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REVIEW ARTICLE

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Childhood obesity and adverse cardiometabolic risk in large for gestational age infants and potential early preventive strategies: a narrative review

Sreekanth Viswanathan[1]✉, Kera McNelis[2], Kartikeya Makker[3], Darlene Calhoun[1], Jessica G. Woo[4] and Babu Balagopal[5,6]

Accumulating evidence indicates that obesity and cardiometabolic risks become established early in life due to developmental programming and infants born as large for gestational age (LGA) are particularly at risk. This review summarizes the recent literature connecting LGA infants and early childhood obesity and cardiometabolic risk and explores potential preventive interventions in early infancy. With the rising obesity rates in women of childbearing age, the LGA birth rate is about 10%. Recent literature continues to support the higher rates of obesity in LGA infants. However, there is a knowledge gap for their lifetime risk for adverse cardiometabolic outcomes. Potential factors that may modify the risk in early infancy include catch-down early postnatal growth, reduction in body fat growth trajectory, longer breastfeeding duration, and presence of a healthy gut microbiome. The early postnatal period may be a critical window of opportunity for active interventions to mitigate or prevent obesity and potential adverse metabolic consequences in later life. A variety of promising candidate biomarkers for the early identification of metabolic alterations in LGA infants is also discussed.

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IMPACT:

- LGA infants are the greatest risk category for future obesity, especially if they experience rapid postnatal growth during infancy.
- Potential risk modifying secondary prevention strategies in early infancy in LGA infants include catch-down early postnatal growth, reduction in body fat growth trajectory, longer breastfeeding duration, and presence of a healthy gut microbiome.
- LGA infants may be potential low-hanging fruit targets for early preventive interventions in the fight against childhood obesity.

INTRODUCTION

Childhood obesity often persists into adulthood posing major public health challenges across the world.[1–3] The prevalence of obesity has reached epidemic proportions over the last two decades.[1,2] As per the latest Centers of Disease Control (CDC) data, about one-third of U.S. children aged 2–19 years are overweight (sex-specific BMI > 85th percentile for age) and nearly 20% have obesity (sex-specific BMI > 95th percentile for age).[4–6] Once obesity is established at a young age, its reversal is difficult, thus setting these children with the possibility of lifelong health issues.[7–9] For example, children who are overweight by kindergarten years have a 4-fold greater risk of developing obesity at adolescence.[8] A large cohort study ($n = 51{,}505$) that tracked the growth data of children from birth to age 18 showed that 90% who had obesity by age three continued to have obesity at age 18.[9] Early-onset obesity and its persistence into adolescence and adulthood are also associated with parallel cardiometabolic changes with the potential for long-term adverse events.[10–12] A large Australian cohort study observed that obesity at age three was significantly associated with subclinical markers of atherosclerosis by age 11.[13] These data emphasize that the origin of childhood obesity and related metabolic derangements are often seeded in the first few years of life. Further, early-onset obesity likely to persists into the later years.[13–16]

Among the modifiable early risk factors for future obesity and adverse cardiometabolic events, both birth weight and weight gain during infancy are consistently reported. Small for gestational age (SGA, birth weight < 10th percentile for age and sex) and large for gestational age (LGA, birth weight > 90th percentile for age and sex) represent two extremes of fetal growth distribution, but both have links to obesity and related comorbidities later in life.[15,17–19] The relationship between birth weight and risk for obesity is curvilinear. Thus, both reduced and increased birth weight infants are at higher risk, with infants born as LGA at the greatest risk category for future obesity, especially if they experience rapid postnatal growth.[15] The effect of developmental "programming" in fetal growth restriction (for example, SGA) and its relationship with cardiometabolic risks have been somewhat

[1]Division of Neonatology, Department of Pediatrics, Nemours Children's Hospital, University of Central Florida College of Medicine, Orlando, FL, USA. [2]Division of Neonatology, Perinatal Institute, Cincinnati Children's Hospital Medical Center, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA. [3]Division of Neonatology, Department of Pediatrics, Johns Hopkins School of Medicine, Baltimore, MD, USA. [4]Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA. [5]Nemours Biomedical Research, Nemours Children's Health System, Jacksonville, FL, USA. [6]Department of Pediatrics, Mayo Clinic College of Medicine, Rochester, MN, USA. ✉email: sreekanth.viswanathan@nemours.org

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well described.[17,18,20–22] However, fetal "programming" pathways and mechanisms in LGA are less clear. In this narrative review, our objectives are threefold. First, to summarize the recent literature connecting LGA birth, early postnatal growth pattern, early childhood obesity, and lifetime risk for adverse cardiometabolic outcomes, to highlight an increasingly recognized, but not adequately addressed, public health challenge. Second, to identify potential early biomarkers in LGA infants that predict the risk for future obesity and adverse cardiometabolic outcomes. Finally, to explore potential intervention strategies in early infancy that can potentially modify the risk for developing early childhood obesity in LGA infants.

METHODOLOGY

To identify the evidence base connecting LGA birth and early obesity risk, a comprehensive literature search was conducted limited to PubMed, Scopus, Cochrane Central Registry of Controlled Trials, and Google Scholar databases published between January 2010 to March 2021. Only articles published in English were considered. Key search terms included were "large for gestational age," "birth weight," "obesity," "overweight," "early nutrition," "breastfeeding," "developmental programming," "infant weight gain", "cardiometabolic risk," "body composition," and "biomarkers." Inclusion was restricted to studies that assessed the association between LGA birth and obesity/cardiometabolic outcomes.

Epidemiology and factors associated with LGA birth

The rate of LGA birth in the US has increased by 24-fold over 30 years; the crude rate (per 1000 live births) of LGA was 0.97 from 1979 to 1981, and increased to 22.97 from 2008 to 2010.[23] A recent 5-year (2010–15) single-center retrospective study from Florida, US, that looked at the incidence and significance of LGA/macrosomic (birth weight > 4000 g) (due to varying definitions used to describe macrosomia in the literature, all macrosomic infants are considered as LGA for the purpose of this review) is considered as LGA infants suggested that the rate of neonatal macrosomia is about 10% of all births and about 12% of macrosomic infants required neonatal intensive care unit (NICU) admissions at birth.[24] Another large population-based cohort study of ~3 million singleton births using 2012 U.S. Natality data, showed that the prevalence of LGA among women without gestational diabetes mellitus (GDM) was about 9% across different racial/ethnic groups with a slightly higher trend with minority women.[25] Data from the WHO's Global Survey on Maternal and Perinatal Health that looked at the prevalence of macrosomia in 23 developing countries in Africa, Asia, and Latin America observed a large variation in the prevalence of macrosomia, ranging from 0.5% to 14.9%.[26]

Factors associated with being born LGA include both fetal (genetic and chromosomal disorders, racial and ethnic factors, tumors) and maternal (pregestational diabetes mellitus, GDM, maternal obesity, excess gestational weight gain, and tall maternal height) variables.[26] Most LGA infants experience fetal overgrowth secondary to excess fetal nutrition which is the focus of this review. Maternal pre-pregnancy obesity and maternal weight gain during pregnancy are among the strongest risk factors for LGA birth.[27–29] The 2017–2018 National Health and Nutrition Examination Survey (NHANES) observed the highest ever recorded age-adjusted prevalence rate of obesity in adults standing at 42.4%.[30] They also documented that the prevalence of severe obesity (body mass index, BMI ≥ 40 kg/m^2) was higher in women than men (11.5% vs. 6.9%).[30] This worrying trend was also observed among women of childbearing age (20–39 years), with the obesity prevalence rate of about 40%.[30] A predictive model for the risk of LGA birth in parous women with BMI ≥ 30 kg/m^2 pre-pregnancy and early pregnancy had an area under the curve (AUC) of 0.80 (95% CI: 0.78–0.82) and 0.81 (95% CI: 0.79–0.82), respectively.[31] The risk for LGA increases by 6.9% with each kg weight gain during pregnancy above IOM recommendations.[32] Along with the increasing obesity rate, the prevalence of pre-existing diabetes during pregnancy and GDM is also steadily increasing, contributing further to the frequency of LGA birth.[33–35] The number of pregnant women with obesity and/or GDM has increased more than 30% in the last few decades producing nearly half a million infants each year in the US alone who are born LGA (about 10% of all births)—a number approaching that of infants who are born prematurely each year—a population of infants who are at higher future risk for childhood obesity and cardiometabolic adverse outcomes.[19,24]

LGA infants: a significant risk factor for future obesity and cardiometabolic events

Being born "LGA" is considered as a marker of events/stressors before and/or during pregnancy rather than the actual cause of adult obesity per se.[19] Most LGA infants are exposed to excessive nutrition and high glucose load in utero with resultant increased fetal insulin secretion driving fetal overgrowth and excessive adipose tissue deposition (fetal macrosomia).[36] These maladapted prenatal and natal developmental programming of body tissues and the resulting altered metabolism predispose them to early life obesity and a higher risk for future cardiovascular events.[37,38] Table 1 summarizes the recent studies (January 2010–March 2021) showing the relationship between being born LGA and future obesity risk and adverse cardiometabolic outcomes.[9,19,39–48] These studies suggest that LGA infants are at higher risk for childhood and adult obesity compared to appropriate for gestational age (AGA) infants. Though studies on cardiometabolic clinical endpoints specific to LGA infants are limited, but considering their potentially higher risk, future-focused studies are needed to address the knowledge gap.

LGA infants: early growth patterns influences the obesity risk

Infancy is characterized by rapid growth and development and inadequate nutrition can compromise growth and long-term neurodevelopmental outcomes.[49] Current nutritional practices in the NICU are guided by weight gain trends[50] and not based on the quality of growth (i.e., changes in body composition). The recommended dietary allowance (RDA) of energy intake in healthy breastfed full-term infants is approximately 90–135 kcal/kg/day in the first three months of life (the equivalent of taking 140–200 ml/kg/day of 20 cal/oz milk) with an expected weight gain of 25–30 g/day.[50] These recommendations are universally applied to infants irrespective of their in utero growth status.

There is strong evidence to support that rapid weight gain (an increase of weight z-score > 0.67 from the birth weight) in infancy is associated with later obesity irrespective of the birth weight.[51–55] A meta-analysis from 10 cohort studies ($n = 47{,}661$) suggested that the risk of obesity increases 2-fold for each one-SD increase in weight between birth and 1 year (OR 1.97; 95% CI: 1.83–2.12).[56] In a nested case–control study that tracked the growth trajectories in children with severe obesity (480 with severe obesity and 783 controls), Smego et al. observed that a BMI ≥ 85th percentile as early as 4–6 months increases the risk of severe obesity by age 6 years by 2.5-fold and the risk of clinical obesity by age 6 years by 3-fold.[7] A prospective birth cohort study ($n = 1971$) observed that weight gain *z*-score in the first four months of life was positively associated with BMI *z*-score and overweight/obesity at age 2–7 years and the risk of overweight/obesity increased by 50% for every increase of one-SD in weight gain in the first four months (OR 1.5; 95% CI: 1.4–1.7).[51] These data suggest that accelerated weight gain during infancy is an important determinant of the lifetime risk for obesity.

However, a prospective study that compared the growth outcomes of LGA infants compared to AGA infants in the first

Table 1. Recent studies (January 2010–March 2021) that have shown the relationship between LGA infants and future obesity risk and adverse cardiometabolic outcomes.

Study	Design	Sample size	Age at outcomes assessed	Obesity or cardiometabolic risk
Mehta et al. 2011, USA[39]	Case–control study	195, inner-city African-American population	2–5 years	LGA infants had higher odds of obesity vs. AGA (aOR 2.5; CI 1.001–6.2)
Cnattingius et al. 2012, Sweden[40]	Retrospective study	162676 (Swedish birth registry 1973–2006)	Adults	LGA was associated with overweight (BMI 25.0–29.9; OR 1.50; 95% CI: 1.39–1.61), obesity class I (BMI 30.0–34.9; OR 1.77; 95% CI: 1.59–1.98), obesity class II (BMI 35.0–39.9; OR 2.77; 95% CI: 2.37–3.24) and obesity class III (BMI ⩾ 40.0; OR 2.04; 95% CI: 1.49–2.80)
Chiavaroli et al. 2014, Italy[41]	Prospective longitudinal study	35 AGA, 24 SGA, and 31 LGA subjects evaluated at mean age 8.4 ± 1.4 years	Adolescence (mean age 13.3 ± 1.8 years)	Cardiometabolic risk *z*-score (calculated by the sum of sex-specific *z*-scores for BMI, blood pressure, HOMA-IR, triglycerides, and triglycerides: high-density lipoprotein cholesterol ratio) was higher in LGA vs. AGA
Kuciene et al. 2018, Lithuania[42]	Retrospective study	4598 (macrosomia as birth weight >4000 g = 424)	12–15 years	Association between high blood pressure and LGA (aOR 1.44; 95% CI: 1.16–1.79) and macrosomia (aOR 1.34; 95% CI: 1.11–1.63)
Kapral et al. 2018, USA[43]	Prospective cohort study	10,186 term or preterm children	5–7 years (assessed at 3 grade levels—kindergarten, 1st, and 2nd grades)	Among children born preterm LGA and term macrosomia (>4500 g), at all three grade levels, had significantly greater BMI *z*-scores than those born AGA or SGA. (aOR 2.34 and 1.91, respectively)
Salahuddin et al. 2018, USA[44]	Cross-sectional survey study	517 low-income Hispanic/Latino sample of children in Texas	9–12 years	For severe obesity (BMI ≥ 120% of 95th percentile), LGA has OR of 2.31 (95% CI: 1.13–4.73)
Geserick et al. 2018, Germany[9]	Prospective and retrospective analysis of a population-based sample	51,505	15–18 years	Obesity rate of 43.7% for LGA vs. 28.7% AGA and 27.2% SGA. (1.55 higher odds for LGA vs. AGA or SGA)
Hammoud et al. 2018, Netherlands[45]	Retrospective study	104 (24% LGA)	Birth–14 years	LGA infants born to mothers with Diabetes/GDM had the highest BMI at adolescence
Kaul et al. 2019, Canada[46]	Retrospective study	81,226 (LGA = 6677)	4–6 years	The obesity adjusted attributable risk % for LGA alone, combinations of GDM/LGA, and pre-existing diabetes/LGA were 39,4%, 50.1%, and 39.1%, respectively
Chen et al. 2020, China[47]	Population-based retrospective cohort study	33,157	1–6 years	LGA infants born to mothers with GDM had higher annual BMI *z*-score
Broccoli et al. 2020, Italy[48]	Prospective population-based cohort study	5173	5 years	Obesity rate in LGA infants was 6.5% vs. 3.8% for the whole cohort. One-SD increase in BMI *z*-score from birth to age three increases the odds of obesity at 5 years by 2.8 (95% CI: 2.5–3.2)
Derraik et al. 2020, Sweden[19]	Retrospective study	195,936 (Swedish birth registry, 1973–2009) LGA = 4026	Adults	Adjusted relative risk for obesity 50% higher for LGA by weight or LGA by weight and length. No increased risk for LGA by length alone

LGA large for gestational age, *AGA* appropriate for gestational age, *SGA* small for gestational age, *OR* odds ratio, *BMI* body mass index, *GDM* gestational diabetes mellitus.

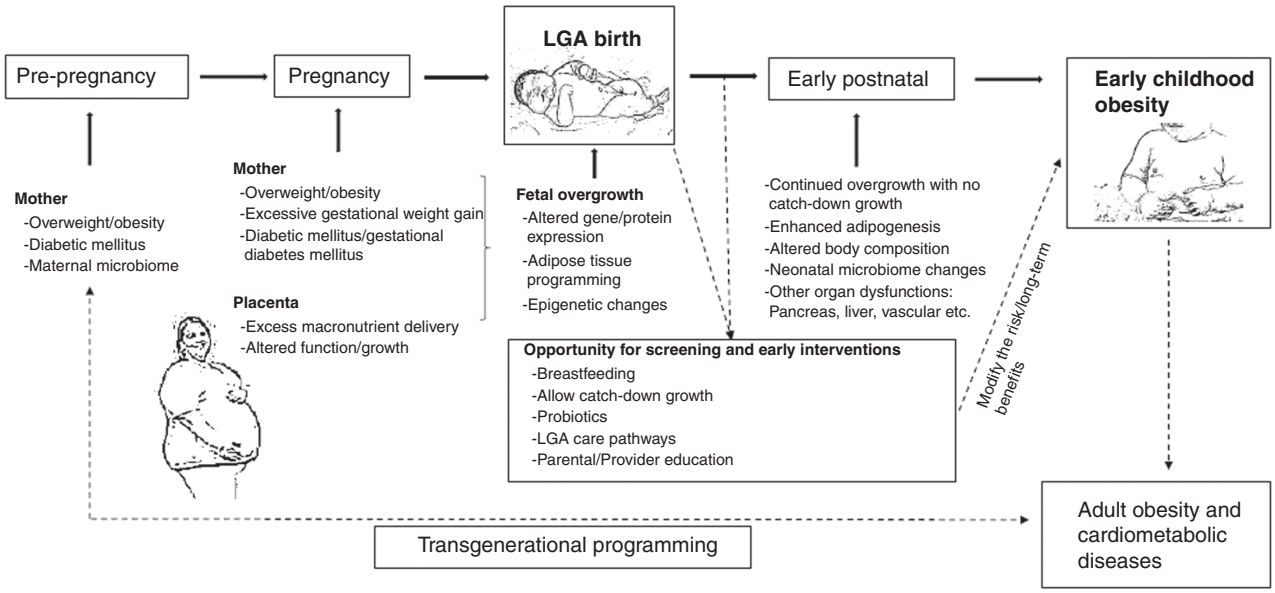

Fig. 1 Current understanding of the early life developmental programming associated with obesity and cardiometabolic diseases in large for gestational age (LGA) infants. (The dashed lines represent the potential opportunities for modifying the early life influences in LGA infants to decrease the transgenerational programming).

year of life found that the anthropometric differences between AGA and LGA disappeared by 6 months, suggesting that LGA infants tend to have a slower growth velocity in infancy or deceleration in weight gain (slow growth or catch-down growth).[57] Catch-down growth in LGA infants was defined as a decrease in weight or height *z*-score more than 0.67 during the first 2 years of life.[57] They also observed that this slower growth was not associated with any significant epigenetic changes (genome-wide DNA methylation analysis).[57] The authors postulated that this might be the result of departure from the energy-rich in utero environment and gradually shifting towards their natural genetic growth patterns postnatally.[57] Another study from Japan that observed a catch-down growth in infants in the first 6 months of life with high-birth weight (>3.5 kg) vs. low-birth weight (<2.5 kg) suggested that early postnatal growth period are physiological events for recovery of deviated growth during the fetal period (catch-up growth in low-birth weight and catch-down growth in high-birth weight infants).[58]

An analysis of a large US birth cohort (Collaborative Perinatal Project) that studied the postnatal weight and BMI growth pattern of LGA infants from birth to age 7 years, observed that LGA infants with no catch-down growth in weight (25.2% of cohort) were associated with a higher risk of obesity (aOR 6.4, 95% CI: 5.2–7.7) and hypertension (aOR 1.7, 95% CI: 1.4–2.0), whereas LGA infants (54.3% of cohort) that demonstrated a small catch-down growth beginning at birth were associated with no increased risk of adverse outcomes.[59] Similarly, the Generation R study which followed about 4000 children, observed that the greatest risk of obesity at age 4 was for LGA infants who did not experience a catch-down growth in the first 2 years of life (a reduction of <0.67 SD for weight, OR 12.46; 95% CI: 6.07–25.58).[60] Other studies in LGA term infants that observed a similar trend that a catch-down growth in the first several months after birth was associated with a lower risk of adverse metabolic outcomes and suggested that the difference in postnatal growth pattern influenced the health outcomes in LGA infants.[54,61]

The "thrifty phenotype" hypothesis by Hales and Barker, explained the developmental adaptations in SGA infants from poor fetal nutrition placing them at risk for metabolic syndrome when exposed to a postnatal environment with plentiful nutrition.[62] In contrast, LGA infants are exposed to excess nutrition in utero and in the postnatal period if provided above a threshold level that is not allowing any catch-down growth in early infancy. The proposed mechanisms associated with altered developmental programming of physiological systems associated with excess nutrition in utero and early postnatal environmental conditions include dysfunction of the adipose tissue (increased total number of adipocytes, increased size of adipocytes, increased adipose tissue inflammation, and altered secretion of adipokines) pancreas (increased inflammation, insulin resistance and compensatory increased insulin production, and reduced islet cell mass), liver (fatty liver, increased oxidative stress, and inflammation), and the vasculature leading to hyperlipidemia.[63–65] We have summarized the current understanding of the early life developmental programming in LGA infants in a conceptual diagram (Fig. 1). In summary, current data suggest that LGA infants, as a result of developmental programming in utero, are at an elevated risk for early childhood obesity, and this risk is further modified based on whether weight gain accelerates or decelerates in early childhood.

LGA infants: body composition

Adverse health consequences of obesity are not contingent on increased absolute weight per se, but they are closely related to the alterations and distribution of body composition parameters. Infant body composition studies have suggested that LGA infants at birth have increased fat mass (FM)% compared to AGA infants.[66–68] A large prospective cohort study from Colorado, US ($n = 979$, included 5% macrosomic infants with birth weight > 4 kg) that studied the body composition of infants using air displacement plethysmography (ADP) at birth observed that higher neonatal FM% is associated with a higher risk for childhood overweight and obesity.[69] In their cohort, the mean FM% was 9.1 ± 4.0 at birth, and each one-SD increase in FM% was associated with 0.12 kg/m^2 higher BMI at 2–6 years which is equivalent to a 2–4% increase in BMI percentile based on the CDC BMI growth charts.[69] In LGA infants, FM is more affected than the fat-free mass (FFM) component, and this differentially elevated body fat at birth may be a better predictor of later obesity than total body weight in these infants.[19,52,67,68,70] Thus, it is important to consider body composition parameters such as FM and FFM of LGA infants and how they impact the later risk for obesity and cardiometabolic outcomes.[52]

The majority of the body fat deposition occurs in late fetal life and during infancy, and accelerated fat accrual in either of these two phases increases the risk for future obesity.[52,71] A birth cohort study from the Netherlands ($n = 401$) that studied infant body composition using ADP observed that a rapid increase or catch-up in FM% in the first 6 months of life (defined in the study as > 0.67 SD in FM%) was associated with more adiposity at 2 years of age and suggested that the first few months of postnatal life is a critical window for adiposity programming.[72] These data suggest that quality of pre- and postnatal growth is important and the quantity of body fat may be a potentially modifiable early risk factor or biomarker for childhood obesity in LGA infants.

A study that looked at the short-term changes in body composition in LGA and SGA infants at birth and again at 3–4 months of age observed that growth rate and fat accretion were significantly higher in the SGA infants versus LGA infants.[67] The majority of the LGA infants in this study were breastfed on demand and demonstrated the slowest gain in weight and FM. Similarly, a longitudinal body composition study LGA and AGA infants who were exclusively breastfed for at least 4 months suggested that FFM remained elevated in LGA infants across the first 2 years of life, while FM accrual slowed down to approach normal FM.[73] Although the presence of maternal diabetes during pregnancy, if well-controlled may result in infants of diabetic mothers (IDM) with similar body composition as healthy-term non-IDM infants, the IDM infants are found to have 14% lower resting energy expenditure (REE) and 26% lower fat oxidation, compared to their healthy-term peers.[74] This suggests that continued provision of excess calories above the metabolic needs (positive energy balance due to caloric intake higher than caloric expenditure) predisposes them to future obesity. It has also been suggested that longitudinal measurement of REE in infants may help to prescribe and promote individualized nutrition regimens.[75] These studies suggest that during the early months of life when the feeding pattern is regulated by the infant, and growth is influenced by nutrition, the inherent patterns of increased or decreased appetite, hunger, and satiety likely steer the infant toward its genetic growth trajectory and normalizing the body composition along the way.

These data also highlight the important role of body composition pattern at birth and its scaffold during infancy on later health consequences among LGA infants. Therefore, body fat trajectory in LGA infants can be a potential therapeutic target for nutritional interventions to modify the risk for obesity and related comorbidities. The LGA infants who do not demonstrate a deceleration in weight and slowing of FM accrual in the first few months of life are likely to be at higher risk for early obesity development. Taken together, in this era of personalized treatment and precision nutrition, it may be time to move beyond the current nutritional strategy of one-size-fits-all dietary prescription for optimal health and disease prevention.[59,76]

LGA infants: other etiological ties and potential biomarkers of later obesity and cardiometabolic dysregulation

Fetal overgrowth as a result of prolonged exposure to nutrient-rich in utero environment is associated with abnormal fetal programming which includes altered insulin kinetics and excessive adipose tissue deposition predisposing them to the risk of metabolic syndrome.[6,77] The trajectory of adipose tissue deposition and distribution in early life may be important in LGA infants as discussed above and attempts have been made to find early and functional biomarkers of adipose tissue that can be linked to future clinical obesity.[52] For example, adipose tissue is an especially important contributor to the pool of circulating exosomal microRNAs (miRNAs), a class of non-coding RNAs that play important roles in regulating gene expression that is important in intercellular communication and fetal programming.[78] Altered adipose tissue or mass is associated with changes in circulating miRNAs and linked with many metabolic conditions.[79] A study that quantified the miRNAs using the dried blood spots on newborn screening cards of different birth weights, as a source of analyzable miRNAs observed that miR-33b and miR-375 were overexpressed 9.8-fold and 1.7-fold respectively in macrosomic newborns and miR-454-3p was overexpressed in both low-birth weight and macrosomic newborns as compared to AGA newborns.[80] Another similar study using the newborn screening cards that looked at the circulating miRNAs in macrosomic newborns found that miR-29a-5p, miR-126-3p, miR-221-3p, and miR-486-5p were significantly overexpressed in macrosomic newborns.[81] These miRNAs are functional regulators of cholesterol levels and insulin secretion, and are linked with obesity, type-2 diabetes, insulin resistance, and proinflammatory reactions.[80,81] These data suggest that birth weight modifies the expression of miRNAs associated with adult metabolic dysfunctions and analyzing miRNAs can be a potential biomarker of fetal programming of adult diseases in LGA infants. Further studies are needed to understand how the overexpressed miRNAs at birth change with different postnatal weight and adipose growth trajectories in LGA infants.

Studies using metabolomics have emerged as effective tools for elucidating early metabolic aberrations in fetal overgrowth.[82] A study using cord-blood metabolomics noted metabolites associated with energy production (malate, succinate, fumarate) and nucleotide turnover pathways were elevated in infants with larger birth size, and these metabolites were also associated with higher cord-blood leptin and insulin-like growth factor-1.[82] In another cross-sectional study of full-term newborns born to mothers without GDM, cord-blood samples were analyzed acylcarnitine profiles (intermediates of fatty acid oxidation viewed as an indicator of insulin resistance and incomplete fatty acid oxidation) along with newborn measures of adiposity (leptin and FM by ADP) and hyperinsulinemia (c-peptide levels).[83] There was an accumulation of acylcarnitine intermediates which was associated with high leptin levels and FM and they have suggested that cord-blood acylcarnitine profiles may be useful early biomarkers for future risk for obesity and insulin resistance.[83] Similarly, a large prospective U.S. urban low-income birth cohort follow up study [1402 mothers-child pairs with mothers with pre-pregnancy overweight or obesity (OWO), with 11.1% LGA birth rate] observed that infants born to maternal acylcarnitine levels at delivery in the top quartile were at the highest risk for childhood OWO at 5 years (OR = 3.78; 95% CI: 2.47, 5.79), which explained about one-third of the inter-generational OBO risk in their cohort.[84] Future metabolomic studies that can be combined with early preventive intervention strategies are warranted to understand whether such interventions can reverse or mitigate the alterations in metabolic programming associated with early overgrowth in LGA infants.

Briana et al. studied potential prognostic cardiac biomarkers [Cardiotrophin-1 (CT-1), Titin, pentraxin (PTX-3), and soluble CD36 (sCD36)] using cord-blood samples in full-term LGA and AGA infants. LGA infants had higher CT-1 and Titin concentrations, compared to AGA infants, while PTX-3 and sCD36 were similar in both groups.[85] A further subgroup analysis of LGA infants showed that CT-1 is up-regulated only in LGAs exposed to maternal diabetes. They suggested that a higher Titin concentration in LGAs may represent the potential molecular mechanism underlying the association between fetal macrosomia and cardiomyocyte/diastolic dysfunction.[85]

Other potential biomarkers of obesity-related cardiometabolic risk in LGA infants include circulating concentrations of inflammatory markers such as high-sensitivity C-reactive protein, interleukin-6, and tumor necrosis factor-α; satiety factors such as leptin, ghrelin, and obestatin; and adipokines such as adiponectin (both high molecular weight and total), visfatin, vaspin, retinol-binding protein-4, and fatty acid-binding protein-4 (FABP4).[63,86] Leptin is produced in proportion to fat mass, but also found in the

Table 2. Potential and emerging biomarkers of later obesity and cardiometabolic risk in LGA infants.

Body adiposity	Body composition assessment (FM)
Functional markers of excess adipose tissue	High circulating microRNAs Low spexin Metabolomics-altered acylcarnitine profiles
Cardiac dysfunction markers	Increased carditrophin-1, titin
Adipokines	Increased leptin, variable ghrelin (satiety factors) Increased leptin/adiponectin ratio Increased visafatin, vaspin, apelin, chemerin, obestatin, FABP4
Inflammatory markers	Increased hs-CRP, IL-6, and TNF-α
Gut microbiome	Changes in gut bacterial diversity and their key metabolites such as SCFA

LGA large for gestational age, *FM* fat mass, *hs-CRP* highly sensitive C-reactive protein, *IL-6* interleukin-6, *FABP4* fatty acid-binding protein-4, *SSFA* short-chain fatty acids.

placenta, informs the brain about the body's energy and nutrient status while adiponectin is solely secreted by adipocytes, and has insulin-sensitizing effects and its level is inversely related to leptin levels.[63] LGA infants born to non-diabetic mothers found to have elevated cord-blood leptin levels and increased leptin/adiponectin ratio compared to AGA infants suggesting a disturbance in adipokines, reported to be associated with subsequent central obesity in children.[87–89] Another study that investigated the relationship between four circulating adipokines (visfatin, apelin, vaspin, adiponectin) with markers of insulin sensitivity in LGA infants, observed that LGA infants, especially those born to a diabetic mother, had high insulin, visfatin, apelin, and low adiponectin levels, along with elevation of the insulin resistance markers.[90] A study that looked at the cord-blood adipokines, chemerin, and obestatin (secreted by adipose tissue and associated with insulin resistance/metabolic syndrome) observed that, compared to AGA infants, LGA infants have higher chemerin (reflecting higher adipose tissue) with similar obestatin levels.[91] Another study that looked at hyperinsulinemia and elevated insulin resistance index (Homeostasis Model assessment for insulin resistance, HOMA-IR) at birth, observed that LGA infants, compared to AGA infants, had higher hyperinsulinemia (27.3% vs. 6.9%, OR 5.02; 95% CI: 1.15–22.3; $p = 0.01$) and elevated insulin resistance index (36.4% vs 13.9%, OR 3.54; 95% CI: 1.03–12.16; $p = 0.02$).[92] Another study that looked at the FABP4-an adipokine associated with obesity and metabolic syndrome—in different birth weight categories at birth found a significant U-shaped correlation between serum FABP4 levels and birth weight with elevated levels both in SGA and LGA infants.[86] A novel neuropeptide, spexin, appears to be emerging as an important factor in obesity.[93] Studies in both children and adults have also demonstrated significantly lower circulating levels of spexin in those with obesity.[94,95] While a potential role for spexin in GDM has been suggested recently,[96,97] the evidence is somewhat inconsistent,[98] and its implications in the in utero environment and potential influence in LGA weight trajectory and cardiometabolic risk remain to be understood.

Several studies have postulated the connection between the gut microbiome and its metabolites such as short-chain fatty acids (SCFAs) with obesity and metabolic disorders.[99–101] It has been suggested that maternal obesity and weight gain during pregnancy and the resulting altered in utero environment can influence the offspring microbiota and the associated epigenetic changes further increase the risk of metabolic diseases in the offspring.[102] A study that explored the relationship between placental microbiota profile and fetal macrosomia observed that the placental microbiota profile is distinct in macrosomic infants compared to AGA infants.[103] Maternal overweight and obesity, which often results in cesarean delivery, is also associated strongly with early childhood obesity, potentially mediated by changes in infant gut microbiome.[104] Studies in older children with obesity have observed that achievement of weight loss in response to interventions such as calorie-restricted diet and increased physical activities are found to be influenced by their individual gut microbiota.[105] One study evaluated the role of probiotic supplementation starting one month before birth and continuing for 6 months after birth found to be associated with reduced excessive weight gain during infancy.[106] Though specific data on LGA infant's early growth and gut microbiome imbalances are scarce and need further study, considering the growing evidence at large, gut microbiome patterns may be a useful early biomarker for their obesity risk.

The potential and emerging biomarkers of later obesity and cardiometabolic risk in LGA infants are given in Table 2.

LGA infants: potential early intervention strategies to reduce the childhood obesity risk and future directions

In addition to the primary prevention strategies focused on improving the mother's health such as regulating maternal obesity and gestational weight gain and better control of diabetes to reduce the risk of LGA birth,[107,108] we also need to consider secondary prevention strategies in LGA infants that can be implemented in early infancy to reduce their risk of childhood obesity. A CDC longitudinal study (Infant Feeding Practices Study II) observed that the factors associated with LGA/macrosomic birth from conception to delivery do not necessarily predict the early infant weight trajectories, and suggested that early life influences especially related to postnatal energy balance that drives the continued overgrowth may be better targeted for intervention to reduce the early obesity risk.[109] Since postnatal growth trajectories can influence the clinical outcomes in LGA infants, allowing a small catch-down growth in the first few months of life in LGA infants is one such strategy.[59,67] Promoting breastfeeding help to prevent excessive weight gain during infancy in LGA infants, e.g., Goetz et al. observed that LGA infants who received proportionately more breast milk had normal weight at 7–12 month of age, while infants who received proportionately more formula milk had excess weight gain.[109] A longer duration of breastfeeding was associated with lower risk for childhood obesity in all birth weight categories including LGA infants.[110,111] Although breastfeeding potentially mitigates the metabolic sequelae for LGA infants and their mothers, women, especially with GDM, have delayed lactogenesis, less likely to exclusively breastfeed, and are more likely to introduce formula milk.[112–114] To optimize breastfeeding outcomes, we need to address the barriers to breastfeeding of mothers with GDM which include maternal obesity, increased need for C-section deliveries, mother–infant separation due to infant hypoglycemia, and other perinatal morbidities, and mother's report of less provider support for breastfeeding.[113] However, most studies on breastfeeding and obesity are

Table 3. Potential early intervention strategies for secondary prevention of early life obesity in LGA infants based on observational data.

• Parental and provider education on the postnatal growth trajectory of LGA infants that allows a small catch-down growth in early infancy (up to −0.67 SD)[59,60,67,72,73]
• Promoting breastfeeding and avoiding calorie-dense and high protein formula[44,46,67,109–111,115–118]
• Probiotic supplementation especially when exposed to prolonged antibiotics[105,106,121,122]
• Creating LGA infant care pathways incorporating multiple strategies at local and regional levels (multicomponent strategies)

LGA large for gestational age.

observational studies and may be explained, at least partly, by confounding.[115] In LGA infants who are formula-fed, simple measures such as reducing bottle size can help to reduce excessive weight gain.[116] Although not specifically studied in LGA infants, the formula milk composition especially with a lower protein or hydrolyzed protein content was associated with slower gain in weight during infancy.[117–119] The interpregnancy period is a golden opportunity to support mothers to achieve a healthy weight to prevent future LGA births and combining interventions directed to mothers of LGA infants is also likely to have synergistic effects.[120,121] With the recent data that suggest the perinatal use of probiotics in low-birth weight and healthy infants was associated with better growth[122,123] and an altered intestinal microbiome can impair postnatal growth, specifically with a propensity for adiposity in early life,[123] relatively inexpensive interventions such as probiotic supplementation to modulate early life microbiota may be a potential therapeutic intervention to reduce their early obesity risk. Based on the current evidence, limited to observational studies, some of the possible strategies for secondary prevention of early life obesity in LGA infants are included in Table 3. Since the evidence base for most of these strategies are from observational studies and not specifically in LGA infants, their clinical efficacy either as single or combination of strategies needs to be determined in future studies with adequate sample sizes. Combining the infant-specific strategies along with family-centered nutritional and lifestyle interventions (multicomponent strategies), may potentially have a significant synergistic effect. This needs to be validated in future studies.

In conclusion, a great deal remains to be learned about LGA and the underlying regulatory mechanisms in its progression into obesity, especially on their potential lifetime risk for developing obesity-related cardiometabolic diseases. However, as our knowledge is expanding, there are copious and tangible opportunities to develop and implement clinical care approaches specifically for LGA infants incorporating many of the strategies discussed in this review. Potential early biomarkers of risk for obesity and related comorbidities in LGA will lead to a better understanding of the risk and serve as a tool to intervene and facilitate attenuation of adverse health outcomes. For effective implementation of the strategies, the involvement of key stakeholders including parents, pediatricians, and health insurance agencies is crucial. Interventions if implemented at a critical, but narrow, time period may have the potential to influence LGA infant's metabolism, weight gain, and risk of subsequent obesity-related comorbidities. Additional research in LGA infants is needed to address and avert the risk factors at an early age, thereby impacting the care and the quality of life for these infants and their parents and potentially reducing the elevated lifetime risk of obesity and cardiometabolic diseases.

REFERENCES

1. (NCD-RisC) NRFC. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *Lancet* **390**, 2627–2642 (2017).
2. Lobstein, T. et al. Child and adolescent obesity: part of a bigger picture. *Lancet* **385**, 2510–2520 (2015).
3. Di Cesare, M. et al. The epidemiological burden of obesity in childhood: a worldwide epidemic requiring urgent action. *BMC Med.* **17**, 212 (2019).
4. Barton, M. Force UPST Screening for obesity in children and adolescents: US Preventive Services Task Force recommendation statement. *Pediatrics* **125**, 361–367 (2010).
5. Grossman, D. C. et al. Screening for obesity in children and adolescents: US Preventive Services Task Force recommendation statement. *JAMA* **317**, 2417–2426 (2017).
6. Daniels, S. R. & Hassink, S. G. Nutrition CO: the role of the pediatrician in primary prevention of obesity. *Pediatrics* **136**, e275–e292 (2015).
7. Smego, A. et al. High body mass index in infancy may predict severe obesity in early childhood. *J. Pediatr.* **183**, 87–93.e1 (2017).
8. Cunningham, S. A., Kramer, M. R. & Narayan, K. M. Incidence of childhood obesity in the United States. *N. Engl. J. Med.* **370**, 1660–1661 (2014).
9. Geserick, M. et al. Acceleration of BMI in early childhood and risk of sustained obesity. *N. Engl. J. Med.* **379**, 1303–1312 (2018).
10. Balagopal, P. B. et al. Nontraditional risk factors and biomarkers for cardiovascular disease: mechanistic, research, and clinical considerations for youth: a scientific statement from the American Heart Association. *Circulation* **123**, 2749–2769 (2011).
11. Kelly, A. S. et al. Severe obesity in children and adolescents: identification, associated health risks, and treatment approaches: a scientific statement from the American Heart Association. *Circulation* **128**, 1689–1712 (2013).
12. Daniels, S. R. et al. Promoting cardiovascular health in early childhood and transitions in childhood through adolescence: a workshop report. *J. Pediatr.* **209**, 240–51.e1 (2019).
13. Lycett, K. et al. Body Mass index from early to late childhood and cardiometabolic measurements at 11 to 12 years. *Pediatrics* **146**, e20193666 (2020).
14. Armstrong, S., Li, J. S. & Skinner, A. C. Flattening the (BMI) curve: timing of child obesity onset and cardiovascular risk. *Pediatrics* **146**, e20201353 (2020).
15. Matthews, E. K., Wei, J. & Cunningham, S. A. Relationship between prenatal growth, postnatal growth and childhood obesity: a review. *Eur. J. Clin. Nutr.* **71**, 919–930 (2017).
16. Woo, J. G. et al. Prediction of adult class II/III obesity from childhood BMI: the i3C consortium. *Int J. Obes.* **44**, 1164–1172 (2020).
17. Barker, D. J. & Osmond, C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet* **1**, 1077–1081 (1986).
18. Ludvigsson, J. F., Lu, D., Hammarström, L., Cnattingius, S. & Fang, F. Small for gestational age and risk of childhood mortality: a Swedish population study. *PLoS Med.* **15**, e1002717 (2018).
19. Derraik, J. G. B. et al. Large-for-gestational-age phenotypes and obesity risk in adulthood: a study of 195,936 women. *Sci. Rep.* **10**, 2157 (2020).
20. Barker, D. J. The fetal and infant origins of adult disease. *BMJ* **301**, 1111 (1990).
21. Ibáñez, L., Ong, K., Dunger, D. B. & de Zegher, F. Early development of adiposity and insulin resistance after catch-up weight gain in small-for-gestational-age children. *J. Clin. Endocrinol. Metab.* **91**, 2153–2158 (2006).
22. Okada, T. et al. Early postnatal alteration of body composition in preterm and small-for-gestational-age infants: implications of catch-up fat. *Pediatr. Res.* **77**, 136–142 (2015).
23. Lavery, J. A., Friedman, A. M., Keyes, K. M., Wright, J. D. & Ananth, C. V. Gestational diabetes in the United States: temporal changes in prevalence rates between 1979 and 2010. *BJOG* **124**, 804–813 (2017).
24. Tolosa, J. N. & Calhoun, D. A. Maternal and neonatal demographics of macrosomic infants admitted to the neonatal intensive care unit. *J. Perinatol.* **37**, 1292–1296 (2017).
25. Tutlam, N. T., Liu, Y., Nelson, E. J., Flick, L. H. & Chang, J. J. The effects of race and ethnicity on the risk of large-for-gestational-age newborns in women without gestational diabetes by prepregnancy body mass index categories. *Matern. Child Health J.* **21**, 1643–1654 (2017).
26. Koyanagi, A. et al. Macrosomia in 23 developing countries: an analysis of a multicountry, facility-based, cross-sectional survey. *Lancet* **381**, 476–483 (2013).

27. Patro Golab, B. et al. Influence of maternal obesity on the association between common pregnancy complications and risk of childhood obesity: an individual participant data meta-analysis. *Lancet Child Adolesc. Health* **2**, 812–821 (2018).
28. Voerman, E. et al. Maternal body mass index, gestational weight gain, and the risk of overweight and obesity across childhood: an individual participant data meta-analysis. *PLoS Med.* **16**, e1002744 (2019).
29. Badon, S. E., Quesenberry, C. P., Xu, F., Avalos, L. A. & Hedderson, M. M. Gestational weight gain, birthweight and early-childhood obesity: between- and within-family comparisons. *Int. J. Epidemiol.* **49**, 1682–1690 (2020).
30. Hales, C. M., Carroll, M. D., Fryar, C. D. & Ogden, C. L. Prevalence of obesity and severe obesity among adults: United States, 2017–2018. *NCHS Data Brief.* **360**, 1–8 (2020).
31. Åmark, H., Westgren, M. & Persson, M. Prediction of large-for-gestational-age infants in pregnancies complicated by obesity: a population-based cohort study. *Acta Obstet. Gynecol. Scand.* **98**, 769–776 (2019).
32. Weschenfelder, F., Lehmann, T., Schleussner, E. & Groten, T. Gestational weight gain particularly affects the risk of large for gestational age infants in non-obese mothers. *Geburtshilfe Frauenheilkd.* **79**, 1183–1190 (2019).
33. Deputy, N. P., Kim, S. Y., Conrey, E. J. & Bullard, K. M. Prevalence and changes in preexisting diabetes and gestational diabetes among women who had a live birth - United States, 2012-2016. *MMWR Morb. Mortal. Wkly Rep.* **67**, 1201–1207 (2018).
34. Mastroeni, M. F. et al. The independent importance of pre-pregnancy weight and gestational weight gain for the prevention of large-for gestational age Brazilian newborns. *Matern. Child Health J.* **21**, 705–714 (2017).
35. Ouyang, F. et al. Maternal BMI, gestational diabetes, and weight gain in relation to childhood obesity: the mediation effect of placental weight. *Obesity* **24**, 938–946 (2016).
36. Castillo-Castrejon, M. & Powell, T. L. Placental nutrient transport in gestational diabetic pregnancies. *Front. Endocrinol.* **8**, 306 (2017).
37. Lawlor, D. A. The Society for Social Medicine John Pemberton Lecture 2011. Developmental overnutrition–an old hypothesis with new importance? *Int J. Epidemiol.* **42**, 7–29 (2013).
38. Maron, B. A., Maron, J. L. & Abman, S. H. The case for bringing birthweight to adult cardiovascular medicine. *Am. J. Cardiol.* **127**, 191–192 (2020).
39. Mehta, S. H., Kruger, M. & Sokol, R. J. Being too large for gestational age precedes childhood obesity in African Americans. *Am. J. Obstet. Gynecol.* **204**, 265. e1–5 (2011).
40. Cnattingius, S., Villamor, E., Lagerros, Y. T., Wikström, A. K. & Granath, F. High birth weight and obesity–a vicious circle across generations. *Int. J. Obes.* **36**, 1320–1324 (2012).
41. Chiavaroli, V. et al. Progression of cardio-metabolic risk factors in subjects born small and large for gestational age. *PLoS ONE* **9**, e104278 (2014).
42. Kuciene, R., Dulskiene, V. & Medzioniene, J. Associations between high birth weight, being large for gestational age, and high blood pressure among adolescents: a cross-sectional study. *Eur. J. Nutr.* **57**, 373–381 (2018).
43. Kapral, N., Miller, S. E., Scharf, R. J., Gurka, M. J. & DeBoer, M. D. Associations between birthweight and overweight and obesity in school-age children. *Pediatr. Obes.* **13**, 333–341 (2018).
44. Salahuddin, M. et al. Predictors of severe obesity in low-income, predominantly Hispanic/Latino children: The Texas Childhood Obesity Research Demonstration Study. *Prev. Chronic Dis.* **14**, E141 (2017).
45. Hammoud, N. M. et al. Long-term BMI and growth profiles in offspring of women with gestational diabetes. *Diabetologia* **61**, 1037–1045 (2018).
46. Kaul, P. et al. Association between maternal diabetes, being large for gestational age and breast-feeding on being overweight or obese in childhood. *Diabetologia* **62**, 249–258 (2019).
47. Chen, Y. L. et al. Adverse pregnancy outcomes on the risk of overweight offspring: a population-based retrospective study in Xiamen, China. *Sci. Rep.* **10**, 1549 (2020).
48. Broccoli, S. et al. Early life weight patterns and risk of obesity at 5 years: a population-based cohort study. *Prev. Med.* **134**, 106024 (2020).
49. Cusick, S. E. & Georgieff, M. K. The role of nutrition in brain development: the golden opportunity of the "first 1000 days". *J. Pediatr.* **175**, 16–21 (2016).
50. American Academy of Pediatrics. *Pediatric Nutrition Handbook* 8th edn (American Academy of Pediatrics, Elk Grove Village, IL, 2019).
51. Wang, G. et al. Weight gain in infancy and overweight or obesity in childhood across the gestational spectrum: a prospective birth cohort study. *Sci. Rep.* **6**, 29867 (2016).
52. Lyons-Reid, J., Albert, B. B., Kenealy, T. & Cutfield, W. S. Birth size and rapid infant weight gain-where does the obesity risk lie? *J. Pediatr.* **230**, 238–243 (2021).
53. Zheng, M. et al. Rapid weight gain during infancy and subsequent adiposity: a systematic review and meta-analysis of evidence. *Obes. Rev.* **19**, 321–332 (2018).
54. Lu, Y., Pearce, A. & Li, L. Weight gain in early years and subsequent body mass index trajectories across birth weight groups: a prospective longitudinal study. *Eur. J. Public Health* **30**, 316–322 (2020).
55. Woo, J. G. Infant growth and long-term cardiometabolic health: a review of recent findings. *Curr. Nutr. Rep.* **8**, 29–41 (2019).
56. Druet, C. et al. Prediction of childhood obesity by infancy weight gain: an individual-level meta-analysis. *Paediatr. Perinat. Epidemiol.* **26**, 19–26 (2012).
57. Chiavaroli, V. et al. Infants born large-for-gestational-age display slower growth in early infancy, but no epigenetic changes at birth. *Sci. Rep.* **5**, 14540 (2015).
58. Nakagawa, Y. et al. Postnatal BMI changes in children with different birthweights: a trial study for detecting early predictive factors for pediatric obesity. *Clin. Pediatr. Endocrinol.* **27**, 19–29 (2018).
59. Lei, X. et al. Childhood health outcomes in term, large-for-gestational-age babies with different postnatal growth patterns. *Am. J. Epidemiol.* **187**, 507–514 (2018).
60. Taal, H. R., Vd Heijden, A. J., Steegers, E. A., Hofman, A. & Jaddoe, V. W. Small and large size for gestational age at birth, infant growth, and childhood overweight. *Obesity* **21**, 1261–1268 (2013).
61. Renom Espineira, A. et al. Postnatal growth and cardiometabolic profile in young adults born large for gestational age. *Clin. Endocrinol.* **75**, 335–341 (2011).
62. Hales, C. N. & Barker, D. J. The thrifty phenotype hypothesis. *Br. Med. Bull.* **60**, 5–20 (2001).
63. Moreno-Mendez, E., Quintero-Fabian, S., Fernandez-Mejia, C. & Lazo-de-la-Vega-Monroy, M. L. Early-life programming of adipose tissue. *Nutr. Res. Rev.* **33**, 244–259 (2020).
64. Kislal, S., Shook, L. L. & Edlow, A. G. Perinatal exposure to maternal obesity: lasting cardiometabolic impact on offspring. *Prenat. Diagn.* **40**, 1109–1125 (2020).
65. Chiarelli, F. & Marcovecchio, M. L. Insulin resistance and obesity in childhood. *Eur. J. Endocrinol.* **159**, S67–74 (2008).
66. Logan, K. M., Gale, C., Hyde, M. J., Santhakumaran, S. & Modi, N. Diabetes in pregnancy and infant adiposity: systematic review and meta-analysis. *Arch. Dis. Child Fetal Neonatal Ed.* **102**, F65–F72 (2017).
67. Larsson, A., Ottosson, P., Törnqvist, C. & Olhager, E. Body composition and growth in full-term small for gestational age and large for gestational age Swedish infants assessed with air displacement plethysmography at birth and at 3-4 months of age. *PLoS ONE* **14**, e0207978 (2019).
68. Donnelley, E. L., Raynes-Greenow, C. H., Turner, R. M., Carberry, A. E. & Jeffery, H. E. Antenatal predictors and body composition of large-for-gestational-age newborns: perinatal health outcomes. *J. Perinatol.* **34**, 698–704 (2014).
69. Moore, B. F., Harrall, K. K., Sauder, K. A., Glueck, D. H. & Dabelea D. Neonatal adiposity and childhood obesity. *Pediatrics* **146**, e20200737 (2020).
70. Ratnasingham, A., Eiby, Y. A., Dekker Nitert, M., Donovan, T. & Lingwood, B. E. Review: is rapid fat accumulation in early life associated with adverse later health outcomes? *Placenta* **54**, 125–130 (2017).
71. Toro-Ramos, T., Paley, C., Pi-Sunyer, F. X. & Gallagher, D. Body composition during fetal development and infancy through the age of 5 years. *Eur. J. Clin. Nutr.* **69**, 1279–1289 (2015).
72. de Fluiter, K. S., van Beijsterveldt, I. A. L. P., Breij, L. M., Acton, D. & Hokken-Koelega, A. C. S. Association between fat mass in early life and later fat mass trajectories. *JAMA Pediatr.* **174**, 1141–1148 (2020). 12.
73. de Zegher, F. et al. Large for gestational age newborns from mothers without diabetes mellitus tend to become tall and lean toddlers. *J. Pediatr.* **178**, 278–280 (2016).
74. Short, K. R., Teague, A. M., Fields, D. A., Lyons, T. & Chernausek, S. D. Lower resting energy expenditure and fat oxidation in Native American and Hispanic infants born to mothers with diabetes. *J. Pediatr.* **166**, 884–889 (2015).
75. Verma, S., Bailey, S. M., Mally, P. V. & Howell, H. B. Longitudinal measurements of resting energy expenditure by indirect calorimetry in healthy term infants during the first 2 months of life. *Am. J. Perinatol.* **36**, 918–923 (2019). 07.
76. Rodgers, G. P. & Collins, F. S. Precision nutrition-the answer to "what to eat to stay healthy". *JAMA* **324**, 735–736 (2020).
77. Lobelo, F. Fetal programming and risk of metabolic syndrome: prevention efforts for high-risk populations. *Pediatrics* **116**, 519 (2005).
78. O'Brien, J., Hayder, H., Zayed, Y. & Peng, C. Overview of microRNA biogenesis, mechanisms of actions, and circulation. *Front. Endocrinol.* **9**, 402 (2018).
79. Mori, M. A., Ludwig, R. G., Garcia-Martin, R., Brandão, B. B. & Kahn, C. R. Extracellular miRNAs: from biomarkers to mediators of physiology and disease. *Cell Metab.* **30**, 656–673 (2019).
80. Rodil-Garcia, P., Arellanes-Licea, E. D. C., Montoya-Contreras, A. & Salazar-Olivo, L. A. Analysis of microRNA expression in newborns with differential birth weight using newborn screening cards. *Int. J. Mol. Sci.* **18**, 2552 (2017).
81. Ortiz-Dosal, A., Arellanes-Licea, E. D. C., Rodil-García, P. & Salazar-Olivo, L. A. Circulating microRNAs overexpressed in macrosomia: an experimental and bioinformatic approach. *J. Dev. Orig. Health Dis.* **11**, 464–472 (2020).

82. Perng, W. et al. Associations of cord blood metabolites with perinatal characteristics, newborn anthropometry, and cord blood hormones in project viva. *Metabolism* **76**, 11–22 (2017).
83. Kadakia, R. et al. Cord blood metabolites associated with newborn adiposity and hyperinsulinemia. *J. Pediatr.* **203**, 144–9.e1 (2018).
84. Wang, G. et al. Inter-generational link of obesity in term and preterm births: role of maternal plasma acylcarnitines. *Int. J. Obes.* **43**, 1967–1977 (2019).
85. Briana, D. D. et al. Potential prognostic biomarkers of cardiovascular disease in fetal macrosomia: the impact of gestational diabetes. *J. Matern. Fetal Neonatal Med.* **31**, 895–900 (2018).
86. Papathanasiou, A. E. et al. Cord blood fatty acid-binding protein-4 levels are upregulated at both ends of the birthweight spectrum. *Acta Paediatr.* **108**, 2083–2088 (2019).
87. Lausten-Thomsen, U., Christiansen, M., Hedley, P. L., Holm, J. C. & Schmiegelow, K. Adipokines in umbilical cord blood from children born large for gestational age. *J. Pediatr. Endocrinol. Metab.* **29**, 33–37 (2016).
88. Dong, Y. et al. Large-for-gestational-age may be associated with lower fetal insulin sensitivity and β-cell function linked to leptin. *J. Clin. Endocrinol. Metab.* **103**, 3837–3844 (2018).
89. Higgins, M., Mc & Auliffe, F. A review of maternal and fetal growth factors in diabetic pregnancy. *Curr. Diabetes Rev.* **6**, 116–125 (2010).
90. Cekmez, F. et al. Apelin, vaspin, visfatin and adiponectin in large for gestational age infants with insulin resistance. *Cytokine* **56**, 387–391 (2011).
91. Boutsikou, T. et al. Cord blood chemerin and obestatin levels in large for gestational age infants. *J. Matern. Fetal Neonatal Med.* **26**, 123–126 (2013).
92. Simental-Mendía, L. E., Castañeda-Chacón, A., Rodríguez-Morán, M. & Guerrero-Romero, F. Birth-weight, insulin levels, and HOMA-IR in newborns at term. *BMC Pediatr.* **12**, 94 (2012).
93. Walewski, J. L. et al. Spexin is a novel human peptide that reduces adipocyte uptake of long chain fatty acids and causes weight loss in rodents with diet-induced obesity. *Obesity* **22**, 1643–1652 (2014).
94. Kumar, S. et al. Decreased circulating levels of spexin in obese children. *J. Clin. Endocrinol. Metab.* **101**, 2931–2936 (2016).
95. Kumar, S., Hossain, M. J., Javed, A., Kullo, I. J. & Balagopal, P. B. Relationship of circulating spexin with markers of cardiovascular disease: a pilot study in adolescents with obesity. *Pediatr. Obes.* **13**, 374–380 (2018).
96. Yavuzkir, S. et al. Maternal and umbilical cord blood subfatin and spexin levels in patients with gestational diabetes mellitus. *Peptides* **126**, 170277 (2020).
97. Akbas, M. et al. Serum levels of spexin are increased in the third trimester pregnancy with gestational diabetes mellitus. *Gynecol. Endocrinol.* **35**, 1050–1053 (2019).
98. Al-Daghri, N. M. et al. Associations of Spexin and cardiometabolic parameters among women with and without gestational diabetes mellitus. *Saudi J. Biol. Sci.* **25**, 710–714 (2018).
99. Gohir, W., Ratcliffe, E. M. & Sloboda, D. M. Of the bugs that shape us: maternal obesity, the gut microbiome, and long-term disease risk. *Pediatr. Res.* **77**, 196–204 (2015).
100. Murugesan, S. et al. Gut microbiome production of short-chain fatty acids and obesity in children. *Eur. J. Clin. Microbiol. Infect. Dis.* **37**, 621–625 (2018).
101. Wei, Y. et al. The associations of the gut microbiome composition and short-chain fatty acid concentrations with body fat distribution in children. *Clin. Nutr.* **40**, 3379–3390 (2020).
102. Zhou, L. & Xiao, X. The role of gut microbiota in the effects of maternal obesity during pregnancy on offspring metabolism. *Biosci. Rep.* **38**, BSR20171234 (2018).
103. Zheng, J. et al. Correlation of placental microbiota with fetal macrosomia and clinical characteristics in mothers and newborns. *Oncotarget* **8**, 82314–82325 (2017).
104. Tun, H. M. et al. Roles of birth mode and infant gut microbiota in intergenerational transmission of overweight and obesity from mother to offspring. *JAMA Pediatr.* **172**, 368–377 (2018).
105. Santacruz, A. et al. Interplay between weight loss and gut microbiota composition in overweight adolescents. *Obesity* **17**, 1906–1915 (2009).
106. Everard, A. et al. Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. *Proc. Natl Acad. Sci. USA* **110**, 9066–9071 (2013).
107. Donnelly, J. M., Walsh, J. M., Byrne, J., Molloy, E. J. & McAuliffe, F. M. Impact of maternal diet on neonatal anthropometry: a randomized controlled trial. *Pediatr. Obes.* **10**, 52–56 (2015).
108. Dodd, J. M. et al. The effects of antenatal dietary and lifestyle advice for women who are overweight or obese on neonatal health outcomes: the LIMIT randomised trial. *BMC Med.* **12**, 163 (2014).
109. Goetz, A. R., Rybak, T. M., Peugh, J. L. & Stark, L. J. Early-life determinants of excess weight in children born heavy. *Pediatr. Obes.* **15**, e12580 (2020).
110. Rito, A. I. et al. Association between characteristics at birth, breastfeeding and obesity in 22 countries: The WHO European Childhood Obesity Surveillance Initiative - COSI 2015/2017. *Obes. Facts* **12**, 226–243 (2019).
111. Woo, J. G. & Martin, L. J. Does breastfeeding protect against childhood obesity? Moving beyond observational evidence. *Curr. Obes. Rep.* **4**, 207–216 (2015).
112. Doughty, K. N. & Taylor, S. N. Barriers and benefits to breastfeeding with gestational diabetes. *Semin. Perinatol.* **45**, 151385 (2021).
113. Nommsen-Rivers, L. A. Does insulin explain the relation between maternal obesity and poor lactation outcomes? An overview of the literature. *Adv. Nutr.* **7**, 407–414 (2016).
114. Preusting, I., Brumley, J., Odibo, L., Spatz, D. L. & Louis, J. M. Obesity as a predictor of delayed lactogenesis II. *J. Hum. Lact.* **33**, 684–691 (2017).
115. Dewey, K. G. et al. Breastfeeding and risk of overweight in childhood and beyond: a systematic review with emphasis on sibling-pair and intervention studies. *Am. J. Clin. Nutr.* **114**, 1774–1790 (2021).
116. Wood, C. T. et al. Association between bottle size and formula intake in 2-month-old infants. *Acad. Pediatr.* **16**, 254–259 (2016).
117. Mennella, J. A., Ventura, A. K. & Beauchamp, G. K. Differential growth patterns among healthy infants fed protein hydrolysate or cow-milk formulas. *Pediatrics* **127**, 110–118 (2011).
118. Weber, M. et al. Lower protein content in infant formula reduces BMI and obesity risk at school age: follow-up of a randomized trial. *Am. J. Clin. Nutr.* **99**, 1041–1051 (2014).
119. Inostroza, J. et al. Low-protein formula slows weight gain in infants of overweight mothers. *J. Pediatr. Gastroenterol. Nutr.* **59**, 70–77 (2014).
120. Ziauddeen, N., Wilding, S., Roderick, P. J., Macklon, N. S. & Alwan, N. A. Is maternal weight gain between pregnancies associated with risk of large-for-gestational age birth? Analysis of a UK population-based cohort. *BMJ Open* **9**, e026220 (2019).
121. Alwan, N. A., Grove, G., Taylor, E. & Ziauddeen, N. Maternal weight change between successive pregnancies: an opportunity for lifecourse obesity prevention. *Proc. Nutr. Soc.* **79**, 272–282 (2020).
122. Uzan-Yulzari, A. et al. Neonatal antibiotic exposure impairs child growth during the first six years of life by perturbing intestinal microbial colonization. *Nat. Commun.* **12**, 443 (2021).
123. Angelakis, E. & Raoult, D. Gut microbiota modifications and weight gain in early life. *Hum. Microbiome J.* **10**, 1–5 (2018).

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AUTHOR CONTRIBUTIONS

S.V. conceived the study, screened articles, interpreted the results, and wrote the first draft of the complete manuscript. K.M. conceived the study, screened articles, and assessed article quality. K.M. and D.C. screened articles and assessed article quality. J. G.W. and B.B. interpreted the results and acted as subject experts. All authors gave constructive comments, reviewed, edited, and approved the final submitted manuscript.

COMPETING INTERESTS

Guarantor of the article: Sreekanth Viswanathan. The remaining authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Sreekanth Viswanathan.