a randomised controlled trial. Lancet. 2005;365:1856–1862.
110. Duthie L, Reynolds RM. Changes in the maternal hypothalamic-pituitary-adrenal axis in pregnancy and postpartum: influences on maternal and fetal outcomes. Neuroendocrinol. 2013;98:106–115.
111. Entringer S, Buss C, Andersen J, et al. Ecological momentary assessment of maternal cortisol profiles over a multiple-day period predicts the length of human gestation. Psychosom Med. 2011;73:469–474.
112. Goedhart G, Vrijkotte TGM, Roseboom TJ, et al. Maternal cortisol and offspring birthweight: results from a large prospective cohort study. Psychoneuroendocrinol. 2010;35:644–652.
113. LeWinn KZ, Stroud LR, Molnar BE, et al. Elevated maternal cortisol levels during pregnancy are associated with reduced childhood IQ. Int J Epidemiol. 2009;38:1700–1710.
114. Aizer A, Stroud L, Buka S. Maternal stress and child outcomes: evidence from siblings. J Hum Resour. 2016;51:523–555.
115. Buss C, Davis EP, Shahbaba B, et al. Maternal cortisol over the course of pregnancy and subsequent child amygdala and hippocampus volumes and affective problems. Proc Natl Acad Sci U S A. 2012; 109: E1312–E1319.
116. Davis EP, Sandman CA, Buss C, et al. Fetal glucocorticoid exposure is associated with preadolescent brain development. Biol Psychiatry. 2013;74:647–655.
117. Stinson LJ, Stroud LR, Buka SL, et al. Prospective evaluation of associations between prenatal cortisol and adulthood coronary heart disease risk: the New England family study. Psychosom Med. 2015;77:237–245.
118. Jung C, Ho JT, Torpy DJ, et al. A longitudinal study of plasma and urinary cortisol in pregnancy and postpartum. J Clin Endocrinol Metab. 2011;96:1533–1540.

119. Dave-Sharma S, Wilson RC, Harbison MD, et al. Examination of genotype and phenotype relationships in 14 patients with apparent mineralocorticoid excess. J Clin Endocrinol Metab. 1998;83:2244–2254.
120. Stewart PM, Rogerson FM, Mason JI. Type 2 11 beta-hydroxysteroid dehydrogenase messenger ribonucleic acid and activity in human placenta and fetal membranes: its relationship to birth weight and putative role in fetal adrenal steroidogenesis. J Clin Endocrinol Metab. 1995;80:885–890.
121. Huh SY, Andrew R, Rich-Edwards JW, et al. Association between umbilical cord glucocorticoids and blood pressure at age 3 years. BMC Med. 2008;6:25.
122. Strandberg TE, Järvenpää AL, Vanhanen H, et al. Birth outcome in relation to licorice consumption during pregnancy. Am J Epidemiol. 2001; 153: 1085–1088.
123. Raikkonen K, Kajantie E, Pesonen A-K, et al. Early life origins cognitive decline: findings in elderly men in the Helsinki birth cohort study. PloS One. 2013;8:e54707.
124. Benediktsson R, Calder AA, Edwards CR, et al. Placental 11 beta-hydroxysteroid dehydrogenase: a key regulator of fetal glucocorticoid exposure. Clin Endocrinol (Oxford). 1997;46:161–166.
125. O'Donnell KJ, Bugge Jensen A, Freeman L, et al. Maternal prenatal anxiety and downregulation of placental 11β-HSD2. Psychoneuroendocrinology. 2012;37:818–826.
126. Cottrell EC, Holmes MC, Livingstone DE, et al. Reconciling the nutritional and glucocorticoid hypotheses of fetal programming. FASEB J. 2012;26:1866–1874.
127. Reynolds RM, Allan KM, Raja EA, et al. Maternal obesity during pregnancy and premature mortality from cardiovascular event in adult offspring: follow-up of 1 323 275 person years. BMJ. 2013;347:f4539.
128. Eriksson JG, Sandboge S, Salonen MK, et al. Long-term consequences of maternal overweight in pregnancy on offspring later health: findings from the Helsinki Birth Cohort Study. Ann Med. 2014;46:434–438.
129. Hochner H, Friedlander Y, Calderon-Margalit R, et al. Associations of maternal prepregnancy body mass index and gestational weight gain with adult offspring cardiometabolic risk factors: the Jerusalem Perinatal Family Follow-up Study. Circulation. 2012;125:1381–1389.
130. Godfrey KM, Reynolds RM, Prescott SL, et al. Influence of maternal obesity on the long-term health of offspring. Lancet Diabetes Endocrinol. 2017;5:53–64.
131. Stirrat LI, O'Reilly JR, Barr SM, et al. Decreased maternal hypothalamic-pituitary-adrenal axis activity in very severely obese pregnancy: associations with birthweight and gestation at delivery. Psychoneuroendocrinol. 2016;63:135–143.
132. Berglund SK, Garcia-Valdes L, Torres-Espinola FJ, et al. Maternal, fetal and perinatal alterations associated with obesity, overweight and gestational diabetes: an observational cohort study (PREOBE). BMC Public Health. 2016;16:207.
133. Cho CE, Pannia E, Huot PSP, et al. Methyl vitamins contribute to obesogenic effects of a high multivitamin gestational diet and epigenetic alterations in hypothalamic feeding pathways in Wistar rat offspring. Mol Nutr Food Res. 2015;59:476–489.
134. Yamagata K, Furuta H, Oda N, et al. Mutations in the hepatocyte nuclear factor-4alpha gene in maturity-onset diabetes of the young (MODY1). Nature. 1996;384:458–460.
135. Lillycrop KA, Phillips ES, Jackson AA, et al. Dietary protein restriction of pregnant rats induces and folic acid supplementation prevents epigenetic modification of hepatic gene expression in the offspring. J Nutr. 2005;135:1382–1386.
136. Lillycrop KA, Slater-Jefferies JL, Hanson MA, et al. Induction of altered epigenetic regulation of the hepatic glucocorticoid receptor in the offspring of rats fed a protein-restricted diet during pregnancy suggests that reduced DNA methyltransferase-1 expression is involved in impaired DNA methylation and changes in histone modifications. Br J Nutr. 2007;97:1064–1073.
137. Lan X, Cretney EC, Kropp J, et al. Maternal diet during pregnancy induces gene expression and DNA methylation changes in fetal tissues in sheep. Front Genet. 2013;4:49.
138. Valera A, Pujol A, Pelegrin M, et al. Transgenic mice overexpressing phosphoenolpyruvate carboxykinase develop non-insulin-dependent diabetes mellitus. Proc Natl Acad Sci U S A. 1994;91:9151–9154.
139. Gomez-Valades AG, Mendez-Lucas A, Vidal-Alabro A, et al. Pck1 gene silencing in the liver improves glycemia control, insulin sensitivity, and dyslipidemia in db/db mice. Diabetes. 2008;57:2199–2210.
140. Fu Q, McKnight RA, Callaway CW, et al. Intrauterine growth restriction disrupts developmental epigenetics around distal growth hormone response elements on the rat hepatic IGF-1 gene. FASEB J. 2015;29:1176–1184.
141. Jenuwein T, Allis CD. Translating the histone code. Science. 2001;293:1074–1080.
142. Marmorstein R, Trievel RC. Histone modifying enzymes: structures, mechanisms, and specificities. Biochim Biophys Acta. 2009;1789:58–68.
143. Park JH, Stoffers DA, Nicholls RD, et al. Development of type 2 diabetes following intrauterine growth retardation in rats is associated with progressive epigenetic silencing of Pdx1. J Clin Invest. 2008;118:2316–2324.
144. Osumek JE, Revesz A, Morton JS, et al. Enhanced trimethylation of histone h3 mediates impaired expression of hepatic glucose 6-phosphatase expression in offspring from rat dams exposed to hypoxia during pregnancy. Reprod Sci. 2014;21:112–121.
145. Khorram O, Han G, Bagherpour R, et al. Effect of maternal undernutrition on vascular expression of micro and messenger RNA in newborn and aging offspring. Am J Physiol Integr Comp Physiol. 2010;298:R1366–R1374.
146. Xu C, Liu S, Fu H, et al. MicroRNA-193b regulates proliferation, migration and invasion in human hepatocellular carcinoma cells. Eur J Cancer. 2010;46:2828–2836.
147. Brennecke J, Stark A, Russell RB, et al. Principles of microRNA-target recognition. PLoS Biol. 2005;3:e85.
148. Ferland-McCollough D, Fernandez-Twinn DS, Cannell IG, et al. Programming of adipose tissue miR-483-3p and GDF-3 expression by maternal diet in type 2 diabetes. Cell Death Differ. 2012;19:1003–1012.
149. Casas-Agustench P, Fernandes FS, Tavares do Carmo MG, et al. Consumption of distinct dietary lipids during early pregnancy differentially modulates the expression of microRNAs in mothers and offspring. PloS One. 2015;10:e0117858.
150. Barra NG, VanDuzer T, Holloway AC, et al. Maternal nicotine exposure (MNE) leads to decreased visceral adipoctyte size associated with endoplasmic reticulum (ER) stress in 26 week old rat offspring. Reprod Sci. 2016;23:314A–314A.
151. Ma N, Nicholson CJ, Wong M, et al. Fetal and neonatal exposure to nicotine leads to augmented hepatic and circulating triglycerides in adult male offspring due to increased expression of fatty acid synthase. Toxicol Appl Pharmacol. 2014;275:1–11.
152. Nolan K, Walter F, Tuffy LP, et al. Endoplasmic reticulum stress-mediated upregulation of miR-29a enhances sensitivity to neuronal apoptosis. Eur J Neurosci. 2016;43:640–652.
153. Hoffman DJ, Sawaya AL, Coward WA, et al. Energy expenditure of stunted and nonstunted boys and girls living in the shantytowns of São Paulo, Brazil. Am J Clin Nutr. 2000;72:1025–1031.
154. Wren RE, Blume H, Mazariegos M, et al. Body composition, resting metabolic rate, and energy requirements of short- and normal-stature, low-income Guatemalan children. Am J Clin Nutr. 1997;66:406–412.
155. Nishimoto Y, Ida S, Etani Y, et al. Resting energy expenditure in short-stature children. Endocr J. 2012;59:265–271.
156. Said-Mohamed R, Bernard JY, Ndzana A-C, et al. Is overweight in stunted preschool children in Cameroon related to reductions in fat oxidation, resting energy expenditure and physical activity?. PloS One. 2012;7:e39007.
157. Grillo LP, Siqueira AFA, Silva AC, et al. Lower resting metabolic rate and higher velocity of weight gain in a prospective study of stunted vs nonstunted girls living in the shantytowns of São Paulo, Brazil. Eur J Clin Nutr. 2005;59:835–842.
158. Hoffman DJ, Sawaya AL, Verreschi I, et al. Why are nutritionally stunted children at increased risk of obesity? Studies of metabolic rate and fat oxidation in shantytown children from São Paulo, Brazil. Am J Clin Nutr. 2000;72:702–707.
159. Kensara OA. Substrate-energy metabolism and metabolic risk factors for cardiovascular disease in relation to fetal growth and adult body composition. Am J Physiol Endocrinol Metab 2006;291:E365–E371.
160. Leonard WR, Sorensen MV, Mosher MJ, et al. Reduced fat oxidation and obesity risks among the Buryat of Southern Siberia. Am J Hum Biol. 2009;21:664–670.
161. Lee S-K, Nam S-Y, Hoffman DJ. Growth retardation at early life and metabolic adaptation among North Korean children. J Dev Orig Health Dis. 2015;6:291–298.
162. Krueger R, Derno M, Goers S, et al. Higher body fatness in intrauterine growth retarded juvenile pigs is associated with lower fat and higher carbohydrate oxidation during ad libitum and restricted feeding. Eur J Nutr. 2014;53:583–597.
163. Li Y, Li F, Chen S, et al. Protein-restricted diet regulates lipid and energy metabolism in skeletal muscle of growing pigs. J Agric Food Chem. 2016;64:9412–9420.
164. Brown LD, Rozance PJ, Bruce JL, et al. Limited capacity for glucose oxidation in fetal sheep with intrauterine growth restriction. Am J Physiol Regul Integr Comp Physiol. 2015;309:R920–R928.
165. Poore KR, Hollis LJ, Murray RJS, et al. Differential pathways to adult metabolic dysfunction following poor nutrition at two critical developmental periods in sheep. PloS One. 2014;9:e90994.
166. Kagura J, Feeley ABB, Micklesfield LK, et al. Association between infant nutrition and anthropometry, and pre-pubertal body composition in urban South African children. J Devel Orig Health Dis. 2012;3:415–423.
167. Million M, Angelakis E, Maraninchi M, et al. Correlation between body mass index and gut concentrations of *Lactobacillus reuteri*, *Bifidobacterium animalis*, *Methanobrevibacter smithii* and *Escherichia coli*. Int J Obes Relat Metab Disord. 2013;37:1406–1466.
168. de Onis M, Branca F. Childhood stunting: a global perspective. Matern Child Nutr. 2016;12(suppl 1):12–26.
169. Kau AL, Ahern PP, Griffin NW, et al. Human nutrition, the gut microbiome and the immune system. Nature. 2011;474:327–336.
170. Guerrant RL, DeBoer MD, Moore SR, et al. The impoverished gut—a triple burden of diarrhoea, stunting and chronic disease. Nat Rev Gastroenterol Hepatol. 2013;10:220–229.
171. Subramanian S, Huq S, Yatsunenko T, et al. Persistent gut microbiota immaturity in malnourished Bangladeshi children. Nature. 2014;510:417–421.
172. Blanton LV, Charbonneau MR, Salih T, et al. Gut bacteria that prevent growth impairments transmitted by microbiota from malnourished children. Science. 2016;351:aad3311.

173. Magnúsdóttir S, Ravcheev D, de Crécy-Lagard V, et al. Systematic genome assessment of B-vitamin biosynthesis suggests co-operation among gut microbes. Front Genet. 2015;6:148.
174. Yajnik CS, Deshpande SS, Jackson AA, et al. Vitamin B12 and folate concentrations during pregnancy and insulin resistance in the offspring: the Pune Maternal Nutrition Study. Diabetologia. 2007;51:29–38.
175. Finer S, Saravanan P, Hitman G, et al. The role of the one-carbon cycle in the developmental origins of type 2 diabetes and obesity. Diabet Med. 2014;31:263–272.
176. Wang N, Wang X, Han B, et al. Is exposure to famine in childhood and economic development in adulthood associated with diabetes?. J Clin Endocrinol Metab. 2015;100:4514–4523.
177. Li Y, Jaddoe VW, Qi L, et al. Exposure to the Chinese famine in early life and the risk of metabolic syndrome in adulthood. Diabetes Care. 2011;34:1014–1018.
178. Li H, Stein AD, Barnhart HX, et al. Associations between prenatal and postnatal growth and adult body size and composition. Am J Clin Nutr. 2003;77:1498–1505.
179. Labayen I, Moreno LA, Blay MG, et al. Early programming of body composition and fat distribution in adolescents. J Nutr. 2006;136:147–152.
180. Labayen I, Moreno LA, Ruiz JR, et al. Small birth weight and later body composition and fat distribution in adolescents: the Avena study. Obesity (Silver Spring). 2008;16:1680–1686.
181. Garg M, Thamotharan M, Pan G, et al. Early exposure of the pregestational intrauterine and postnatal growth-restricted female offspring to a peroxisome proliferator-activated receptor-{gamma} agonist. Am J Physiol Metab. 2010;298:E489–E498.
182. Bartoszewski R, Brewer JW, Rab A, et al. The unfolded protein response (UPR)-activated transcription factor X-box-binding protein 1 (XBP1) induces microRNA-346 expression that targets the human antigen peptide transporter 1 (TAP1) mRNA and governs immune regulatory genes. J Biol Chem. 2011;286:41862–41870.
183. Kyle UG, Pichard C. The Dutch famine of 1944–1945: a pathophysiological model of long-term consequences of wasting disease. Curr Opin Clin Nutr Metab Care. 2006;9:388–394.
184. Ravelli AC, van Der Meulen JH, Osmond C, et al. Obesity at the age of 50 y in men and women exposed to famine prenatally. Am J Clin Nutr. 1999;70:811–816.
185. van Abeelen AFM, Elias SG, Bossuyt PMM, et al. Famine exposure in the young and the risk of type 2 diabetes in adulthood. Diabetes. 2012;61:2255–2260.
186. de Rooij SR, Painter RC, Roseboom TJ, et al. Glucose tolerance at age 58 and the decline of glucose tolerance in comparison with age 50 in people prenatally exposed to the Dutch famine. Diabetologia. 2006;49:637–643.
187. Hales CN, Barker DJP. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Int J Epidemiol. 2013;42:1215–1222.
188. Ornoy A, Tsadok MA, Yaffe P, et al. The Cohen diabetic rat as a model for fetal growth restriction: vitamins C and E reduce fetal oxidative stress but do not restore normal growth. Reprod Toxicol. 2009;28:521–529.
189. Lillycrop KA, Rodford J, Garratt ES, et al. Maternal protein restriction with or without folic acid supplementation during pregnancy alters the hepatic transcriptome in adult male rats. Br J Nutr. 2010;103:1711–1719.
190. Steegers-Theunissen RP, Obermann-Borst SA, Kremer D, et al. Periconceptional maternal folic acid use of 400 microg per day is related to increased methylation of the IGF2 gene in the very young child. PloS One. 2009;4:e7845.
191. Sardinha FLC, Fernandes FS, Tavares do Carmo MG, et al. Sex-dependent nutritional programming: fish oil intake during early pregnancy in rats reduces age-dependent insulin resistance in male, but not female, offspring. Am J Physiol Regul Integr Comp Physiol. 2013;304:R313–R320.
192. Boujendar S, Arany E, Hill D, et al. Taurine supplementation of a low protein diet fed to rat dams normalizes the vascularization of the fetal endocrine pancreas. J Nutr. 2003;133:2820–2825.
193. Boujendar S, Reusens B, Merezak S, et al. Taurine supplementation to a low protein diet during foetal and early postnatal life restores a normal proliferation and apoptosis of rat pancreatic islets. Diabetologia. 2002;45:856–866.
194. Devakumar D, Fall CHD, Sachdev HS, et al. Maternal antenatal multiple micronutrient supplementation for long-term health benefits in children: a systematic review and meta-analysis. BMC Med. 2016;14:90.
195. Pinney SE, Jaeckle Santos LJ, Han Y, et al. Exendin-4 increases histone acetylase activity and reverses epigenetic modifications that silence Pdx1 in the intrauterine growth retarded rat. Diabetologia. 2011;54:2606–2614.
196. Gatford KL, Sulaiman SA, Mohammad SNB, et al. Neonatal exendin-4 reduces growth, fat deposition and glucose tolerance during treatment in the intrauterine growth-restricted lamb. PloS One. 2013;8:e56553.
197. Liu H, Schultz CG, De Blasio MJ, et al. Effect of placental restriction and neonatal exendin-4 treatment on postnatal growth, adult body composition, and in vivo glucose metabolism in the sheep. Am J Physiol Endocrinol Metab. 2015;309:E589–E600.
198. Ibáñez L, López-Bermejo A, Díaz M, et al. Metformin treatment for four years to reduce total and visceral fat in low birth weight girls with precocious pubarche. J Clin Endocrinol Metab. 2008;93:1841–1845.
199. Clarson CL, Brown HK, De Jesus S, et al. Effects of a comprehensive, intensive lifestyle intervention combined with metformin extended release in obese adolescents. Int Sch Res Not. 2014;2014:659410.
200. Clarson CL, Mahmud FH, Baker JE, et al. Metformin in combination with structured lifestyle intervention improved body mass index in obese adolescents, but did not improve insulin resistance. Endocrine. 2009;36:141–146.
201. Cleasby ME, Livingstone DEW, Nyirenda MJ, et al. Is programming of glucocorticoid receptor expression by prenatal dexamethasone in the rat secondary to metabolic derangement in adulthood? Eur J Endocrinol. 2003;148:129–138.
202. Chiswick C, Reynolds RM, Denison F, et al. Effect of metformin on maternal and fetal outcomes in obese pregnant women (EMPOWaR): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2015;3:778–786.
203. Syngelaki A, Nicolaides KH, Balani J, et al. Metformin versus placebo in obese pregnant women without diabetes mellitus. N Engl J Med. 2016;374:434–443.
204. Rowan JA, Rush EC, Obolonkin V, et al. Metformin in gestational diabetes: the offspring follow-up (MiG TOFU): body composition at 2 years of age. Diabetes Care. 2011;34:2279–2284.
205. Sohi G, Revesz A, Arany E, et al. The liver X receptor mediates the impaired cholesterol metabolism exhibited in the offspring of maternal protein restricted rats. Reprod Sci. 2011;18:F163.
206. Onubi OJ, Poobalan AS, Dineen B, et al. Effects of probiotics on child growth: a systematic review. J Health Popul Nutr. 2015;34:8.
207. Million M, Angelakis E, Paul M, et al. Comparative meta-analysis of the effect of *Lactobacillus* species on weight gain in humans and animals. Microb Pathog. 2012;53:100–108.
208. Steenhout PG, Rochat F, Hager C. The effect of *Bifidobacterium lactis* on the growth of infants: a pooled analysis of randomized controlled studies. Ann Nutr Metab. 2009;55:334–340.
209. Sazawal S, Dhingra U, Hiremath G, et al. Effects of *Bifidobacterium lactis* HN019 and prebiotic oligosaccharide added to milk on iron status, anemia, and growth among children 1 to 4 years old. J Pediatr Gastroenterol Nutr. 2010;51:341–346.
210. Saran S, Gopalan S, Krishna TP. Use of fermented foods to combat stunting and failure to thrive. Nutrition. 2002;18:393–396.
211. He T, Priebe MG, Zhong Y, et al. Effects of yogurt and bifidobacteria supplementation on the colonic microbiota in lactose-intolerant subjects. J Appl Microbiol. 2008;104:595–604.
212. Sheridan PO, Bindels LB, Saulnier DM, et al. Can prebiotics and probiotics improve therapeutic outcomes for undernourished individuals? Gut Microbes. 2014;5:74–82.