Birth size and rapid infant weight gain – where does obesity risk lie?

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List of abbreviations:

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

There are two 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 risk of future adiposity; however, their relative contributions have not been determined. Though 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 are often 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 SGA children also experience weight acceleration, or an absence of weight deceleration in the case of those born LGA, which have also 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] In order to identify those at risk, large and small infants have been defined using fixed definitions such as macrosomia (>4kg) and low birth weight (<2.5kg), 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 two or more

standard deviations (SD) 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 two 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, SGA infants 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 BMI, with SGA infants presenting with various phenotypes including short and light, short but of normal weight, or light but of normal height.[16] Likewise, although LGA infants 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 body mass index (BMI), which may not accurately reflect differences in body composition. Although SGA infants are small, and LGA infants are large, little research has explored how these differences in weight are distributed between the fat- and fat-free mass 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 SGA and LGA infants is related to differences in body composition compared to 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 SGA infants having reduced, and LGA infants increased, body fat. Larsson and colleagues[19] assessed 50 Swedish term infants in the first week of life using air displacement plethysmography (ADP, i.e. the PEA POD Infant Body Composition system). These infants were all small or large for gestational age, defined as birth weight two SD below or above the mean on Swedish growth charts, respectively. Compared to a well-described cohort of Swedish AGA infants[20] (*n* = 108), SGA infants 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). So, while fat-free mass was approximately three-quarters of that seen in AGA infants, fat mass was less than 20%. Similarly, LGA infants were found to have greater increases in mean fat mass (773 vs 484 g) than mean fat-free mass (3677 vs. 3163 g) compared to AGA infants. Others have also shown that the greatest differences between AGA, SGA and LGA infants 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 SGA and LGA infants overlaps with those born AGA. Schmelzle *et al.*[24] evaluated 159 healthy term and preterm neonates within 10 days of birth using dual-energy x-ray absorptiometry (DXA). Although overall SGA infants had less, and LGA infants had more, body fat than AGA infants, there was a large overlap between the three groups. Thus, among the term infants, although none of the SGA infants had >20% body fat and none of the LGA infants had <10% body fat, nearly 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 SGA (*n* = 20) and LGA (*n* = 13) infants, and few had body fat percentages outside of the range of 10–20%. Nonetheless, Donnelley and colleagues[23] observed a similar trend among term infants (*n* = 536). These infants were assessed within 48 hours of birth using ADP. While LGA infants as a group had a greater body fat percentage than AGA infants, approximately half of the LGA infants 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

Though SGA and LGA infants are smaller and larger than those born AGA, they may not necessarily have abnormal body fat percentage. Further, while 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 (e.g. brown vs. white fat),[25, 26] its distribution (e.g. 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 one SD increase in weight between birth and 1 year resulted in a two-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 obese children 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 SGA and LGA infants

Although accelerated weight gain may contribute to excessive adiposity, not all SGA infants experience the same rate of weight gain. A longitudinal study of 3,004 term SGA infants identified five typical growth trajectories in the first two years of life. The two accelerated weight gain groups were associated with increased risk of childhood overweight. These were defined by accelerated weight gain in the first four 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 to 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, i.e. weight acceleration.[44]

Among those born LGA, it is those that 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 3,941 children were followed up until 4 years of age. The greatest risk of obesity at age 4 was among children born LGA who did not experience a deceleration in their weight gain in the first two years of life (a reduction of <0.67 SD for weight, OR = 12.46 [95% CI: 6.07, 25.58]). Interestingly, those AGA children 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]

While 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 LGA children, 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 to the AGA reference group.[49]

Combined, these data show that there are groups of SGA and LGA infants that have an elevated risk of obesity, and that the weight gain trajectory, i.e. 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

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

At birth, SGA infants have greater deficits in fat- than fat-free mass; however, evidence suggests that by early childhood SGA infants have more body fat than those born AGA. Data from the third National Health and Nutrition Examination Survey (NHANES III, 1988–94) suggests 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 to 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.*[51] 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.

This trend for enhanced central adiposity among SGA infants has been echoed by others, who have demonstrated comparable gains to AGA infants in fat-free mass and bone mineral content, but increased gains in total and central adiposity.[52-54] Indeed, Ibáñez *et al.*[53] 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, SGA children had elevated central visceral adiposity compared to AGA children. However, the research findings are not consistent. Lindberg *et al.*[55] assessed Swedish children with marginally low birth weight using DXA at 7 years of age. 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 (FFMI) was reduced by ~3%, the fat mass index (FMI) 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 LGA infants. However, this changes during infancy, so that LGA children 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 higher in children born LGA, body fat percentage is not different between LGA and AGA children, when assessed via DXA.[51] Indeed, a longitudinal study of LGA and AGA infants suggested that although children born LGA have elevated lean mass across the first two 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.*[19] followed up their cohort at 3 to 4 months of age. At follow-up, although SGA infants remained smaller and LGA infants remained larger in all measurements, when compared with Eriksson, Löf and Forsum*'s*[20] AGA infants, the tendency to track towards the mean is evident, not only for weight and length, but also for fat and fat-free mass. 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 Larsson *et al.*'s[19] study, SGA infants 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 to the 2.8-fold increase seen among the LGA infants. While it appears some SGA and LGA infants 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.*[54] demonstrated that although SGA children gain weight faster in the first two years of life, by 2 years of age their mean height and weight were not different from AGA children. However, between 2 and 4 years of age, SGA children continued to gain greater amounts of abdominal fat mass and total body fat compared to AGA children. Thus, despite having similar BMIs and growth trajectories during this period, SGA children 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 SGA infants may be related to increased adiposity in later childhood.

By comparison, a study of over 50,000 children assessed longitudinally throughout childhood and adolescence saw an increased prevalence of overweight and obesity among those born LGA compared to 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 standard deviation score (SDS) between the three birth weight groups. Among children born LGA, BMI SDS was largely steady, meaning the children tracked along a higher BMI SDS compared to the AGA and SGA infants throughout childhood and adolescence.[39] As there is

disagreement whether LGA infants 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 LGA infants are big and lean, or are more adipose. Likewise, SGA infants 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.*[18] 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 to those born AGA (aRR = 1.40 [95% CI: 1.39, 1.63); and 1.51 [1.37, 1.67], respectively). 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.

Conclusion

Although at birth, SGA infants are smaller and LGA infants are larger than AGA infants, 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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