# 23 Fetal Origins of Obesity, Cardiovascular Disease, and Type 2 Diabetes

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## CONTENTS



## INTRODUCTION

The first 1,000 days of life is a critical window of development, determining susceptibility to adult obesity and cardiometabolic health [1,2]. Environmental insults during this rapid development phase may result in irreversible adverse outcomes. Animal and human studies provide evidence for the fetal origins of adult noncommunicable disease hypothesis [3–5]. This hypothesis suggests that intrauterine exposures affect the fetus's development during sensitive periods, and increases the risk of noncommunicable diseases in adult life [3–5]. Systematic reviews confirm evidence of inverse epidemiological associations between birth weight and later development of hypertension [2] and coronary heart disease [6]. The fetal origins of disease hypothesis has

been challenged as a possible statistical artifact [7], but has been confirmed by later studies with high follow-up rates and adjustment for confounders [8,9].

Early animal studies of severe undernutrition [10] and later human studies both showed a relation between fetal stressors and subsequent development of chronic diseases [3,4]. Natural experiments such as the Dutch famine cohort showed that prenatal undernutrition was associated with low birth weight, followed by adult obesity and glucose intolerance when adults were raised outside of a famine environment [11]. Birth weights and cardiovascular death rates studied in men born during 1911 to 1930 in the United Kingdom showed that low birth weight was associated with hypertension and ischemic heart disease mortality [3]. In adults born in Finland between 1924 and 1933, and who were followed up in 1971, the incidence of type 2 diabetes increased with decreasing birth size and placental weight [12]. Based on these early studies, small birth size was regarded as a marker of poor fetal nutrition and intrauterine growth restriction, independent of gestational age. Fetal programming and low fetal growth rates increased susceptibility to adult diseases [4], and promoters of pre- and postnatal growth were regarded as protective against ischemic heart disease [3].

## THE CRITICAL PERIOD DETERMINING SUSCEPTIBILITY TO ADULT CHRONIC DISEASE: FETAL OR POSTNATAL LIFE?

Fetal nutrition is a more important programming stimulus affecting fetal growth than birth weight [13]. Birth weight may be an intermediate, rather than a primary indicator of the relationship between fetal growth and adult disease. Low birth weight infants who became overweight later in life were at an increased risk of several adverse events: insulin resistance at the age of 8 years [14], higher blood pressure at the age of 50 [15], and a higher incidence of coronary heart disease during late adulthood [6,16]. Thus, childhood or adult adiposity may modify the association between birth weight and later cardiovascular outcomes, indicating that catch-up growth can modify early intrauterine stressors [14,15,17].

Many early studies reported birth weight together with weight later in life. It is difficult to distinguish if later cardiovascular outcomes are triggered by either birth weight or later overweight, or an interaction between fetal and postnatal exposures [7]. Although later studies of multiple postnatal growth measures suggest that both periods are important, it is not clear whether decreased postnatal growth or catch-up growth is harmful [1]. In a Finnish cohort, both low birth weight and accelerated growth from 0 to 7 years were associated with adult hypertension [18], whereas combined low birth weight followed by suboptimal infant growth gave rise to the highest risk of adult ischemic heart disease [19]. These results indicate a need for more serial growth data to determine the contribution of growth periods to future health outcomes [1]. Three possible explanations for the association between early growth and later cardiovascular outcomes emerge from recent studies, namely, (1) fast postnatal growth itself increases risk of later obesity and cardiovascular disease [20,21]; (2) factors related to fetal growth restriction increase risk of cardiovascular disease [15]; and (3) an interaction between the two increases risk [22]. Studies of the fetal origins of adult disease should include the fetal period and repeated growth measures through the life course. A simplified diagrammatic presentation of developmental programming is shown in Figure 23.1.

<table>
<tr><th colspan="3">Pregnancy</th><th>Infant Outcomes</th><th>Early Infancy to Age 2 years</th><th>Childhood</th><th>Adulthood</th><th>Adult Outcomes</th></tr>
<tr><td colspan="3">First 1,000 Days</td><td colspan="4"></td></tr>
<tr><td colspan="3">In utero Programming</td><td></td><td>Postnatal Programming</td><td colspan="3"></td></tr>
<tr><td>Maternal health</td><td>Early fetal development</td><td>Late fetal development</td><td colspan="5"></td></tr>
<tr><td>Gestational hypertension</td><td>Organ development</td><td></td><td></td><td></td><td>Genetic susceptibility</td><td>Genetic susceptibility</td><td>Hypertension</td></tr>
<tr><td>Gestational diabetes</td><td colspan="2">Hyperglycemia<br>Hyperinsulinemia</td><td rowspan="2">Macrosomia</td><td>Determination of appetite</td><td>Energy, protein, and micronutrient intakes</td><td>Energy, protein, and micronutrient intakes</td><td rowspan="2">Type 2 diabetes</td></tr>
<tr><td>Obesity</td><td colspan="2">Changes in DNA methylation</td><td>Protein intake</td><td rowspan="2">Overweight child</td><td>Physical activity</td></tr>
<tr><td>Smoking</td><td colspan="2">Hypoxia</td><td></td><td>Rapid early weight gain</td><td rowspan="3">Overweight/obese adult</td><td rowspan="5">Cardiovascular disease</td></tr>
<tr><td>Stress</td><td colspan="2">Brain development<br><br>Structural changes in the pancreas</td><td></td><td>Brain development</td><td>Stress responsiveness, behavior<br>Impaired glucose tolerance</td></tr>
<tr><td rowspan="2">Under-nutrition</td><td colspan="2">Insufficient supply of nutrients<br>Changes in DNA methylation</td><td rowspan="4">Low birth weight</td><td rowspan="2">Gut microbiome established</td><td rowspan="2"></td></tr>
<tr><td>Programming of obesity and cardiovascular disease</td><td>Dysregulation of glucose homeostasis</td><td>Inflammation</td></tr>
<tr><td>Inflammation</td><td colspan="2">Oxidative stress</td><td></td><td></td><td>Oxidative stress</td></tr>
<tr><td>Immature mother</td><td colspan="2">Reduced insulin and IGF-1</td><td></td><td></td><td></td><td>Obesity</td></tr>
<tr><td>Poor placenta development</td><td colspan="2">Poor placenta function</td><td></td><td></td><td></td><td>Short adult</td></tr>
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**FIGURE 23.1** The lifecycle stages of fetal programming. Factors involved in *in utero* and postnatal programming, possible mediators, and infant and adult outcomes. Factors in the same row may, but do not necessarily, indicate a direct temporal association.

A clear definition of catch-up growth is needed to differentiate between the effects of growth periods on adult disease. Catch-up growth is defined as a growth trajectory above the normal limits for age after transient growth inhibition, and refers to a beneficial realignment to genetic potential after growth faltering and not excessive infant weight gain [1]. This interpretation is important, since associations of birth weight with later outcomes span the entire birth weight spectrum, not just the low-birth-weight end [1].

## CRITICISMS OF THE FETAL ORIGINS OF DISEASE HYPOTHESIS

Epidemiologists from a variety of fields have challenged the fetal origins of disease hypothesis. In the field of the fetal origins of adult disease, perinatal epidemiologists regard increasing birth weight as beneficial, while developmental origins epidemiologists regard low birth weight as less important and higher birth weight as not necessarily beneficial [1,2].

Lucas et al. [7] criticized the statistical adjustment for current body size widely applied in longitudinal studies of the fetal origins of disease, and stated that the statistical interpretation of some growth results was incorrect. They stated that failure to distinguish between the prenatal and postnatal factors affecting adult disease is problematic. Further, they argued that postnatal catch-up growth, rather than fetal programming, may primarily affect later health [7].

Other critics maintain that epidemiological studies disregard the role of genetics, because a gene mutation may be associated with low birth weight and offspring insulin resistance, resulting in type 2 diabetes and hypertension, both phenotypes of the same insulin-resistant genotype [23]. Monogenic diseases may impair the sensing of maternal hyperglycemia, decreasing insulin secretion or increasing insulin resistance, and impairing fetal growth. Polygenic influences resulting in fetal insulin resistance may result in lower birth weight. Genetic insulin resistance may cause abnormal perinatal vascular development, and explain increased adulthood risk of hypertension and vascular disease. However, it is likely that both genetic and environmental factors may predispose the infant to type 2 diabetes and hypertension [23].

## EPIDEMIOLOGICAL CHALLENGES IN STUDYING THE FETAL ORIGINS OF ADULT CHRONIC DISEASE

### Adjustment for Adiposity at the Endpoint

Low birth weight is not associated with adult chronic disease risk in all studies. In some, this inverse relationship was only present after adjustment for endpoint adiposity, since adult adiposity is positively associated with adult chronic disease [15]. In studies of the relationship between birth weight and type 2 diabetes, unadjusted for endpoint body mass index (BMI), the relationship is J-shaped, with increased risk at both ends of the birth weight spectrum [9]. The underlying mechanism at the high birth weight end may be that maternal gestational diabetes is causing obesity and diabetes risk in offspring. Adjustment for endpoint BMI reveals an inverse and linear association across the birth weight spectrum, reflecting reduced risk at

higher birth weights, a pattern attributed to a "thrifty phenotype" [4]. This hypothesis proposes early undernutrition, programming permanent dysregulation of glucose homeostasis, and development of type 2 diabetes. Reduced insulin secretion and insulin resistance, combined with obesity, aging, and physical inactivity, are the most important determinants of type 2 diabetes, confirmed by epidemiological evidence [14]. The relationship between poor fetal growth and insulin secretion and possible gene and environment interactions is less clear [1]. More research is necessary to better understand the contributions of maternal hyperglycemia and postnatal growth on offspring type 2 diabetes risk later in life.

### Social and Economic Factors as Confounders or Explanatory Variables

Cardiovascular diseases are related to both low birth weight and poor adulthood socioeconomic circumstances. Controlling for offspring socioeconomic factors in adulthood is necessary to determine prenatal influences, particularly when social class changes across generations [2]. Poor maternal diet and strenuous physical work due to low socioeconomic circumstances may directly affect maternal energy and nutrient reserves, and have adverse effects on fetal growth and birth weight [24].

### Fetal Growth and Size at Birth Are Two Different Indicators

As birth weight is only one aspect of fetal growth, stronger associations may exist between birth length, or lean and fat masses and later outcomes, possibly due to a trimester-specific restriction of fetal growth [3]. Measures of fetal size at birth are prone to measurement error [25]; ultrasound measures of fetal growth are therefore more useful. The contribution of gestational age on adult outcomes is unclear, and determinants of preterm birth and fetal growth may differ [13,25]. Birth weight is the result of many determinants, some possibly unrelated to susceptibility to adult disease. Conversely, some prenatal determinants of adult outcomes may be unrelated to fetal growth [25].

## BIOLOGICAL MECHANISMS OF THE FETAL ORIGINS OF ADULT OBESITY, CARDIOVASCULAR DISEASE, AND TYPE 2 DIABETES

### Maternal Nutrition during Pregnancy

In animal models, maternal undernutrition during pregnancy had lasting effects on offspring metabolism, growth, and disease [10]. Pregnant rats on low-protein diets delivered offspring of lower birth weight that went on to exhibit elevated blood pressure and glucose intolerance in adult life [5]. In humans, the nutritional needs of a young, physically immature, undernourished mother compete with those of the fetus, while the placenta also competes with both for energy and protein sources [26].

Except at extremes of intake, maternal energy and macronutrient intake have relatively little impact on birth weight [25], but may be important in circumstances of prolonged negative energy balance [24]. In an animal study, insufficient glucose supply to the fetus was associated with reduced insulin and insulin-like growth factor-1

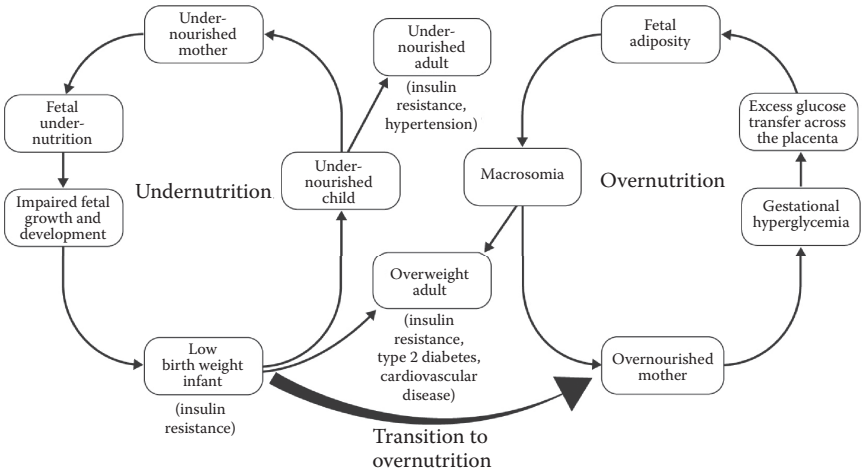


**FIGURE 23.2** Fetal programming. The intergenerational insulin resistance cycle in an environment of undernutrition and overnutrition, or a transition from undernutrition to overnutrition. (Adapted from Tomar AS, Tallapragada DS, Nongmaithem SS et al., *Curr Obes Rep* 2015, 4(4):418–28.)

(IGF-1) concentrations, restricting fetal growth [27]. Infants of mothers with type 2 diabetes and gestational diabetes tend to have high birth weights, due to increased glucose availability [28]. Figure 23.2 presents the intergenerational insulin resistance cycle in an environment of undernutrition and overnutrition, or a transition from undernutrition to overnutrition and the resultant fetal programming of insulin resistance [22].

Subsistence farming populations from developing countries experience seasonal energy shortages, due to variations in food availability and energy expenditure related to food production. The impact of seasonal maternal diet and physical activity on neonatal size was examined in a prospective study in rural India [24]. Maternal energy and protein intakes were around 70% of recommended dietary allowances, and showed significant seasonal variation, with peak values during harvest time. Mean birth weight and length, adjusted for prepregnancy weight, parity, gestation, and offspring sex, was highest after longer exposure to harvest time during pregnancy and lowest after longer exposure to the lean season. Regression analysis showed that maternal energy intake at 18 weeks of gestation had a significant positive association with birth weight and length, whereas maternal physical activity at 28 weeks was negatively associated with birth weight. Higher maternal energy intakes, coupled with lower physical activity in late gestation, were associated with higher birth weight. These observations indicate that complete exposure to harvest time in late gestation could increase birth weight by 90 g, increasing further by lowering excessive maternal physical activity during harvest time [24,29].

Apart from the known roles of n-3 fatty acids in reducing the incidence of preterm birth [30], and folate deficiency in causing neural tube defects, little is known about the role of other nutrients in the programming of chronic disease risk. The

relationship between maternal body size and circulating fuels, respectively, and neonatal size, was studied in the Pune Maternal Nutrition Study (1993–1996) [29]. The mothers were Indian, young, short and thin, and mostly vegetarian. At between 18 and 28 weeks gestation, fasting glucose concentrations remained stable, whereas total cholesterol and triglyceride concentrations increased and HDL-cholesterol concentrations decreased. The mean birth weight of the offspring was relatively low, at 2,666 g. Total cholesterol and triglycerides at both 18 and 28 weeks, and plasma glucose only at 28 weeks, were positively associated with birth size. The results did not change when preterm deliveries were also considered, suggesting an influence of maternal lipids on neonatal size in addition to the well-established effect of glucose during late pregnancy.

Folate is a methyl donor in the placenta for amino acid conversion and the generation of intermediates essential for cell division. Disordered one-carbon metabolism during early fetal development may increase later metabolic risk [31]. The reproducibility of the associations between maternal homocysteine concentrations and fetal growth found in the Pune birth cohort were explored in an observational study in Mysore, India. In this latter study, plasma vitamin $B_{12}$, folate, and homocysteine concentrations were measured at around 30 weeks gestation in the mothers, and the children's glucose and insulin concentrations, as well as neonatal anthropometry were measured at three ages: 5, 9.5, and 13.5 years [31]. Maternal homocysteine concentrations were inversely associated with all neonatal anthropometric measurements, and positively associated with glucose concentrations in the children at 5 and 9.5 years of age. Maternal serum folate concentrations, but not maternal vitamin $B_{12}$, were positively associated with insulin resistance in the children at 9.5 and 13.5 years of age [31].

In rural Gambia, cycles of rainy and dry seasons and a dependence on subsistence farming lead to annual variations in dietary intakes, compounded by the seasonal cycles of energy expenditure [32]. These cycles of nutrient availability and energy expenditure in mothers may affect fetal growth and development, offering a natural experiment to explore mechanisms by which early nutrient availability affects long-term pregnancy outcomes. In a prospective study of mothers' periconceptional dietary intakes and the plasma concentrations of key methyl-donor pathway substrates, 2,040 women were followed until pregnancy. Conception at the peak rainy ("hungry") season or the peak dry ("harvest") season, and predicted biomarker concentrations at conception were modeled. The offspring of rainy season conceptions, when mothers depended more on fresh green plant foods from the field, which are high in folate, had significantly higher levels of DNA methylation at the six remaining metastable epialleles (MEs) in peripheral blood lymphocytes (PBL). During the harvest season, when pregnant women had unlimited access to dry cereal foods and lower physical activity, there were increased periconceptional serum cysteine and homocysteine concentrations, predicting decreased systemic infant DNA methylation. Maternal serum riboflavin concentrations predicted increased ME methylation, while increased maternal BMI predicted decreased systemic infant DNA methylation. The consequences of these variations in methylation are unknown, but the possible implications of epigenetic variation at MEs induced by differences in maternal micronutrient status

and BMI at conception may have important implications for noncommunicable disease risk later in life [32].

The effects of periconceptional multiple micronutrient supplementation on placental function in later pregnancy were assessed in a double-blind randomized placebo-controlled trial [33]. Primary outcomes were midgestational uteroplacental vascular endothelial function and placental active transport capacity. Uteroplacental vascular endothelial function was not significantly different between the two groups, but placental active transport capacity improved marginally, indicating a possible benefit of periconceptional micronutrient supplementation [33].

## Placenta Size and Function

Placenta size increases until late in gestation, supporting ongoing fetal growth. Placental vascularization during early pregnancy determines later placental nutrient transfer capacity and, ultimately, fetal growth [13]. Maternal undernutrition restricts placenta development, compromising nutrient and oxygen delivery to the fetus in both term and preterm infants. Larger placentas were associated with higher prepregnancy BMI, excessive gestational weight gain (GWG), and gestational diabetes mellitus (GDM) among the mothers. Low placental weight was associated with lower birth weight-for-gestational-age z-score in both term and preterm infants [28]. The placenta has endocrine as well as metabolic and transfer functions, and is important to understanding associations of fetal growth with adult health [13].

Women with gestational diabetes transfer excess glucose across the placenta, which contributes to fetal overgrowth. Placental size may be an important mediator between pre-pregnancy BMI, GWG, gestational diabetes, and increased fetal growth. A study showed that excessive GWG and GDM may represent a state of intrauterine overnutrition, with abundant placental nutrient supply, causing macrosomia [28]. Prepregnancy obesity and excessive GWG were positively associated with birth weight-for-gestational-age z-score at birth only among term births [28]. Other adverse risk factors may contribute to preterm birth and also impact fetal growth. Intrauterine inflammation may induce preterm birth, as well as poor fetal growth, which may in turn influence placental growth [13]. Placental weight, thickness, width, length, and cord placement position may predict neonatal outcomes. Placental size may also increase due to remodeling from a prior injury. Therefore placenta weight alone may not reflect placental function as a determinant of fetal growth [28].

Evidence suggests that the placenta plays a key role in fetal programming of cardiometabolic diseases [13,34]. The oxygen and nutrients that support fetal growth rely on the entire nutrient supply line, from maternal diet and body size to uterine perfusion, placental function, and fetal metabolism. Interruptions of this line at any point could result in programming the fetus for future risk of cardiovascular disease [34]. Progesterone and placental lactogen promote maternal glucose delivery, IGF-1 promotes fetal growth, and 11 β-hydroxy-steroid dehydrogenase type 2 inactivates glucocorticoids. These endocrine functions may play a role in fetal programming of future metabolic diseases [34].

A possible mechanism to explain the development of hypertension in later life is that pressure in the fetal circulation might be raised as a method of maintaining placental perfusion when the mother is undernourished [35]. The raised blood pressure may persist after birth. Alternatively, intrauterine growth retardation may trigger accelerated postnatal growth, accompanied by an accelerated increase in blood pressure [35].

Certain periods of fetal life may be critical for organ development. One proposed underlying causal pathway for the fetal origins of adult chronic disease is based on the hypothesis that a congenital nephron deficit underlies predisposition to hypertension in adult life [36].

### Maternal Metabolism during Pregnancy

Maternal metabolism may influence fetal metabolic profiles directly through the placenta, or indirectly via influences of maternal hormones and/or placental metabolism. *In utero* exposures may include maternal behaviors, such as smoking and diet, or maternal metabolism, which may be associated with obesity or diabetes. The relationship of maternal midpregnancy corticotropin-releasing hormone (CRH) levels and offspring levels of adiponectin and leptin at the age of 3 years was studied in a prospective prebirth cohort study in the United States [37]. Maternal CRH blood levels were positively associated with levels of adiponectin, but not with leptin levels at age 3 years. There was no association between maternal CRH and birth weight for gestational age. The mechanism underlying the positive association between maternal levels of CRH and offspring adiponectin is unclear, but higher adiponectin may not be associated with a healthy metabolic profile in young children. The authors speculated that the increase in adiponectin was a compensatory response to increased insulin resistance in those children whose mothers had high midpregnancy CRH [37].

There is evidence from animal studies that the gut microbiome influences the diet-related metabolic profile [38]. Further research is necessary to explore metabolite profiles associated with gut microbiota in human populations during pregnancy. The gut microbiome is explored in detail in Chapter 19 of this book.

### Smoking and Pollution during Pregnancy

The deleterious effects of pollution and maternal smoking during pregnancy are well-known examples of prenatal exposures affecting fetal growth, but with unknown long-term health effects. A systematic review of 14 observational studies ($n$ = 84,563 children) examining the association between maternal prenatal cigarette smoking and overweight offspring showed that offspring of smokers were at increased risk for being overweight at ages 3 to 33 years, compared with children of nonsmokers [38]. Differences between smokers and nonsmokers could not be explained by sociodemographic or behavioral confounders [39].

### Genetic and Epigenetic Factors

Inherited fetal gene expression potentially underlies susceptibility to disease, but the maternal genome also affects the fetal environment and may affect fetal gene

expression. The association between maternal hypertension, low birth weight, and hypertension in the offspring could be partly of genetic origin [13]. However, the subsequent pattern of development appears to be responsive to environmental influences. Developmental plasticity evolved to match an organism to its environment, but a mismatch between the resultant phenotype and the current environment increases cardiovascular risk [40]. Epigenetic processes appear to be key mechanisms in the developmental origins of chronic noncommunicable disease [40].

A study of undernutrition over 50 generations in a rat model showed low birthweight, high visceral adiposity, and insulin resistance (using hyperinsulinemic-euglycemic clamps) in undernourished rats, compared to age-/sex-matched control rats [41]. Undernourished rats also had higher serum insulin, homocysteine, endotoxin, and leptin levels, but lower adiponectin, vitamin $B_{12}$, and folate levels. The undernourished rats had an eightfold increased susceptibility to *Streptozotocin*-induced diabetes compared to controls. These metabolic abnormalities could not be reversed after two generations of nutrient rehabilitation. Altered epigenetic signatures in the insulin-2 gene promoter region of undernourished rats were also not reversed by nutrition, and may contribute to the persistent adverse metabolic profiles in similar multigenerational undernourished human populations [41].

In the Pune Maternal Nutrition Study and the Parthenon Cohort Study in Mysore, India (discussed earlier), evidence of causality within a Mendelian randomization framework of the association between maternal total homocysteine and offspring birth weight was studied [42]. This was assessed using a methylenetetrahydrofolate reductase (MTHFR) gene variant rs1801133 by instrumental variable and triangulation analysis, separately, and meta-analysis. Offspring birth weight was inversely related to maternal homocysteine concentration adjusted for gestational age and offspring sex in these studies and in the meta-analysis. Maternal risk genotype at rs1801133 predicted higher homocysteine concentration and lower birth weight, adjusted for gestational age, offspring sex, and rs1801133 genotype. Instrumental variable and triangulation analysis supported the causal association between maternal homocysteine concentration and offspring birth weight. These findings suggest a causal role for maternal homocysteine metabolism in fetal growth and support interventions to reduce maternal homocysteine concentrations [31,42].

A quasi-experimental study was performed to evaluate the impact of the Dutch famine of 1944–1945 during specific periods of pregnancy, or any time in gestation, on genome-wide DNA methylation levels of offspring at 59 years [43]. They compared individuals with prenatal famine exposure and time or sibling controls without prenatal famine exposure. They also studied the impact of shorter pre- and postconception exposure periods. Famine exposure during gestation weeks 1 to 10, but not during later gestation, was associated with increased DNA methylation of four specific dinucleotides. Exposure during any time in gestation resulted in increased methylation of two specific dinucleotides, while exposure around conception was associated with methylation of only one dinucleotide. This dinucleotide, cg23989336, is involved in the determination of body size in knockout mice studies [44]. All dinucleotides identified in this study were linked to genes involved in growth, development, and lipid metabolism. The authors identified early gestation, but not mid or late gestation, as a critical time period for DNA methylation changes affecting body size after prenatal famine exposure [43].

## FUTURE STUDIES

Animal studies of fetal growth will continue to contribute new knowledge and are useful to study nutrient and oxygen delivery, as well as processes altering these pathways. Serial ultrasound measures to measure human fetal growth parameters throughout pregnancy will also contribute useful information due to potential issues with statistical growth trajectory models. Placental morphological pathology, as well as using specimens of placenta, maternal prenatal blood, and umbilical cord blood may be applied to measure markers of altered blood flow, endocrine and transport characteristics, or activity of specific enzymes related to later noncommunicable disease risk [34].

The fetal origins of disease theory arose from historical cohort studies, namely, the Dutch famine cohort [11]. A collaboration of five birth cohorts from low and middle-income countries (Brazil, Guatemala, India, Philippines, and South Africa) has made it possible to analyze pooled longitudinal data from Consortium for Health Orientated Research in Transitioning Societies (COHORTS) [45]. More than 22,000 mothers were enrolled before or during pregnancy and almost 20,000 children are being followed up; analyses will be adjusted for maternal variables and breastfeeding duration [45]. New cohort studies of preconceptional and pregnant women have been and are continuing to be planned to overcome the limitations of the earlier studies and to explore mechanisms of pathways gleaned from these early studies [21,39]. These studies will take decades for adult disease outcomes to occur. The associations between maternal exposures and offspring health in adolescence are being studied in the Growing Up Today Study cohort and their mothers, from the Nurses' Health Study II [39].

Metabolomics studies focus on systematic analysis of low-molecular intermediates in biological fluids. Such investigations may target specific intermediates associated with obesity or insulin resistance, or could search for novel biomarkers [46]. Metabolomics studies have potential to provide valuable information on the physiological response to nutrient intake and could be informative for fetal origins research when quantified during key developmental stages of pregnancy. Metabolite profiles associated with specific dietary patterns, or behaviors, such as smoking and physical activity can be identified [46]. Whereas birth weight and fetal growth are crude measures of the intrauterine environment, cord blood metabolomic profiling at delivery could improve assessment of adverse fetal growth outcomes, and guide future interventions to avoid such risks. The metabolomic profile could give an indication of impaired nutrient transfer to the fetus during development [46].

## PUBLIC HEALTH INTERVENTIONS REGARDING FETAL PROGRAMMING

Epidemiological findings of associations between birth weight and later health outcomes provide evidence of programming of noncommunicable disease in humans. Experimental animal evidence also shows that *in utero* environmental stressors produce lifelong alterations in metabolism and pathology. These implications are important for developing countries undergoing a transition from infectious disease

to noncommunicable disease burdens, as well as the nutrition transition from an active, low-calorie lifestyle to a sedentary, high-calorie lifestyle occurring globally [47]. Available data indicate that a lower birth weight combined with later higher attained BMI confers the highest risk for obesity and cardiovascular disease later in life [6,14,15,17]. Successive generations in developing countries are likely to have increasing proportions with a high cardiometabolic risk profile. Efforts to prevent the development of obesity in areas undergoing such epidemiological, economic, and nutrition transitions are paramount.

The implications for policy recommendations regarding fetal programming are not yet clear. Birth weight is only a marker for underlying etiological pathways, whereas the true etiological factors are largely unknown. More targeted interventions to modify cardiometabolic risks due to fetal programming can be designed when these factors are more clearly identified. Interventions to increase birth weight per se may not be effective and could be harmful. The focus should rather be on improving the health of women of reproductive age to improve the well-being of their offspring. Examples include the strengthening of efforts to prevent childbearing before the age of 19 years [45], and restriction of maternal weight gain to 20 kg or less for overweight and obese women to curb adolescent adiposity [39]. Strategies to reduce excessive adiposity gains during early postnatal life and in the preschool years may reduce midchildhood blood pressure, which may also affect adult blood pressure and cardiovascular disease risk [21]. These results indicate that interventions to prevent excessive weight gain during pregnancy and early postnatal life may be beneficial.

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