Born large-for-gestational-age: bigger is not always better

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Introduction

Over the past 60-90 years, there seems to have been a change in the growth trajectories of large-for-gestational-age (LGA) babies and the associated health effects later in life. Subjects classified as large at birth in the 1920s were found to have reduced morbidity and mortality in their seventh decade compared to those born of lower birth weight [1,2]. Indeed, across the birth weight range there was a progressive increase in cardiovascular and metabolic risk with reducing birth weight, even among those in the normal range [1,2]. These findings suggested that, historically, larger size at birth provided metabolic advantages, contributing to improved health and possibly longevity.

Long-term outcomes in those born LGA have dramatically changed in the last 30 years, with LGA being now associated with early obesity, and increased cardiovascular and metabolic risk [3,4]. The association between birth weight and the risk of later adult diseases currently seems to be U-shaped [5]. It is likely that this relatively recent increased risk of adult disease in those born large is related to the underlying factors influencing fetal growth as well as changes in post-natal environmental conditions. For instance, from 1910 to the late 1940s, events including the World Wars and the Great Depression were characterized by limited available nutrition to the wider population [6,7]. Thus, in the past, babies were much less likely to be over-nourished *in utero*, as shown by lower maternal weight gain and overweight/obesity rates during pregnancy [8,9], so that LGA babies were more likely to have been 'long and lean'. Much higher rates of post-term births and increased sibship may represent risk factors for lean LGA babies [10,11]. Prior to active obstetric intervention to avoid prolonged pregnancies the post-term birth rate was 10% [12] compared to approximately 3% nowadays [13]. Conversely, there has been a nutritional excess *in utero* in recent decades [14], leading to LGA neonates that are 'long and fat' [15], with post-natal exposure to an "obesogenic" environment responsible for a further acceleration in growth [16].

Why are babies being born larger?

There has been a progressive increase in the prevalence of large babies over the last three decades [17] that is now approximately 10% of all newborns [18]. However, the literature is conflicting regarding the definition of "large" at birth, which would indirectly estimate the severity of adiposity. Birth weight appears to be the most widely adopted parameter to define large babies, as weight represents a crude measure of fetal growth, involving length, head circumference, and fatness [19]. The terms LGA and macrosomia have been used somewhat interchangeably, although different criteria have been adopted for both, leading to conflicting classifications. LGA babies are usually defined as having a birth weight >90th centile according to gestational age and sex [20], while macrosomia tends to refer to babies with a birth weight >4,000 g [21]. As LGA is a more precise term, it is more commonly used to identify larger babies.

Higher birth weights and greater neonatal adiposity represent the expression of a complex fetal-maternal interaction, which is driven by fetal genetic factors and the intrauterine environment [22]. While the factors that have led to large birth weight in previous generations are unclear, the current underlying causes of LGA appear to be mainly due to nutritional excess *in utero*. This either directly or via epigenetic mechanisms results in increasing obesity post-natally [23-25]. This increased *in utero* nutrition most likely reflects maternal nutrition, in particular obesity and maternal diabetes mellitus. Higher rates of maternal obesity and gestational diabetes represent some of the main components of a proposed "obesity cycle", responsible for *in utero* programming of later adiposity and transgenerational amplification of obesity [14,26].

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This was first proposed by Pedersen who hypothesized that obese and diabetic mothers provided increased nutrition to the fetuses, who then became larger with greater adiposity [27]. Increasing fetal adiposity/over-nutrition 'programs' the fetuses to grow more rapidly post-natally and develop early obesity. As obesity tracks with age, these children are more likely to become obese adults.

The classification of infants as LGA based on customised percentiles for birth weight has been proposed [18,28,29]. These have strengths and limitations, the latter likely hindering wider usage. Customised percentiles incorporate maternal and infant factors, such as maternal weight, height, parity, gestational age and infant sex, resulting in some LGA infants being re-categorised as AGA [18]. It has been argued that ethnicity should also be taken into account, as for example, American Indian and Pacific Islander mothers are at increased risk of having LGA infants [28,30]. Adjusting for maternal height is reasonable, as a longer baby would be proportionally heavier but not necessarily fatter. In a large prospective cohort study, newborns defined LGA by customised percentiles had a four-fold increase in risk of severe neonatal morbidity/mortality compared to those born macrosomic or defined LGA by population centiles [18].

However, there are issues with customised percentiles. In the above-cited study, mothers of large babies who were defined as AGA by customised percentiles had a 1.6-fold increase in the overall rate of caesarean section [18]. Further, it is important to consider that pre-pregnancy maternal BMI is likely to be the main predictor of birth weight. Maternal obesity represents the main factor leading to fetal obesity at any maternal height [31], and the increasing prevalence of LGA infants mirrors increasing maternal adiposity. As a result, the use of percentiles adjusting for maternal weight may be misguided; if the mother is obese, the adjustment of the baby's weight would be inappropriate as it would likely normalise obesity-driven fetal growth and adiposity. In addition, certain ethnic groups have increased incidence of adult obesity that may contribute to increased size of their babies, and adjustment for ethnicity may lead to the inappropriate classification of newborns. Therefore, moving an LGA infant to an AGA category should not diminish birth-size related pathology, and recent reviews have criticised the substantive support for clinical use of customised percentiles in classifying babies as LGA [32].

Measurement of adiposity in babies

Birth weight does not define body composition, an issue critically important in LGA newborns. For more than three decades ponderal index (g/cm^3) has been considered a practical approach to characterize neonatal adiposity [33], differing from BMI (kg/m^2) for providing greater adjustment for length and, thus, being a more reliable measure of neonatal adiposity [34]. In infants born LGA, ponderal index has been found to be significantly higher than in those born AGA [35-37], and a greater ponderal index at birth has also been associated with increased adiposity in childhood [38]. Although this index appears easy to perform and inexpensive, its accuracy is limited by observers' variability in length measurement [39,40]; however, birth length is still not routinely measured in many centres [40,41]. In addition, ponderal index does not distinguish between fat mass and lean mass and does not clarify which body compartment is over-represented in LGA babies; indeed a poor correlation has been shown between ponderal index and fat mass estimated by direct assessments of neonatal body composition [34,42,43].

Therefore, in recent years, direct techniques have been proposed to measure neonatal adiposity, such as dual energy x-ray absorptiometry (DXA) and air displacement plethysmography [43-45]. These methods have consistently shown increased fat mass in LGA babies compared to AGA babies [45,46]. Nonetheless, these studies have not estimated body fat distribution, which would help clarify whether higher birthweight is associated with increased central adiposity. Lean and fat mass have been reported differently (as total or percentage mass), which may have created confusion regarding the body composition of LGA infants. Higher adiposity in LGA infants has been found in combination with an increased lean mass (as absolute values) measured by DXA, consistent with an increased muscularity when compared to AGA infants [46,47]. Specifically, breastfed LGA infants born to non-diabetic mothers were found to have greater adiposity at birth and increased muscularity by age 4 months [47]. Similarly, an increase in lean mass in children born LGA through age 47 months has also been shown [48]. In other studies, the proportion of lean body mass as a percentage of body weight was lower in LGA

babies with greater absolute values of lean mass [45,49].

Collectively, these studies of LGA infants suggest an increase in fat mass and often a smaller increase in lean mass, so that percentage body fat is increased, notably in those born to obese/diabetic mothers [45]. However, more robust studies are needed to clarify the pattern of fat distribution and levels of adiposity in these babies, ideally using direct methods for assessment of neonatal body composition.

Will a large baby become a fat adult with an increased cardio-metabolic risk?

There are contradictory long-term outcomes reported in those born LGA for adiposity and cardio-metabolic disorders [3,50-53]. As discussed above, this probably reflects subjects from different eras with different environmental factors affecting intrauterine nutrition, neonatal anthropometry, post-natal nutritional exposure, and growth trajectories during infancy and childhood.

Nutrition before conception and during pregnancy plays a fundamental role in influencing maternal weight gain, fetal growth, and neonatal outcomes [54-56], but the evidence is limited in the case of LGA births. A lower prevalence of LGA infants was observed amongst healthy mothers who followed a low-glycaemic diet compared to those assigned to a high-glycaemic diet (3.1% *vs.* 33.3%) [57]. Conversely, a randomised controlled trial involving women who had previously delivered a large infant showed that a low-glycaemic diet did not reduce incidence of LGA babies [58], although there was an associated reduction in gestational weight gain and in the prevalence of gestational diabetes [58]. Further, a recent meta-analysis showed that dietary interventions in pregnancy were associated with increased birth size (by both weight and length) and reduced low-birth-weight incidence, but there was no significant effect on the prevalence of infants born LGA or small-for-gestational-age [55]. However, overall it is difficult to differentiate the effects of maternal obesity from those of an obesogenic diet on the prevalence of LGA births, since both tend to be closely intertwined [56].

The early post-natal nutritional environment, particularly breastfeeding, has also been suggested to be a modulator of long-term obesity risks [59], which may affect outcomes amongst those born LGA. Unfortunately, many epidemiological studies do not report information on feeding practices in infants born LGA, such as data on early infant feeding and age at weaning into solid foods. Breastfeeding is associated with a small but consistent reduction in later childhood obesity (odds ratio 0.78 compared to formula-fed infants) [59]. A similar or longer breastfeeding duration has been observed in LGA infants compared to those born AGA [60]; except for large babies of obese diabetic or extremely obese non-diabetic women who are more likely to experience breastfeeding failure and/or breastfeed for a shorter period of time [61]. Macrosomic infants were also more likely to be introduced earlier to solid food (before the age of 6 months) than AGA infants, with a synergistic effect of macrosomia and early introduction to solids on the development of high weight-for-length between 1 and 3 years of age in boys [62]. Notably, being born LGA remains a risk factor for higher BMI status during early childhood independently of early feeding practices [63]. Similarly, the association between birth weight and adolescent obesity remains after adjustment for breastfeeding [64].

Growth patterns in infancy and childhood are also associated with the long-term risks of obesity in those born LGA [65-67]. The majority of LGA infants display a growth deceleration for weight and length ('catch-down growth') early in life, with some studies reporting similar growth parameters at 12 months compared to AGA infants [36,37,65]. Thus, after escaping maternal influence on intrauterine growth, it has been speculated that LGA infants physiologically return to their genetically-determined growth trajectories [36]. Conversely, other studies have reported that, despite the catch-down growth, LGA infants tend to remain heavier and longer in infancy and early childhood [67], which ultimately leads to a higher risk of overweight [66]. LGA infants born of diabetic mothers are particularly likely to remain heavier with greater abdominal adiposity [15]. Further, in approximately 20% of LGA infants there is a lack of catch-down growth, with weight gain continuing in the upper centiles over the first year [36]. Indeed, LGA children without catch-down growth represent a high-risk subgroup, as they have been found to have increased fat mass in early childhood [65]. In this respect, two systematic reviews have shown that infants who are larger based on weight or BMI or who have an

acceleration in post-natal growth are at greater risk of later obesity [68,69].

In those LGA infants who display accelerated weight gain, epigenetics has been proposed as a possible mechanism leading to higher birth weight and altered body composition and metabolism. Potential epigenetic changes *in utero* associated with the LGA phenotype have recently been examined. Hypermethylation of a specific gene locus (fibroblast growth factor receptor 2, *FGFR2*, involved in modulation of cell growth regulation and maturation) has been identified as being associated with high birth weight [23]. Further, recent studies have highlighted the importance of considering the potential effects of DNA methylation in determining adipose tissue development [70,71]. Specifically, prenatal adipose tissue development is characterized by the appearance of fat lobules at 14 weeks of gestation, which intensely proliferate through to 23 weeks followed by an increase in size from 24 to 29 weeks [70]. Exposure to excessive nutrition and adverse environments *in utero* have been hypothesized to result in epigenetic modifications affecting adipocyte development, with lasting effects during post-natal life (e.g. greater ability to store energy, or to generate new cells in fat tissue) [71]. This contrasts with earlier views that fat cells number was set at birth with increased adipocyte size the only mechanism to increase post-natal fat mass [72]. Thus, it has been speculated that LGA babies born to obese and/or diabetic mothers are prone to become obese in adulthood because of being born with more and larger adipocytes, as birth size tracks overtime [25]. In animal model of diet-induced obesity, higher body weight has been observed in early life in offspring together with adipocyte hypertrophy and greater fat depots [73]. In addition, in rat offspring maternal low-protein and post-natal high-fat diets induce increased *IGF2* gene expression and DNA methylation within adipocytes, leading to rapid adipose tissue growth [74]. However, it is also possible that these changes may simply represent epigenetic signatures of the phenotype, and their influence on birth size still remains speculative.

Later in life, the association between heavier birth weight and increased adiposity has been found to persist [75]. During childhood, there is a progressive increase in the risk of overweight with greater birth weight [76]. A meta-analysis reported that adults of higher birth weight had a 2-fold increase in the long-term risk of overweight [50], with greater abdominal adiposity [51,77].

The long-term cardiovascular and metabolic outcomes in adults born LGA are conflicting. An increased risk of cardiovascular and metabolic disease has been reported in adolescents born LGA to healthy mothers [78], and a higher risk of coronary heart disease has also been found during adulthood [79]. Furthermore, a number of studies have found adults born LGA to be at increased risk of diabetes [3,80]. Conversely, higher birth weight has been associated with lower incidence of coronary heart disease and stroke in adulthood [53], although it has been speculated that some of these data might be have been obtained from subjects born in the 1950s, when environmental circumstances were likely different (as previously discussed) for pregnant women and their children [53]. Still, another study revealed no increased risk of cardiovascular events after being born LGA to non-diabetic mothers [52]. It is tempting to speculate that these results reflect LGA cohorts from previous generations who were 'long and lean' at birth and, thus, with favourable long-term outcomes. The different underlying causes of LGA birth have probably led to the conflicting outcomes observed.

Conclusions

The balance of evidence indicates that being born LGA is now associated with an increased risk of later obesity, particularly in those born of obese/diabetic mothers. However, the data on long-term cardio-metabolic outcomes are conflicting, probably reflecting LGA subjects of contrasting phenotypes, with different nutritional environments *in utero* and in post-natal life. In addition, the group of LGA babies who remain fatter at the end of infancy are likely to have differences in adipocyte numbers/size together with epigenetic changes to metabolic genes. Birth weight alone is inadequate to assess infant body composition and size. More detailed anthropometric data at birth are necessary to better define body composition and the underlying etiology of increased birth size, as well as the long-term health risks.

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