Birth Size and Rapid Infant Weight Gain—Where Does the Obesity Risk Lie?

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There are 2 major phases of fat accrual: the first appearing in late fetal life, and the second in infancy.[1] Both are thought to be related to the risk of future adiposity; however, their relative contributions have not been determined. Although fat accumulation during these periods is reflected in weight, body weight alone is a poor index of the relative size and adiposity of children. Despite this, children often are identified as being small or large at birth according to weight alone (small or large for gestational age, SGA or LGA). Those born at the extremes of birth size are thought to be at an increased risk of obesity and associated metabolic disorders later in life. However, many children who are born SGA also experience weight acceleration, or an absence of weight deceleration in the case of those born LGA, which also have been associated with future obesity. Therefore, it is difficult to determine whether it is the status at birth, or the rate of weight gain and associated fat development during infancy, that is a more important determinant of future obesity risk. Here, we discuss the importance of understanding body composition both at birth and its evolution during infancy on later health among those born small and large. We have restricted our discussion to those born at term, as being born premature is independently associated with obesity.[2]

Size at Birth and Obesity

Babies born at the extremes of body size are at a greater risk of a range of short- and long-term health problems.[3-6] To identify those at risk, large and small infants have been defined using fixed definitions such as macrosomia (>4 kg) and low birth weight (<2.5 kg), or based on growth chart percentiles. Percentile-based definitions have the advantage of accounting for gestational age, and, where the appropriate reference growth chart is available, stratifying or otherwise adjusting for ethnicity. Generally, SGA is defined as having a birth weight below the 10th percentile, or a birth weight or crown–heel length 2 or more SDs below the mean. Similarly, LGA is defined as having a birth weight above the 90th percentile, or having a birth weight or crown–heel length 2 or more SD above the mean. Other definitions have been used, which range from below the 3rd to below the 20th percentile, and from above the 80th to above the 97th percentile, respectively.[7] However, all these definitions are arbitrary, as there is a continuum of risk for later morbidity associated with both reduced and increased birth weight.[8-12]

Previous studies have identified birth weight as a significant predictor of obesity and metabolic disorders later in life.[8-12] Although evidence supports a curvilinear association between birth weight and later obesity, with those born large at the greatest risk, it is less clear to what extent those born small are at risk.[13,14] Nevertheless, it is likely that both being born large and small increases risk for obesity. However, it is important to note that SGA and LGA are imperfect definitions, and that infants classified into these groups are heterogeneous. For example, infants who are born SGA have historically been classified as symmetric or asymmetric, with the former including those equally affected in length, weight, and head circumference, and the latter, long thin babies, where weight is primarily affected. These subtypes can offer insight into the cause and timing of growth restriction. For example, asymmetrical SGA is thought to occur late in the pregnancy and is commonly related to placental dysfunction.[15] However, there are other common causes of smaller size at birth, such as being genetically small.[15] These differences may be partially reflected in body mass index (BMI), with infants who are SGA presenting with various phenotypes including short and light, short but of normal weight, or light but of normal height.[16] Likewise, although infants who are LGA were historically genetically long and lean, they are now more likely to be of normal length but have disproportionately increased weight. This change is in part due to the increased prevalence of maternal obesity and hyperglycemia, which lead to fetal overnutrition.[17,18]

Why Weight Is Not Enough

Most studies looking at obesity risk have relied on anthropometric measurements such as weight, which does not indicate body size, or the BMI, which may not accurately reflect differences in body composition. Although infants who are born SGA are small, and infants who are born LGA are large, little research has explored how these differences in weight are distributed between the fat- and fat-free mass

AGA	Appropriate for gestational age
BMI	Body mass index
DXA	Dual-energy X-ray absorptiometry
LGA	Large for gestational age
SGA	Small for gestational age

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compartments. It is likely that differences in adiposity at birth predict metabolic dysfunction; therefore, body fat should be measured specifically. Despite this, few studies have attempted to understand the relationship between adiposity at birth and later obesity in those born small or large. As obesity is a condition of excess adipose tissue (and not greater weight per se), there is interest in understanding if the increased risk of later obesity seen among infants who are SGA and LGA is related to differences in body composition compared with those born at a weight appropriate for gestational age (AGA).

Limited evidence suggests that the fat mass compartment is more affected than the fat-free mass compartment in those born SGA or LGA, with infants who are SGA having reduced, and infants who are LGA increased, body fat. Larsson et al assessed 50 Swedish term infants in the first week of life using air-displacement plethysmography (ie, the PEA POD Infant Body Composition system; COSMED).[19] These infants were all SGA or LGA, defined as birth weight 2 SD below or above the mean on Swedish growth charts, respectively. Compared with a well-described cohort of Swedish infants born AGA (n = 108),[20] infants who were SGA were not only smaller in weight and length but also had reductions in fat-free mass (mean 2337 vs 3163 g), and to a greater extent, fat mass (90 vs 484 g). Although fat-free mass was approximately three-quarters of that seen in infants who were AGA, fat mass was less than 20%. Similarly, infants who were LGA were found to have greater increases in mean fat mass (773 vs 484 g) than mean fat-free mass (3677 vs 3163 g) compared with infants born AGA. Others have also shown that the greatest differences between infants who were AGA, SGA, and LGA were in fat mass.[21-23]

Providing further evidence that size for gestational age classification is imperfect, the ratio of body fat to lean mass in infants born SGA and LGA overlaps with those born AGA. Schmelzle et al evaluated 159 healthy neonates born term and preterm within 10 days of birth using dual-energy x-ray absorptiometry (DXA).[24] Although overall infants born SGA had less, and infants born LGA had more, body fat than infants born AGA, there was a large overlap between the 3 groups. Thus, among the infants born at term, although none of the infants who were SGA had >20% body fat and none of the infants born LGA had <10% body fat, nearly one-half of both neonates with low (<10%) and high (>20%) body fat were classified as AGA. However, the study must be interpreted cautiously, as it included relatively small numbers of infants born SGA (n = 20) and LGA (n = 13), and few had body fat percentages outside of the range of 10%-20%. Nonetheless, Donnelley et al observed a similar trend among infants born at term (n = 536).[23] These infants were assessed within 48 hours of birth using air-displacement plethysmography. Although infants born LGA as a group had a greater body fat percentage than infants born AGA, approximately one-half of the infants born LGA had normal body fat, with the remainder having elevated body fat (defined as >1 SD above the mean percentage of body fat).

Beyond Percentage Body Fat: Adipose Tissue Composition, Distribution, and Function

Although infants born SGA and LGA are smaller and larger than those born AGA, they may not necessarily have abnormal body fat percentage. Further, although the key factor linking body size to morbidity and mortality is adipose tissue distribution and function, like body weight and BMI, percentage body fat is merely a surrogate overall measure of body fat. In addition to understanding the amount of adiposity an individual may have relative to their body size, research has implicated the composition of body fat (eg, brown vs white fat),[25,26] its distribution (eg, central vs peripheral),[26,27] the rate of its accretion,[28,29] and various biomarkers[30,31] as indices of adipose tissue function. Exploring differences in these factors may provide more information regarding adipose tissue function than investigating body size and its evolution in insolation.

Rate of Weight Gain and Obesity

Numerous studies have shown an association between rapid weight gain in early life and later obesity.[32-38] An individual participant data meta-analysis of nearly 50 000 individuals found that each 1-SD increase in weight between birth and 1 year resulted in a 2-fold increase in risk of childhood obesity (OR 1.97; 95% CI 1.83-2.12).[37] A recent meta-analysis identified 17 studies that have also explored this association.[38] Rapid weight gain in infancy was associated with both childhood obesity (OR 4.16; 95% CI 3.26-5.32) and adult obesity (OR 2.02; 95% CI 0.93-4.36).[38] This in the context of evidence that most children with obesity continue to be obese in adulthood,[39,40] suggests that the rate of weight gain in the first year of life is important in setting a lifetime risk of obesity.

The Importance of Weight Trajectory in Infants Born SGA and LGA

Although accelerated weight gain may contribute to excessive adiposity, not all infants born SGA experience the same rate of weight gain. A longitudinal study of 3004 infants born SGA at term identified 5 typical growth trajectories in the first 2 years of life. The 2 accelerated weight gain groups were associated with increased risk of childhood overweight. These were defined by accelerated weight gain in the first 4 months of life followed by either a persistent weight-for-age z score >1 in the first year of life ("excessively rapid"), or a weight-for-age z score between 0 and 1 in the first year of life ("rapid"). The infants who experienced excessively rapid and rapid accelerated weight gain had 11- and 2-times increased odds of being overweight or obese in early childhood, respectively (OR 11.6; 95% CI 8.8-15.3/2.3; 1.8-3.0).

These infants also experienced earlier adiposity rebound (the age at which BMI rises after its initial fall after infancy) compared with those who did not experience accelerated weight gain.[41] Early adiposity rebound itself has previously been associated with an increased risk of obesity later in life.[42,43] This is unsurprising, as early adiposity rebound is statistically related to both high BMI and to upwards crossing of percentiles, ie, weight acceleration.[44]

Among those born LGA, it is those who do not experience a deceleration in weight gain that are at the greatest risk of obesity in early childhood. As part of the Generation R study, 3941 children were followed up until 4 years of age. The greatest risk of obesity at age 4 years was among children born LGA who did not experience a deceleration in their weight gain in the first 2 years of life (a reduction of <0.67 SD for weight, OR 12.46; 95% CI 6.07-25.58). Interestingly, those children born AGA with accelerated weight gain (>0.67 SD increase in weight) were also at increased risk (OR 3.11; 95% CI 2.37-4.08).[45]

Even though it is well established that maternal characteristics such as hyperglycemia and obesity influence size at birth,[46,47] probably by fetal overnutrition,[48] postnatal weight trajectories are also determined, in part, by these factors. Among 600 children born LGA, those whose mother was overweight or obese, or had diabetes during pregnancy, demonstrated accelerated weight gain from 9 months to 4 years of age. This led to these children having the greatest BMI z score among the LGA subgroups at 4 years of age (mean BMI z score = 2.14 [95% CI 1.20-2.98]). In contrast, the LGA subgroup without maternal conditions or excessive gestational weight gain had a BMI trajectory and mean BMI z score at 4 years of age that was comparable with the AGA reference group.[49]

Combined, these data show that there are groups of infants born SGA and LGA that have an elevated risk of obesity, and that the weight gain trajectory, ie, whether weight gain accelerates or decelerates in early childhood, is an important predictor of obesity in early childhood.

Beyond Weight: the Importance of Changes in Body Composition During Childhood

Although the body weight trajectory in early life seems important when considering risk of future obesity, perhaps the body fat trajectory is even more so. Although many infants born SGA experience a period of accelerated, and infants born LGA a period of decelerated, weight gain, little research has evaluated the associated longitudinal changes in body composition.

At birth, infants who are SGA have greater deficits in fat- than fat-free mass; however, evidence suggests that by early childhood infants who are born SGA have more body fat than those born AGA. Data from the third National Health and Nutrition Examination Survey III (1988-1994) suggest that, among children aged 2 months to 4 years, deficits in fat-free mass are greater than deficits in fat mass in children born SGA compared with AGA, meaning they have elevated adiposity. These associations, however, were drawn using skinfold thicknesses and circumferences, which are crude measures of body composition.[50] Nonetheless, evidence has emerged using accepted reference standards, such as DXA, which support this notion. At school age, Biosca et al found fat-free mass to be lower among those born SGA than AGA, resulting in elevated body fat, particularly in the abdominal region, after adjustment for age, sex, and height.[51]

This trend for enhanced central adiposity among infants born SGA has been echoed by others, who have demonstrated comparable gains to infants born AGA in fat-free mass and bone mineral content, but increased gains in total and central adiposity.[52-54] Indeed, Ibáñez et al showed that, even after matching for age, sex, height, weight, and BMI, at 6 years of age, despite comparable total lean mass and fat mass, children born SGA had elevated central visceral adiposity compared with children born AGA.[53] However, the research findings are not consistent. Lindberg et al assessed Swedish children with marginally low birth weight using DXA at 7 years of age.[55] Among those further classified to be SGA, the phenotype of increased adiposity was not observed; these children were proportionally smaller with fat-free mass, bone mineral content, and fat mass all found to be lower than control children who were born at term and AGA. Indeed, among these infants although the fat-free mass index was reduced by ~3%, the fat mass index was reduced by ~15%, suggesting that they had reduced adiposity. However, this group experienced a greater degree of weight acceleration between 3.5 and 7 years, which may be an indicator that this group was at risk of gaining excess body fat in later childhood and adolescence.

At birth, it is the fat mass compartment that is most enlarged in infants who are LGA. However, this changes during infancy, so that children born LGA experience greater increases in fat-free mass than fat mass, the reverse of the pattern reported in those born SGA.[50] Thus, although at school age, fat-free mass remains greater in children born LGA, body fat percentage is not different between children born LGA and AGA, when assessed via DXA.[51] Indeed, a longitudinal study of infants born LGA and AGA suggested that although children born LGA have elevated lean mass across the first 2 years of life, fat mass accrual slows to approach a more normal fat mass.[56]

Similar trends in weight acceleration and deceleration were apparent when Larsson et al followed up their cohort at 3 to 4 months of age.[19] At follow-up, although infants who were born SGA remained smaller and infants who were born LGA remained larger in all measurements, when compared with Eriksson et al's infants born AGA, the tendency to track toward the mean is evident, not only for weight and length, but also for fat and fat-free mass.[20] For example, body fat as a percentage of body weight increased from 3.7%, 12.9%, and 17.3% at birth to 25.8%, 26.4%, and 27.6% at 3 to 4 months of age among children born SGA, AGA, and LGA, respectively.

In the study by Larsson et al, infants born SGA experienced rapid weight gain and a dramatic change in body

composition so that between birth and 3 to 4 months of age, their fat mass increased 23-fold compared with the 2.8-fold increase seen among the infants born LGA.[19] Although it appears some infants born SGA and LGA will regress to the mean, some may maintain greater adiposity. The rapid growth experienced by some of these infants may help to explain this discrepancy. Few studies have evaluated differences in body composition within birth weight subgroups; therefore, it is difficult to disentangle the effects of size at birth from rapid weight gain, and whether this affects body composition.

Are They Actually Obese?

Given that both being born at the extremes of birth size and the rate of weight gain in early childhood have been associated with later obesity risk, there is a need to establish if there are identifiable groups of infants whose risk is particularly magnified; for example, those born SGA who experience accelerated weight gain. To do so, however, one must consider how obesity is being defined. As obesity is a condition of excess adiposity, defining this by BMI, which is a measure of weight in relation to height and not a measure of actual adiposity, may obscure associations.

For example, Ibáñez et al demonstrated that although children born SGA gain weight faster in the first 2 years of life, by 2 years of age their mean height and weight were not different from children born AGA.[54] However, between 2 and 4 years of age, children born SGA continued to gain greater amounts of abdominal fat mass and total body fat compared with children born AGA. Thus, despite having similar BMIs and growth trajectories during this period, children who are born SGA become progressively more adipose. This important finding is unidentifiable when BMI is used as a surrogate for adiposity/obesity and suggests that an early period of accelerated weight gain in infants born SGA may be related to increased adiposity in later childhood.

By comparison, a study of more than 50 000 children assessed longitudinally throughout childhood and adolescence saw an increased prevalence of overweight and obesity among those born LGA compared with those born AGA or SGA (43.7%, 28.4%, and 27.2%, respectively). Despite this, there were no clear differences in the annual change in BMI SDS between the 3 birth weight groups. Among children born LGA, BMI SDS was largely steady, meaning the children tracked along a greater BMI SDS compared with the infants born AGA and SGA throughout childhood and adolescence.[39] As there is disagreement whether infants born LGA become children who are proportionally larger in both fat and fat-free mass,[51] or fat-free mass alone,[56] one must consider if those children born LGA are actually obese, or are just larger?

A problem with these, and other, studies is that the authors have not dissected out whether infants born LGA are big and lean, or are more adipose. Likewise, infants who are SGA may be genetically small at birth (rather than abnormally lean). Recent evidence suggests that perhaps it is only those born LGA by weight that are at an increased risk of obesity. Derraik et al retrospectively studied 195 936 Swedish women and found that those born LGA by weight, or weight and length combined, had an increased risk for obesity compared with those born AGA (adjusted relative risk 1.40; 95% CI 1.39-1.63 and 1.51; 1.37-1.67, respectively).[18] In contrast, being born LGA by length only was not associated with increased obesity risk. These authors and others have speculated that being born excessively long is genetically driven, whereas, being born excessively heavy is related to in utero factors. However, whether these women had excessive adiposity remains unknown.

Conclusions

Although at birth, infants who are SGA are smaller and infants who are LGA are larger than infants born AGA, both may be at an increased risk of obesity later in life. What may be more important, however, is the rate of weight gain in infancy and early childhood. It is unclear to what extent risk is then inflated by being born small or large. An issue with much of the available research is that authors have not dissected out differences in body composition, so it is unclear how the fat- and fat-free mass compartments evolve. We speculate that the best estimates of later obesity and metabolic risk could be made by taking into account body composition in infancy and its changes in the early years. There is a need for further research to disentangle the effects of birth size and rate of gain in fat mass on future obesity risk. This research should investigate body composition both at birth and during early childhood. Researchers should avoid relying solely on anthropometric measures to define excess adiposity and should instead focus on other indices of adiposity, including its composition, distribution, and function. ■

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