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PATHOGENESIS OF TYPE 2 DIABETES AND INSULIN RESISTANCE (M-E PATTI, SECTION EDITOR)

Developmental Programming of Body Composition: Update on Evidence and Mechanisms

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Abstract

Purpose of Review A growing body of epidemiological and experimental data indicate that nutritional or environmental stressors during early development can induce long-term adaptations that increase risk of obesity, diabetes, cardiovascular disease, and other chronic conditions—a phenomenon termed "developmental programming." A common phenotype in humans and animal models is altered body composition, with reduced muscle and bone mass, and increased fat mass. In this review, we summarize the recent literature linking prenatal factors to future body composition and explore contributing mechanisms.

Recent Findings Many prenatal exposures, including intrauterine growth restriction, extremes of birth weight, maternal obesity, and maternal diabetes, are associated with increased fat mass, reduced muscle mass, and decreased bone density, with effects reported throughout infancy and childhood, and persisting into middle age. Mechanisms and mediators include maternal diet, breastmilk composition, metabolites, appetite regulation, genetic and epigenetic influences, stem cell commitment and function, and mitochondrial metabolism.

Summary Differences in body composition are a common phenotype following disruptions to the prenatal environment, and may contribute to developmental programming of obesity and diabetes risk.

Keywords Adiposity · Fat mass · Lean mass · Muscle mass · Bone mass · Developmental programming · Low birth weight · Epigenetics

Introduction

Environmental and nutritional exposures during prenatal and early postnatal development can result in increased risk for chronic diseases, a phenomenon known as "developmental programming." Thus, optimizing maternal and child health during the "first 1000 days," i.e., the critical period between conception and age 2, has become a key focus of public health efforts [1, 2]. With obesity, metabolic syndrome, and type 2 diabetes (T2D) reaching unprecedented levels in both Western and developing societies [3–5], it is crucial to understand the mechanisms by which suboptimal prenatal or early postnatal environments contribute to future disease vulnerability.

Identifying mechanisms and mediators of developmental programming has been an area of active research for the past two decades. A number of experimental models have been used, including rodents, large mammals, and primates, with a variety of dietary paradigms (e.g., high-fat diet, Western diets, low-protein diets, global caloric restriction, micronutrient restriction, etc.), surgical paradigms (e.g., uterine artery ligation), chemical exposures, psychological stress, transgenic models, and other systems [6–11]. Based on these experimental data, developmental programming may be caused by a number of overlapping and interacting factors, including epigenetic signals, mitochondrial inheritance, milk composition, the intestinal microbiome, and features of the maternal metabolic environment, such as insulin resistance, fatty acids, and inflammation. In many cases, the effects of the prenatal perturbations are exacerbated by postnatal exposure to a high-calorie diet, accelerated postnatal growth, stress, or other factors. While numerous markers and mediators have been implicated (and are reviewed

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elsewhere [12–15]), a common phenotype is altered body composition, with reduced lean mass and increased fat mass. This review summarizes recent publications on the prenatal determinants of abnormal body composition, with an emphasis on recent data in human populations published between 2012 and 2019. We will discuss evidence addressing mechanisms by which diet and appetite regulation, epigenetic regulation, differences in stem cell commitment and function, and impaired mitochondrial metabolism may contribute to obesity and diabetes risk.

Historical Observations

Early evidence for developmental programming came from studying historical cohorts. Studies of individuals exposed to the Dutch Famine during World War 2, in which a German blockade of the Western Netherlands caused a severe famine in a previously prosperous society, demonstrated that maternal exposure to undernutrition during pregnancy led to multiple adverse health outcomes for offspring, including fetal growth restriction [16, 17], and increased risk of visceral obesity, metabolic syndrome, T2D and other chronic diseases [18–20]. Subsequent work by David Barker, who discovered an association between low weight at birth and future cardiometabolic disease [21], further underscored the importance of early nutritional exposures as determinants of adult chronic disease risk. Barker hypothesized that stress experienced in utero—or during other critical developmental windows—induces compensatory responses in tissue structure and function that may persist permanently. Such developmental programming may allow the organism to withstand the stressor initially, but may create disease vulnerability in the future. Initial observations in the field focused on the deleterious effects of low birth weight and undernutrition during key developmental windows on future diabetes and obesity risk. A strong effect of prenatal exposure to undernutrition and low birth weight on T2D has been observed among ethnically diverse populations, in both historical and contemporary cohorts, including survivors of the Chinese Famine (1959–1961), the U.S. Nurses' Health Study, a French cohort of women born between 1925 and 1950, the Shanghai Men's and Women's Health Studies, the Japanese Nurses' Health Study, and other international cohorts [22–26].

Subsequent work demonstrated that *over*-nutrition or nutrient excess during critical developmental windows may also contribute to long-term chronic disease risk. For example, in utero exposure to maternal obesity can significantly increase risk of obesity, metabolic syndrome, and T2D in offspring [27–29]. Studies among siblings born before versus after maternal weight loss surgery (where the comparison of sibling pairs reduces the influence of genetics) indicate that risk of childhood obesity is increased by prenatal exposure to maternal obesity [30]. Similarly, studies of siblings discordant for in utero diabetes exposure (i.e., comparing siblings born before vs. after maternal T2D diagnosis) demonstrate that prenatal exposure to diabetes results in higher risk of obesity, hyperglycemia, dyslipidemia, and hypertension [31–33]. These effects are not limited to maternal T2D: type 1 diabetes, monogenic diabetes, gestational diabetes (GDM), and subclinical hyperglycemia not reaching the threshold for GDM are also linked to adiposity and glucose intolerance in offspring [34, 35]. More recently, there has been growing evidence for pollutants and chemical exposures, including vehicle emissions, cigarette smoke, endocrine-disrupting chemicals, and pesticides, as inducers of developmental programming [36–45]. Thus, a diverse range of prenatal exposures has been linked to obesity and metabolic diseases in the offspring.

Developmental Programming of Adiposity

Birth Weight and Future Adiposity

Prenatal exposure to a suboptimal in utero environment is associated with increased BMI, increased fat mass, and central/abdominal fat distribution—body composition patterns linked to T2D risk. Since prenatal growth is influenced by a wide range of factors (e.g., maternal nutrition, placental insufficiency, hypoxia, smoking, etc.), birth weight can be considered a biomarker for disruptions in the prenatal environment. Many population-based studies indicate that both low and high birth weight are associated with excess adiposity throughout the lifespan; these studies are summarized in Table 1. Several groups have documented associations between small for gestational age (SGA) birth weight and future risk of central or visceral adiposity [85–87], but the literature has not been entirely consistent, with several large studies failing to document such associations [54, 62]. At the other end of the spectrum, large for gestational age (LGA) infants are at increased risk for increased fat mass and high BMI [86], so that the association between birth weight and future adiposity has been described as a "U-shaped" distribution [88]. Although the studies vary in methodology and sample size, the effect of birth weight on future BMI seems most reproducible for infants with high birth weight, whereas increases in central adiposity (assessed by MRI, DXA, or skinfold thickness) appear more reproducible among those born SGA.

Some of the discordance in the literature may stem from differences in statistical adjustment for confounders. A recent analysis in the Danish National Birth Cohort indicated that socioeconomic confounders including low maternal education and household income were associated with both low birth weight and high childhood BMI [89]; careful adjustment for these factors is therefore essential. Adjusting for offspring BMI may also introduce variability in study outcomes. For example, Kramer et al. applied two statistical approaches to the same

Table 1 Summary of recent studies in human populations examining associations of prenatal exposures with obesity or adiposity

Prenatal exposure	Effect on adiposity	Outcome measure	Age	Sample size	Study population	Reference
SGA	↓	DXA	0–3 y	95	Spain	[46]
	↑	BMI	4–18 m	23,871	China	[47]
	↓	BMI	9 m–5 y	11,134	Ireland	[48]
	↑	MRI	2–6 y	51	Spain	[49]
	↑	MRI	3–6 y	46	Spain	[50]
	↓	BMI	3.5–11 y	547	New Zealand	[51]
	↓	BMI, SF	3.5–7 y	380	Sweden	[52]
	–	BMI	5 y	23,871	China	[47]
	–	BMI	5–8 y	10,186	U.S.	[53]
	↓	BMI	6–12 y	2016	Canada	[54]
	–	BMI	12.5 y	96	Netherlands	[55]
	↑	BMI	9–15 y	7194	China	[56]
	–	BMI	10–11 y	3054	USA	[57]
	↓	BMI, SF	11.5 y	17,046	Belarus	[58, 59]
	–	BMI	15–18 y	51,505	Germany	[60]
	↑	BMI, SF, BIA	22–30 y	851	France	[61]
	–	BMI	29 y	165	Brazil	[62]
ELBW	↑	MRI	34 y	46	Canada	[63]
	↑	DXA	31.8 y	100	Canada	[64]
Decreased birth weight	↑	SF	Birth	235	France	[65]
	↑	DXA	Birth	311	Denmark	[66]
Increased birth weight	↑	BMI	3–9 y	1759	Australia	[67]
	↑	BMI, SF	5–13 y	612	Brazil	[68]
	↑	DXA	22 y	1088	South Africa	[69]
	↑	Weight, WC	24–50 y	587	USA	[70]
LGA	↑	DXA	Birth	311	Denmark	[66]
	↑	BMI	9 m–5 y	11,134	Ireland	[48]
	↑	BMI	5–8 y	10,186	USA	[53]
	↑	BMI, SF	6–12 y	2016	Canada	[54]
	↑	BMI	9–15 y	7194	China	[56]
	↑	BMI	10–11 y	3054	USA	[57]
	↑	BMI	15–18 y	51,505	Germany	[60]
Maternal BMI	↑	DXA	Birth	311	Denmark	[66]
	↑	BMI, SF	4–5 y	6060	UK	[71]
	↑	BMI	5–6 y	1727	Netherlands	[72]
	↑	BMI, WC	16 y	4168	Finland	[73]
	↑	BMI	33 y	863	USA	[29]
	↑	BMI	62 y	2003	Finland	[74]
Maternal glucose	↑	Weight, BMI	0–7 y	661	Denmark	[75]
	↑	Weight, BMI	0–3 y	937	Singapore	[76]
	↑	BMI	5–7 y	1320	Ireland	[77]
	↑	BMI, SS, WC	10–14 y	4832	Multi-national	[78]
	↑	Weight	Birth	264	Denmark	[79]

Table 1 (continued)

Prenatal exposure	Effect on adiposity	Outcome measure	Age	Sample size	Study population	Reference
GDM	↑	DXA, WC	3–12 y	86	Canada	[80]
	↑	BMI, WHR	9–16 y	1158	Denmark	[81]
	↑	BMI, WC, SS	11.4 y	4832	Multi-national	[82]
Maternal T1D	↑	DXA	16 y	581	Denmark	[83]
	↑	BMI, DXA	5–18 y	313	UK	[84]

SGA small for gestational age, *ELBW* extremely low birth weight, *GDM* gestational diabetes, *T1D* type 1 diabetes mellitus, *DXA* dual-energy X-ray absorptiometry, *SF* skinfold thickness, *WC* waist circumference, *BIA* bioimpedance analysis

dataset and showed that the association between SGA and childhood body fat had the opposite directionality depending on how the statistical models dealt with BMI. Adjustment for the child's current BMI indicated increased percent body fat with SGA, but decreased body fat with SGA in an unadjusted analysis. Notably, the association between SGA and increased subscapular/triceps skinfold thickness was significant using both statistical approaches [58•].

Genetic factors, too, can influence the relationship between birth weight and future adiposity. For example, genetic variation at many SNPs linked to obesity and/or diabetes are also linked to birth weight [90, 91]. However, a recent pooled analysis of 27 twin cohorts confirmed a strong influence of birth weight on BMI, in both fraternal and monozygotic twin pairs, suggesting that these effects are not fully explained by genetic factors [92].

Maternal Obesity and Future Adiposity

Maternal pre-pregnancy BMI is among the strongest risk factors for childhood obesity and is estimated to account for 10–20% of the population attributable risk of childhood obesity [93–95]. Effects of maternal obesity on offspring adiposity emerge early: higher maternal BMI is linked to higher birth weight and greater newborn skinfold thickness, with differences in body weight detectable by 32 weeks' gestation [96–98]. Maternal obesity has been reproducibly associated with offspring adiposity throughout the lifespan, as summarized in Table 1. Maternal pre-pregnancy BMI is associated with higher childhood BMI and with increased adiposity (percent body fat and skinfold thicknesses) [71, 72]. Based on a meta-analysis of data from 162,129 mothers and their children from 37 pregnancy and birth cohort studies from Europe, North America, and Australia, maternal BMI has the strongest effect in late childhood (age 10–18 years) [95], but effects remained detectable into late adulthood [74]. Moreover, maternal obesity has also been linked to accelerated weight gain throughout early and mid-adulthood [29].

While the association between maternal pre-pregnancy BMI and offspring adiposity is strong and reproducible across ethnically diverse populations, it is unclear whether the effect is due to programming by the in utero environment, or by confounders such as shared genetic, nutritional, or socioeconomic risk factors. Studies of siblings born before versus after maternal weight loss (e.g., following obesity surgery) show increased childhood obesity risk for the sibling born before maternal weight loss, supporting the concept that in utero exposure to maternal obesity plays a pathogenic role [30, 99]. Moreover, recent studies using Mendelian randomization have indicated that genetic variants linked to maternal BMI (e.g., rs3736485 in *DMXL2*) are associated with higher offspring birth weight and childhood BMI, independent of offspring genotype [100, 101], although a similar analysis in the ALSPAC and Generation R cohorts found no effect of maternal BMI on childhood BMI after adjusting for shared genetics [102]. Taken together, these data support an important effect of prenatal exposure to maternal obesity on offspring adiposity, although the relative role of genetic versus epigenetic and environmental factors remains unclear.

Maternal Hyperglycemia or Diabetes and Future Adiposity

Prenatal exposure to maternal diabetes, or to hyperglycemia not reaching diagnostic cut-offs for GDM, is associated with increased adiposity in offspring. Some of the most compelling evidence for this effect has come from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Follow-up Study, a large international cohort study designed to examine associations of glucose levels during pregnancy with multiple adverse perinatal outcomes, in order to establish diagnostic cut-offs for GDM [103]. In the HAPO Follow-up Study, maternal glucose levels at 28 weeks' gestation were found to be positively associated with birth weight and newborn adiposity, and with childhood BMI, skinfold thicknesses, waist circumference, and percent body fat between 10 and 14 years of age [78, 104]. Similarly, associations between higher maternal glucose during gestation and childhood adiposity were reported in the Danish National Birth Cohort, the US-based EPOCH Study, and other cohort studies (Table 1) [79, 81].

A longstanding controversy centers around whether maternal hyperglycemia per se contributes to offspring obesity, independent of maternal BMI, given that women with GDM are more likely to be obese. However, in HAPO and many recent studies, the effects of maternal GDM or hyperglycemia persisted after adjustment for maternal pre-pregnancy BMI [75••, 78, 79, 81, 82••]. Moreover, the EPOCH Study demonstrated that effects of maternal GDM on offspring adiposity were not explained by the child's genetic risk score for obesity [105]. Prenatal exposure to maternal type 1 diabetes has similarly been linked to increased total body fat in offspring [83]. Together, these data support a strong effect of maternal hyperglycemia and diabetes on offspring adiposity, and raise the possibility that interventions to detect and treat gestational hyperglycemia might be a promising strategy for preventing childhood obesity.

Developmental Programming of Muscle Mass

Decreased muscle mass has been reported across several types of in utero disruptions, spanning undernutrition, maternal diabetes, and prenatal stress. Paucity of muscle mass may be an important contributor to diabetes risk: muscle is a crucial insulin target tissue, and decreased muscle mass is linked to insulin resistance due to reduced whole-body glucose uptake, independent of BMI [106].

Effects of Birth Weight on Muscle Mass

Low birth weight infants have been reported to have reduced muscle mass throughout childhood, adolescence, and young adulthood (reviewed in [65, 107]), and reduced muscle strength both in later childhood [108] and in adulthood [109, 110]. These effects have been reported among infants born low birth weight due to intrauterine growth restriction, as well as those born premature. Among the latter group, low birth weight is strongly correlated with reduced lean mass in childhood [111]. Based on one of the earliest cohorts of extremely low birth weight (ELBW, < 1000 g, typically < 27 weeks' gestation) infants born between 1977 and 1982, ELBW infants have detectable reductions in lean body mass into their fourth decade as compared to normal birth weight infants [64]. Conversely, infants born LGA have higher lean mass in later life [69, 70]. Recent studies linking birth weight to lean mass are summarized in Table 2.

While the association between birth weight and lean mass is strong and reproducible, it is unclear whether it is driven by prenatal versus postnatal factors. For example, decreased prenatal growth velocity (calculated as the change in fetal weight percentiles between 22 weeks' gestational age and birth) is a strong predictor of reduced lean mass at birth, independent of birth weight [65]. Moreover, low birth weight is often associated with postnatal catch-up growth, a growth pattern characterized by upward crossing of weight for age percentiles, and with "catch-up fat," or accelerated adipose tissue growth outstripping the growth of lean mass [116]. Catch-up weight gain following intrauterine growth restriction is associated with higher fat mass and lower lean mass in later life, independent of birth weight [117, 118]. Conversely, LGA infants have been reported to have accelerated growth of lean mass during the early postnatal period [119]. Thus the role of prenatal versus postnatal factors in developmental programming of lean mass remains an important question.

In utero exposure to hyperglycemia is also linked to reductions in lean body mass, similar to prenatal undernutrition and low birth weight, which is paradoxical given that maternal hyperglycemia tends to increase birth weight. Effects of maternal GDM on lean mass have been reported in early childhood and in adolescence [80, 81]. Prenatal exposure to nutrient excess has been linked to impaired myogenesis in offspring rodents and pigs [120], but it is unclear whether similar mechanisms are at play in humans.

Developmental Programming of Bone Mass

Bone density is known to influence osteoporosis and fracture risk, and is linked to healthy aging. Recent studies have highlighted connections between bone density, marrow adipocytes, and systemic metabolism, leading some to propose that osteoporosis should be viewed as "obesity of bone" [121]. Loss of bone density is usually accompanied by increases in bone marrow adipocyte populations. Osteocytes and marrow adipocytes are derived from common precursors, mesenchymal stem cells. Although they were historically viewed as "filler," bone marrow adipocytes are increasingly recognized as playing an important role in bone health and metabolic disease. For example, leptin and other adipokines can stimulate osteocyte development [122], and marrow adipocytes can influence bone metabolism and hematopoiesis [123]. Thus, effects of prenatal exposures on bone density may have broad implications for healthy aging and metabolism.

Birth Weight and Future Bone Mass

Nutritional exposures during early development can significantly impact future skeletal health, bone mineral density, and osteoporosis risk. Bone mineral density accrues fastest during the third trimester of pregnancy, but continues to increase postnatally and peaks in young adulthood [124]. Thus, periods of suboptimal nutrition, or other stressors (e.g., inflammation,

Table 2 Summary of recent studies in human populations examining associations of prenatal exposures with lean mass

Prenatal exposure	Effect on lean mass	Age	Sample size	Study population	Reference
Decreased birth weight	↓	Birth	235	France	[65]
	↓	5 and 9 y	61	Germany	[111]
	↓	9 y	574	India	[108]
	↓	25 y	1061	Sweden	[112]
	↓	30 y	3701	Brazil	[110]
ELBW	↓	31.8 y	100	Canada	[64]
SGA	↓	Term	42	Japan	[113]
	↓	3.5 and 7 y	380	Sweden	[52]
	↓	6.7 y	67	Chile	[114]
	↓	22 y	1088	South Africa	[69]
Increased birth weight	↑	22 y	1088	South Africa	[69]
	↑	24–50 y	587	USA	[70]
	↑	60–64 y	1558	UK	[115]
GDM	↓	3–12 y	86	Canada	[80]
	↓	9–16 y	1158	Denmark	[81]

chronic disease, glucocorticoid treatment, etc.) during early life can impair peak bone mass, increase osteoporosis risk, and "program" future bone health (available data summarized in Table 3). For example, birth weight is predictive of childhood bone mineral density: individuals with lower birth weight (< 10th percentile) had lower forearm cortical bone

Table 3 Summary of recent studies in human populations examining associations of prenatal exposures with bone mass

Prenatal exposure	Effect on bone mass	Age	Sample size	Study population	Reference
Decreased birth weight	↓	Adolescence	961	Norway	[125]
	↓	25 y	1061	Sweden	[112]
VLBW (< 1500 g)	↓	25–28 y	134	Norway	[126]
LBW	↓	5–19 y	284	Germany	[127]
SGA	↓	Term	42	Japan	[113]
	↓	6 y	123	Netherlands	[128]
	↓	11 y	91	Italy	[129]
	↓	25–28 y	134	Norway	[126]
LGA	↑	6 y	123	Netherlands	[128]
Macrosomia	↓	Birth	40	Israel	[130]
Maternal BMI	↑	9.9 y	7121	UK	[131]
GDM	–	Birth	40	Israel	[130]
	↓	Birth	37	Israel	[132]
	↑	Birth	40	France	[130, 133]
Maternal T1D	↑	5–18 y	313	UK	[84]

mineral density [127], whereas whole-body bone mineral density and content are positively associated with birth weight [134]. Intrauterine growth indices, too, may be predictive of childhood bone density, with increases in fetal abdominal circumference between 19 and 34 weeks' gestation positively associated with greater bone mineral density at age 4 years [135]. Meta-analyses and systematic literature reviews support a role for prenatal growth on future skeletal health: higher birth weight has been reproducibly associated with higher bone mineral content in childhood and adulthood [136, 137]. However, there is some heterogeneity between studies: some groups have demonstrated only sex-specific effects or have only noted effects on certain bone indices (e.g., bone mineral content vs. density) [112]; moreover, effects of birth weight on bone mass may be stronger in childhood and adolescence than in later life [126, 137, 138]. These effects are recapitulated in animal models: Wallace et al. reported that prenatal growth restricted lambs had lower bone mineral density (as compared to normal birth weight lambs) throughout the lifespan [139], whereas Devlin et al. reported increased trabecular bone volume in female offspring of high-fat diet fed mouse dams [140].

Maternal Diabetes and Offspring Bone Mass

Despite positive associations between LGA and higher bone mass, some reports have suggested that infants of mothers with GDM have decreased bone strength [132] and bone mineral density, with more severe defects in offspring of mothers with uncontrolled diabetes (reviewed in [141]). However, other studies have found no effect, or a higher bone density, in offspring of mothers with diabetes [84, 130, 133]. Thus, further analyses are needed to better define the net effect of maternal hyperglycemia and diabetes on offspring bone health.

Mechanisms

From a mechanistic standpoint, developmentally programmed differences in body composition may be caused by numerous factors, including: diet or lifestyle, reduced numbers and/or function of muscle progenitors, increased numbers and/or function of adipose progenitors, adipocyte hypertrophy and lipogenesis, altered nutrient uptake by lean versus adipose tissues, altered signaling through pathways regulating muscle growth (e.g., GH, IGF1, myostatin [119]), genetics, and/or by persistent changes in epigenetic marks. Based on recent data in experimental models and in translational studies of human tissues, each of these potential pathways has been implicated in developmental programming of body composition (Fig. 1). We review the evidence supporting each of these possibilities in this section, with an emphasis on mechanistic studies in humans.

Maternal Diet and Metabolites

Maternal diet is a key potential mediator of the association between prenatal exposures and postnatal body composition. Maternal intake of macronutrients or micronutrients may create a metabolic milieu that modulates infant growth. For example, higher maternal carbohydrate intake during pregnancy is associated with higher fat mass in childhood [142]; conversely, high-protein/low-carbohydrate intake during pregnancy is associated with lower abdominal adiposity in the newborn period [143]. Associations have also been reported between offspring waist circumference and maternal adherence to the Mediterranean diet during pregnancy [144], and between neonatal adiposity and maternal intake of pro-inflammatory foods (positively correlated) [145] and maternal diet quality (inversely correlated) [146].

Maternal intake of micronutrients has also been linked to offspring obesity and altered body composition. For example, lower maternal intake of vitamin D has been linked to reduced

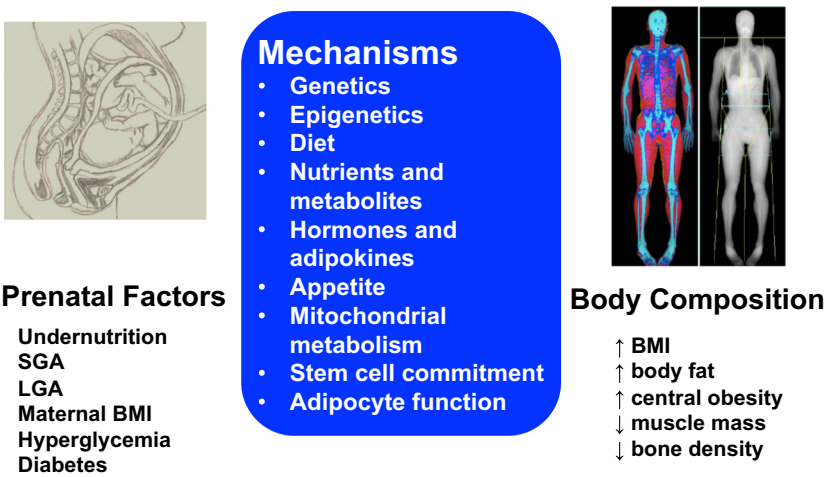

Fig. 1 Overview of mechanisms linking prenatal exposures to body composition in later life

adiposity at birth, but higher fat mass at ages 1, 4, and 6 years [147, 148]. Although the association was not detected in a population with a low prevalence of vitamin D deficiency [149], a large meta-analysis (35,032 mother–infant pairs) confirmed associations between low prenatal maternal vitamin D and low birth weight, and with increased infant weight at 9 months (unadjusted for birth weight) [150].

Maternal diabetes and obesity may influence levels of specific metabolites that influence fetal growth or metabolism. For example, a metabolomic analysis in women with GDM identified increased levels of the furan fatty acid metabolite CMPF (derived from the diet/microbiome), which, when administered to mice, induced beta cell dysfunction and impaired mitochondrial metabolism [151]. Moreover, higher maternal intake and cord blood concentrations of the long-chain fatty acids DHA and EPA, and a higher ratio of cord plasma *n*-6:*n*-3 PUFAs, were associated with higher infant skinfold thicknesses and increased odds of obesity [152]. In this same cohort, cord blood levels of metabolites related to tryptophan and the one-carbon methyl donor pathway were associated with more rapid infancy weight gain and higher childhood BMI [153]. Moreover, higher maternal levels of the choline metabolite and methyl donor betaine have been associated with lower infant birth weight and abdominal fat [154].

Although maternal diet is a modifiable risk factor and an attractive target for interventions to prevent childhood obesity, dietary interventions during pregnancy among obese women have largely been unsuccessful. For example, a randomized controlled intervention to reduce the omega-6 to omega-3 PUFA ratio throughout pregnancy and lactation yielded no detectable effects on childhood body composition, assessed by MRI at age 5–6 years [155], nor did a trial of maternal DHA supplementation result in any differences in adiposity measures in offspring [156]. Further studies will be essential to identify effective nutritional strategies during gestation to prevent childhood obesity and adiposity.

Breast Feeding and Milk Composition

The mode of infant feeding and milk composition are important contributors to childhood obesity and body composition. Formula feeding is associated with more rapid postnatal weight gain, higher childhood BMI, and greater acquisition of lean mass, as compared to breast feeding [157, 158]. However, obesity risk is increased by maternal obesity even in exclusively breastfed infants [159], raising the possibility that differences in human milk composition could contribute to mother–child transmission of obesity risk. Consistent with this, several groups have identified differences in bioactive compounds in milk from obese versus lean mothers, including increased insulin, leptin, adiponectin, ghrelin, IL-6, TNF-alpha, and lower omega-3 fatty acids (reviewed in [160] and [161]). However, for many of these compounds, there is a positive association with maternal BMI and a negative association with infant adiposity (notably insulin, adiponectin and IL-6), or no association, so that it is unclear whether milk composition differences play a pathogenic role in infant adiposity.

Recent data suggest that milk content of fructose and human milk oligosaccharides are linked to body composition in exclusively breastfed infants [162, 163]; however, these were not significantly associated with maternal BMI. A recent metabolomics analysis of human milk in obese versus lean mothers found associations between the abundance of several milk metabolites and infant fat mass, assessed by DXA. Although there was only minimal overlap between metabolites associated with maternal and infant adiposity, some intermediates of nucleotide metabolism were linked to both maternal BMI and infant fat mass, raising the possibility that these metabolites might play a mechanistic role in mother–child transmission of obesity [164]. Further evidence for milk composition as contributor to childhood obesity has come from experimental studies. For example, in mice, cross-fostering experiments indicate that lactational exposure to maternal obesity confers obesity in the offspring [165]. Moreover, in a rat model, maternal HFD was associated with reduced prolactin receptor expression and prolactin content in milk, and normalizing milk prolactin levels reduced visceral adiposity and normalized insulin sensitivity [166]. Together, these data provide strong support for the role of milk in shaping childhood body composition.

Postnatal Diet and Appetite Regulation

Postnatal diet is another potential mechanism for developmentally programmed effects on body composition. For example, the nutritional environment that may have contributed to suboptimal (or excessive) prenatal growth could also affect postnatal phenotypes. Consistent with this, in a study from rural Southern India, LBW individuals had lower average daily protein intake at age 20 years, in association with significantly reduced lean mass and trends for reduced bone mineral content [167]. Moreover, in Western societies, dietary patterns associated with higher maternal BMI are also associated with childhood obesity, e.g., sugar-sweetened beverages, highly processed snack foods, food insecurity, etc. Thus, it can be challenging to disentangle effects of prenatal nutrition versus postnatal diet on offspring body composition.

Prenatal perturbations may also affect appetite regulation and eating behaviors. For example, children with higher birth weight had differences in eating behavior survey measures, such as Satiety Responsiveness (lower), Food Responsiveness (higher), and Enjoyment of Food (higher) in early childhood [168]. Similarly, prenatal exposure to hyperglycemia or GDM was associated with altered eating

behavior; adolescent offspring were more likely to score highly on the Eating in the Absence of Hunger in Children and Adolescents questionnaire [169, 170]. Mechanistic studies of appetite regulation are challenging in humans. However, based on experimental animal models, maternal HFD may alter the formation of satiety regulating hypothalamic neuronal projections in offspring, via insulin signaling and endoplasmic reticulum (ER) stress pathways [171, 172]. The satiety hormone leptin also may shape appetite pathways during the perinatal period, based on experimental studies in which postnatal leptin administration reversed developmental programming by prenatal undernutrition [173, 174].

Postnatal Lifestyle

Body composition can be influenced by physical activity and exercise, and these too may be associated with prenatal exposures. For example, reductions in lean mass in individuals with a history of LBW may be due in part to differences in postnatal exercise patterns. Several studies have reported that a history of very low birth weight (birth weight < 1500 g) was associated with reduced levels of leisure time physical activity in young adulthood [175, 176]. Postnatal physical activity and fitness may also mediate the association between maternal BMI and childhood adiposity: for example, higher maternal BMI was associated with lower physical fitness measures in preschool-aged children [177]. These data suggest that postnatal exercise interventions might mitigate the effects of prenatal exposures on postnatal body composition. Consistent with this, data from two observational studies indicate that physical activity may reverse the adverse effects of LBW on body composition and insulin resistance [178].

Endocrine Factors

Several endocrine factors and signaling pathways have been implicated in developmental programming of body composition. For example, maternal adipokines including leptin and adiponectin have been linked to offspring adiposity in infancy [179, 180], while cytokines including IL4, IL5, and IL13 have been linked to decreased risk of early childhood adiposity [181]. Differences in growth hormone and its effectors have been reported in several human studies and experimental paradigms of prenatal perturbation. In a longitudinal study of VLBW and SGA infants over the first 2 years of life, IGF1 levels at 1 week and 3 months post partum were positively correlated with lean mass at 24 months [182]. Children with a history of SGA birth weight are sometimes treated with recombinant human growth hormone (GH) for short stature; GH treatment is associated with a reduction in fat mass and an increase in lean mass [183, 184]. However, it is not clear that such changes persist into adulthood [185, 186]. Recent studies have also implicated myostatin (an inhibitor of myogenesis) and the fibroblast growth factor family members FGF19 and FGF21 in differences in body composition between SGA and LGA offspring [119, 187].

Adipose Tissue Growth

Growth of adipose tissue depots occurs through two main processes: adipogenesis, i.e., commitment of precursor stem cells toward the adipocyte lineage, and hypertrophy, i.e., growth of existing adipocytes through lipid uptake and lipogenesis. Both processes have been implicated in the developmental programming of adiposity. For example, expression of Pref-1, a key inhibitor of adipogenesis, was reduced in placenta from SGA versus AGA infants and inversely correlated with total fat mass at 4 and 12 months post partum [188]. Adipose expression of Pref-1 was also reduced in a mouse model of prenatal calorie restriction and low birth weight [189]. In a rat model of maternal gestational obesity, offspring developed visceral adiposity with adipocyte hypertrophy and upregulation of lipogenesis genes (Srebp1, Fas), together with decreased expression and epigenetic silencing of adipogenesis genes [190]. Other groups have reported that gestational exposure to maternal obesity is associated with increased adipocyte commitment and differentiation [191].

Epigenetic Mechanisms

The dominant mechanistic model for developmental programming of body composition (and other phenotypes) is that exposure to an adverse prenatal environment induces lasting changes in epigenetic regulation; such changes may include hyper- or hypomethylation of DNA, changes in chromatin marks, and/or expression of large and small noncoding RNA [13]. There is now a robust body of data supporting such epigenetic mechanisms in human obesity. Based on epigenome-wide association studies in a consortium of cohort studies, adult BMI is associated with widespread changes in DNA methylation, with enrichment of loci near genes involved in lipid and lipoprotein metabolism and inflammation. However, analysis of genetic variants suggested that the changes in DNA methylation were largely the consequence of BMI rather than the cause [192]. In another adult population, DNA methylation within or near genes related to ER function was associated with BMI and percent fat mass, which is intriguing in light of evidence linking nutrient-mediated ER stress to the pathogenesis of insulin resistance and obesity [193]. Epigenome-wide studies have also identified associations between DNA methylation and lean muscle mass [194].

In contrast to studies in adult populations, where epigenetic changes may occur as a consequence of obesity,

studies in early childhood indicate that changes in DNA methylation precede and predict childhood body composition. For example, analysis of DNA methylation patterns in dried blood spots in neonates identified associations between methylation at 69 genomic regions and BMI z-score at age 5, and 27 genomic regions were associated with percent body fat at age 5 [195]. Moreover, DNA methylation at retinoid X receptor alpha (RXRA) in umbilical cord tissue was associated with total and percent fat mass at age 9 years [196], as well as with childhood bone mineral content [197, 198]. Additional epigenome-wide association studies in European and US-based populations have similarly uncovered associations between DNA methylation in whole blood in early childhood, and body composition [199, 200].

Birth Weight and Body Composition: Epigenetic Mediators Recent studies have suggested that DNA methylation changes in placenta and cord blood may mediate the association between birth weight and body composition. In a small study of term infants born appropriate-for-gestational-age (AGA) or small-for-gestational-age (SGA), hypermethylation near *ATG2B*, *NKX6.1*, and *SLC13A5*, and hypomethylation of *GPR120*, in placenta and cord blood from SGA newborns was linked to changes in gene expression levels (opposite to methylation status), and total and abdominal fat at age 2 weeks [201]. Moreover, in a prospective pregnancy cohort, umbilical cord DNA methylation at six loci was linked to birth weight, offspring size, and adiposity in early childhood [202].

Maternal Obesity and Offspring Body Composition: Epigenetic Mediators In the ALSPAC study ($N = 1018$), offspring epigenome-wide DNA methylation was analyzed in relation to maternal and offspring adiposity. In total, 28 and 1621 CpG sites were differentially methylated in offspring of obese and underweight mothers, respectively, compared with offspring of normal weight mothers [203]. Lower methylation at the *SLC6A4* locus in umbilical cord was associated with higher maternal gestational weight gain and with higher adiposity in early childhood (total fat mass and % fat mass between 4 and 7 years); moreover, adipose tissue methylation and expression of *SLC6A4* was lower in obese compared with lean individuals [204]. *SLC6A4* encodes a serotonin transporter which may play a role in energy balance.

Maternal Diabetes and Offspring Body Composition: Epigenetic Mediators In the setting of maternal diabetes, analysis of genome-wide DNA methylation patterns has identified strong effects on the epigenome of placenta [205], cord blood, and peripheral leukocytes throughout childhood and early adulthood [206]. Mechanistically, DNA methylation differences in placenta may affect nutrient transfer: for example, GDM is associated with increased methylation at CpG2 of placental lipoprotein lipase, decreased mRNA expression, and abundance of lipids in the neonatal circulation [207]. Interestingly, a subset of genomic loci for which cord blood DNA methylation levels have been linked to maternal glucose exposure (Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study) overlaps with loci linked to birth weight in the Cambridge Baby Growth Study and to maternal prenatal undernutrition in a Gambian population; these loci (*TERF2IP*, *SUSD1*, *C6orf96*, and *ACYP2*) may be especially sensitive to nutritional status during development [208].

Taken together, these data provide strong support for the concept that epigenetic regulation mediates the association between prenatal exposures and offspring body composition. However, it remains uncertain whether epigenetic marks play a causal role or alternatively reflect alterations in transcriptional activity at these loci, in turn mediated by additional pathway-specific or generalized chromatin modulating mechanisms. While more experimentally challenging than methylation analyses, these studies will be critical to determine causal relationships.

Stem Cells as Mediators of Developmentally Programmed Phenotypes

Stem cell populations are established in utero and may carry an "epigenetic memory" of nutritional or other insults during development. Thus, they have been proposed as potential mediators of developmental programming of obesity and body composition [209, 210]. Consistent with this, our group has described reductions in the number and regenerative capacity of skeletal muscle stem cells in a mouse model of late gestation undernutrition and low birth weight [211]. A leading hypothesis posits that developmental exposures may alter commitment of mesenchymal cells toward the adipocyte lineage. Adipose-derived stem cells (ADSCs) from a small study of young adults born either LBW or normal weight showed significant differences in gene expression and in genome-wide DNA methylation patterns. Interestingly, such differences were more pronounced in ADSC than in mature differentiated adipocytes, suggesting that stem cells may carry an epigenetic memory of prenatal disruptions [212].

In the past, studying stem cell function in human infants was complicated by the unavailability of relevant cells for analysis. However, the discovery of fetal mesenchymal stem cells—a precursor cell able to differentiate into adipocytes, myocytes, cartilage, and bone—in perinatal tissues such as amniotic membranes and in umbilical cord Wharton's jelly has allowed new insights into stem cell biology and developmental programming

[213–215]. How closely such perinatal stem cells recapitulate the biology of adipose tissue-derived precursor cells is unclear. Still, data from such translational model systems support an effect of prenatal exposures on infant stem cell fate and function. For example, umbilical Wharton's jelly mesenchymal stem cells from SGA infants exhibit increased proliferation capacity, impaired oxidative metabolism, and increased expression of the lipid synthesis gene fatty acid elongase *ELOVL2* [216, 217]. Adipocytes derived from MSC of SGA infants showed increased expression of acyl-coenzyme A synthetase 1 (*ACSL1*), which in turn was noted to regulate cellular lipid uptake and adipogenesis [218].

Maternal obesity, too, has been reported to alter mesenchymal stem cell function. For example, one human study reported increased adipogenic capacity in amniotic membrane stem cells from offspring of obese women [219]. Another group has reported that prenatal exposure to maternal obesity results in increased adipogenic capacity and reduced myogenesis in infant mesenchymal stem cells isolated from umbilical cord, and that in vitro adipogenic capacity of such MSC was correlated with postnatal weight gain and accelerated adipose tissue growth from birth to 5 months [220••, 221–223]. Higher adiposity at age 5 months was associated with higher acylcarnitine levels, higher expression of genes involved in lipid metabolism, and markers of oxidative stress in MSC [221]. Together, these data suggest that mesenchymal stem cells from infants exposed to abnormal prenatal environments can be used to model developmentally programmed changes in body composition and may shed new insights into pathophysiology and treatment.

Mitochondrial Metabolism

Multiple lines of evidence suggest that disruptions to the prenatal environment—both undernutrition and overnutrition—can result in impaired mitochondrial function in offspring tissue. For example, umbilical mesenchymal stem cells from SGA infants have decreased mitochondrial oxygen consumption rates [217]. Similar impairments in mitochondrial metabolism in skeletal muscle [224], cardiac muscle [225], adipose tissue [226], and liver have also been described in rodent models of intrauterine growth restriction and LBW. Moreover, such mitochondrial perturbations can be exacerbated by postnatal diet. For example, in a study of LBW versus normal birth weight (NBW) young men, overfeeding via high-fat diet increased adipose tissue DNA methylation of *PPARGC1A*, a critical regulator of mitochondrial biogenesis and oxidative metabolism, in LBW, but not NBW, young men, suggesting that prenatal factors may alter the postnatal adipose response to nutrient excess [227]. However, the data are not homogeneous: some groups have reported normal mitochondrial function in skeletal muscle of LBW young men [228] or increased skeletal muscle mitochondrial content and function following prenatal undernutrition in rodents [229, 230].

By contrast, prenatal overnutrition and maternal obesity have been more consistently associated with impaired offspring mitochondrial metabolism. Both mitochondrial biogenesis and function are reduced in placenta of obese women [231]. Similarly, transcriptomic analysis in human umbilical vein endothelial cells, umbilical mesenchymal stem cells, and skin fibroblasts showed reductions in OXPHOS gene expression and altered mitochondrial function in infants of obese mothers [219, 232, 233]. In animal models, maternal high-fat diet has been linked to reduced mitochondrial biogenesis and impaired mitochondrial metabolism in oocytes (both F0 mothers' and F1 daughters') [234–237], placenta [238], and in offspring skeletal muscle [239, 240], cardiac muscle [241], adipose tissue, liver [242], and hypothalamus [243].

Resting Energy Expenditure and Thermogenesis

Reductions in resting energy expenditure can contribute to weight gain and adiposity, and energy expenditure in turn is strongly influenced by body composition. The main contributor to resting energy expenditure is muscle, which expends energy through physical activity and shivering, but mitochondria-rich brown and beige adipose tissue may also contribute through thermogenesis, or heat production. Brown adipose tissue (BAT) was once thought to be present only in small mammals and babies, but BAT depots have recently been discovered in adult humans, and their size and activity have been linked to obesity and metabolic outcomes. Emerging data suggest that prenatal growth restriction is linked to altered BAT function. In a study of BAT activation in prepubertal SGA versus AGA children, Malpique et al. reported that BAT activity was associated with smaller visceral fat mass and improved metabolism [244]. Prenatal growth restriction may be associated with long-term changes in resting energy expenditure. For example, birth weight was positively associated with lean mass and resting metabolic rate in adult women [245]. However, these effects have not been consistently reported, perhaps due to differences in how energy expenditure was normalized. In studies in which resting energy expenditure was normalized to lean mass, adults with history of prematurity and very low birth weight may even have higher resting energy expenditure per unit lean body mass [246]. Moreover, diet may cause differences in energy expenditure: when challenged with a 5-day high-fat overfeeding challenge, energy expenditure

and fat oxidation were significantly higher among young men with a history of LBW as compared with NBW controls [247]. These data highlight the interaction of prenatal stress with postnatal nutrition.

Cellular Aging/Senescence

In an interesting translational study, De Zegher et al. recently reported that birth weight was directly correlated with leukocyte telomere length at birth, and that telomere length in turn predicted lean mass at age 12 months [248]. Similarly, prenatal exposure to GDM has also been linked to reduced telomere length in childhood (age 9–16 years) [249]. These data raise the possibility that prenatal stressors may activate cellular aging and senescence pathways.

Conclusion

With advances in "-omics" techniques and increased interest in the prenatal environment as a determinant of chronic health and disease, the last decade has brought a greater understanding of the developmental programming of offspring body composition. Birth weight (which can be viewed as a biomarker for the adequacy of the prenatal environment), maternal obesity, and gestational diabetes are each linked to increased adiposity in childhood and later life. Birth weight is also robustly linked to muscle mass and bone density later life. On the other hand, associations between prenatal exposure to diabetes and offspring lean mass and bone density differ between populations. Mechanistically, programming of body composition may arise via differences in nutrients or metabolites, postnatal lifestyle factors, epigenetic regulation, impaired mitochondrial metabolism, and/or increased mesenchymal stem cell commitment to the adipose lineage. The hope is that an improved mechanistic understanding will allow the development of early markers of future risk, to facilitate targeted nutritional, metabolite-based, or other therapeutic interventions that might curb the ongoing epidemics of obesity and diabetes.

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Compliance with Ethical Standards

Conflict of Interest E.I. declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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