The road between early growth and obesity: new twists and turns

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An association between low birth weight, indicative of restricted fetal growth, and increased metabolic and cardiovascular disease in later life was first noted in the seminal studies by Barker et al (1) and Hales et al (2) >20 y ago. These observations led Hales et al and Barker et al to propose the “thrifty phenotype” hypothesis, which suggests that poor fetal and postnatal nutrition imposes adaptations for nutritional thrift in an individual and that these adaptations predispose the individual to metabolic disease on exposure to plentiful nutrition later in life (3). The link between small-for-gestational-age (SGA) births and increased risk of cardiovascular disease and type 2 diabetes (T2D) is now well established, and the initial findings have been replicated in many studies worldwide incorporating many different ethnic groups. It has also become increasingly apparent that rapid postnatal “catch up” growth after SGA birth appears to exaggerate the effect of suboptimal growth in utero on risk of metabolic and cardiovascular diseases later in life (4). In addition, there is evidence that accelerated early postnatal growth, independent of growth in utero, is associated with increased cardiometabolic disease (5). The realization that such “programming” effects were not limited to only the fetal period led to what is now widely called the developmental origins of health and disease hypothesis (6).

Although an association between SGA birth and increased risk of cardiovascular disease and T2D is established, the link between fetal growth and adiposity is less clear. Early reports from the 1970s–1990s suggested that children born SGA consistently remain smaller and lighter than their appropriate-for-gestational-age counterparts (4). However, some more recent studies have reported a U-shaped curve between birth weight and adiposity and suggest that increased adiposity may underlie the later development of chronic metabolic diseases (7).

The disparity in findings from the aforementioned studies of fetal growth and adiposity may arise from the confounding impact of complex socioeconomic patterns of obesity in Western societies as well as differences in patterns of early postnatal growth. In this issue of the Journal, Kramer et al (8) present observations in a cohort of children from the nontraditional study setting of the Republic of Belarus. The study is unusual in its use of a cohort from a former Soviet-bloc country that is classified as middle income, where childhood obesity rates are lower than those seen in Western countries and socioeconomic patternng of obesity is different (9).

Kramer et al examined the effects of birth weight and growth during early infancy on adiposity outcomes at age 11.5 y. The authors report a dose-response relation between both birth weight and fetal growth with later adiposity, with SGA children remaining smaller and thinner and with reduced adiposity compared with their appropriate-for-gestational-age counterparts. When the cohort is grouped according to BMI at 11.5 y, SGA birth children contribute the least, whereas large-for-gestational-age children contribute the most, to the overweight and obese group, regardless of postnatal growth rate. The association between fetal growth and adiposity is amplified during childhood from 6.5 to 11.5 y, presumably due to persistent influences of the environment and genetics. This study also addresses the timely issue of the relative importance of fetal growth compared with growth during early infancy and finds the dose-response relation persists even in the presence of either “catch up” growth of SGA children or “catch down” growth of large-for-gestational-age children over the first 3–6 mo of life. It is notable that all children in this study were initially breastfed. This may be important because the timing of the catch-up growth may be critical in terms of effects on long-term obesity risk. There is some evidence that the most critical period is the first few weeks postnatally (5, 10).

Although this study provides invaluable information on the association between birth weight and later adiposity in a middle-income country, a major limitation of the study acknowledged by the authors is the exclusion of newborns with a birth weight <2500 g from the original cohort. Birth weight <2500 g is the classification officially used by the WHO to define SGA, and therefore this study unfortunately does not include individuals who would be considered by official guidelines to be severely growth-restricted. Thus, whether an association between more severe growth restriction and adiposity exists within the socioeconomic setting of a middle-income country remains unknown.

Whether the children within the Belarus cohort will develop other cardiovascular and metabolic phenotypes related to birth weight and infant growth as they age remains to be examined. However, any further phenotypes that develop will be independent of adiposity, and these initial findings thus rule out adiposity as an underlying cause of later metabolic disease in this cohort. The authors

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are currently analyzing the data from the children at age 16.5 y, and it will be interesting to see whether the onset of puberty affects adiposity outcomes, especially because there is some evidence that early growth and nutrition can affect the timing of puberty.

The authors wisely urge caution when extrapolating their results to other non-Western countries, particularly low-income countries where maternal and childhood malnutrition may affect growth and adiposity associations. However, it is clear from this study that socioeconomic factors have a strong influence on outcomes related to the perinatal environment, and this is something that must be considered when developing health guidelines based on proposed associations between fetal growth and adult disease risk.

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REFERENCES