

Size at Birth, Postnatal Growth and Risk of Obesity

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Key Words

Birth weight · Catch-up · Diabetes · Obesity · Weight gain

Abstract

Epidemiological studies over the last 15 years have shown that size at birth, early postnatal catch-up growth and excess childhood weight gain are associated with an increased risk of adult cardiovascular disease and type 2 diabetes. At the same time, rising rates of obesity and overweight in children, even at pre-school ages, have shifted efforts towards the identification of very early factors that predict risk of subsequent obesity, which may allow early targeted interventions. Overall, higher birth weight is positively associated with subsequent greater body mass index in childhood and later life; however, the relationship is complex. Higher birth weight is associated with greater subsequent lean mass, rather than fat mass. In contrast, lower birth weight is associated with a subsequent higher ratio of fat mass to lean mass, and greater central fat and insulin resistance. This paradoxical effect of lower birth weight is at least partly explained by the observation that infants who have been growth restrained in utero tend to gain weight more rapidly, or 'catch up', during the early postnatal period, which leads to increased central fat deposition. There is still debate as to whether there are critical early periods for obesity: does excess weight gain during infancy, childhood or even very early neonatal life have a greater

impact on long-term fat deposition and insulin resistance? Early identification of childhood obesity risk will be aided by identification of maternal and fetal genes that regulate fetal nutrition and growth, and postnatal genes that regulate appetite, energy expenditure and the partitioning of energy intake into fat or lean tissue growth.

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Introduction

Recent surveys report continuing secular trends in increasing rates of obesity in adults and young children [1], and childhood obesity has important consequences for morbidity and mortality in childhood and later life [2]. Prevention of obesity therefore requires the identification of factors that predict its very early development (table 1). Such studies will provide information about the aetiology of obesity and the potential development of early targeted interventions.

Relationship between Size at Birth and Size in Later Life

Overall, higher birth weight, adjusted for sex and gestational age, weakly predicts larger childhood and adult body size and body mass index (BMI). For example, in the East Flanders Prospective Twin Survey, each 1 kg

Table 1. Current opportunities to prevent childhood obesity and related disease risks

<i>Antenatal</i> Repeated screening and early intervention for gestational diabetes & hypertension (particularly in obese mothers) Generalized or targeted healthy lifestyle advice through routine healthcare contacts
<i>Infancy</i> Follow World Health Organization recommendations to encourage breast feeding and introduce complementary foods at 6 months
<i>Early childhood</i> Avoid excess weight gain Multi-disciplinary promotion of healthy lifestyle advice

increase in birth weight in males predicted a 3.3-cm increase in adult height, and a 4.2-kg increase in adult body weight [3], with similar findings being seen in females [4].

A different picture emerges, however, when we consider body composition (i.e., fat vs. lean body mass) and the distribution of body fat, which are more important determinants of obesity-related disease than body weight or BMI. In the East Flanders Prospective Twin Survey, adults with lower birth weights had relatively larger skinfold thicknesses and waist-to-hip ratios than individuals with higher birth weights [3, 4]. Similarly, in the third National Health and Nutrition Examination Survey (NHANES III, 1988–1994) children born small for gestational age (SGA, defined as a birth weight <10th percentile) remained slightly smaller than their peers [5]. However, on assessment of skinfolds and arm circumference measurements, their deficiency in size was found to be largely due to reduced lean tissue mass without a reduction in fat mass, and therefore they had a higher percentage of body fat [5].

Using dual-energy X-ray absorptiometry (DXA) in 70- to 75-year-old men and women, Gale et al. [6] also showed that low birth weight is associated specifically with reduced lean tissue mass. These abnormalities in body composition are greatly enhanced when low birth weight is followed by rapid postnatal weight gain. Gale et al. also showed that total body fat was highest in individuals with low birth weight and high current weight. Among men born in Hertfordshire and Preston, England, after adjustment for current BMI, mean waist-to-hip ratio increased with decreasing birth weight [7], and in a study of 14- to 16-year-old girls, the relationship be-

tween low birth weight and increased subscapular-to-triceps skinfold thickness ratio was especially seen in those who were overweight [8]. The adverse combination of low birth weight and increased postnatal weight gain on body composition is clearly demonstrated in Pune, India, where poor intrauterine growth is related to increased central fat at age 8 years in affluent urban children, but not in poorer rural children [9]. Finally, new data show that children born SGA who completed catch-up growth at the age of 2 years continued to accumulate excess central fat, as assessed by DXA, over the following 2 years, despite no further catch-up in overall height or weight [10].

Infant Weight Gain and Later Obesity Risk

Infants with low birth weight have a predisposition to gain weight rapidly during the first 2 years of postnatal life; this particularly applies to infants who were growth restrained in utero, for example due to maternal smoking or a primiparous pregnancy [11]. As described above, this rapid postnatal weight gain contributes greatly to adverse body composition. Larger epidemiological studies have also confirmed that rapid postnatal weight gain contributes to later obesity risk. A recent systematic review identified 13 articles that associated rapid weight gain from birth with risk of overweight or obesity at age 3–70 years. Despite the different definitions used, all 13 studies found significant associations between infant weight gain and later obesity risk [12].

These observational findings are further supported by the long-term follow-up of randomized feeding trials in nasogastrically tube-fed preterm infants, which report that greater dietary energy content may have remarkable adverse effects on body size and risk of developing metabolic disease later in life [13, 14]. Intriguingly, these studies, in which the nutrient exposure was delivered only during the first four weeks of life, raise the question as to how such short-term nutrition may have such long-term effects.

Infant Diet and Appetite

A recent study has shown that infants at higher risk of obesity had higher energy intakes and different sucking behaviours than infants at low risk, but there was no difference in total and non-sleeping energy expenditure [15], indicating that during infancy, diet may have a greater

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impact on nutrient balance and hormone responses than energy expenditure. In another recent report, dietary energy intake assessed in bottle-fed infants at the age of 4 months predicted infant weight gain and childhood BMI [16]. Beneficial effects of breast feeding on avoiding excess infant weight gain, childhood obesity and higher blood pressure have also been described [11, 17, 18].

Novel neonatal actions of leptin that may programme long-term appetite in rodents have recently been described [19, 20]. Both models explored the observation that in utero growth restriction due to maternal undernutrition results in increased susceptibility to gain weight and fat mass in response to a postnatal high-fat diet. In antenatally undernourished rats, Vickers et al. [19] demonstrated that neonatal leptin treatment, from postnatal day 3 to day 13, transiently slowed neonatal weight gain and normalized long-term caloric intake, locomotor activity, body weight, fat mass and fasting plasma glucose, insulin and leptin concentrations. In a very different study design, Yura et al. [20] observed that antenatally undernourished mice exhibited a premature onset of the normal neonatal leptin surge (days 8–10 compared with day 16). They then artificially induced a similar premature leptin surge in mice with normal birth weight, which went on to exhibit accelerated weight gain and leptin resistance.

In humans, studies of rare monogenic obesity clearly show that genetic factors, particularly in the leptin signalling pathway, may have a major influence on infant appetite [21]. However, there is no evidence yet as to whether a postnatal leptin surge is present in humans, let alone subject to long-term alteration by infant nutrition. Recently, it was reported that remarkably high rates of weight gain during the first week of life was independently associated with overweight in adulthood [22]. This finding certainly indicates that much future research is needed to understand the mechanisms that regulate infant and subsequent postnatal appetite.

Childhood Weight Gain and Later Obesity Risk

There is still debate as to which is more detrimental to long-term obesity risk: rapid weight gain in infancy or in early childhood [23]. A preliminary report of one study compared the effects of weight gain in infancy with that in early childhood on adult BMI and fat mass [24]. Both time periods had similar important effects on later obesity risk, but there was less variance during early childhood and, therefore, infant weight gain explained more

of the variation in adult fat mass. Another recent study, using skinfold thicknesses in 9-year-old Brazilian children, reported that infant weight gain predicted greater BMI but not fat mass at age 9 years; in contrast, rapid weight gain between 1 and 4 years of age was associated with increased fat mass at 9 years of age [25]. In that study, the whole population showed significant gains in weight SDS compared with the growth reference. Therefore, in certain populations, or with changing 'obesogenic' lifestyles in early childhood such as increased consumption of high-fructose corn syrup drinks, early childhood may also represent a critical period for the development of obesity, and interventions to prevent excess weight gain at this later age will have a beneficial effect on long-term obesity risk. However, it remains uncertain whether rapid infant and childhood weight gain have similar impacts on the risk of developing specific metabolic disease markers.

The Obese Mother

Obese mothers are four times more likely to have obese children; the risk rises to over tenfold if the father is also obese [18]. Whether driven by genetic or behavioural factors, much of this risk is due to excess childhood weight gain, rather than to increased adiposity at birth ([26] and Hany Laschen, unpublished data). In contrast, in one study, increased risk of cardiovascular disease in the offspring was highest when maternal obesity plus thin offspring size at birth were combined [27]. This could reflect offspring with in utero growth restraint due to maternal gestational hypertension, which can be up to fivefold higher in mothers who were obese prior to pregnancy than in non-obese mothers. Offspring of such mothers may be expected to show postnatal catch-up weight gain.

Particular risk factors for obesity and poor long-term health in offspring may also be associated with obese mothers who have gestational diabetes. Compared with offspring of non-diabetic obese mothers, offspring of mothers with gestational diabetes have increased fat mass at birth, but no difference in lean mass [28], and on follow-up they have an increased risk of type 2 diabetes due to the dangerous combination of persisting increased adiposity, insulin resistance and reduced beta-cell capacity [29, 30]. Therefore, particularly among populations with a high predisposition to type 2 and gestational diabetes, an association emerges between large birth weight and risk of type 2 diabetes in the offspring, and combined with

the established risks of low birth weight, results in a U-shaped birth weight association [31].

Conclusion

Attempts to prevent childhood obesity and its long-term health consequences need to start very early. Obese mothers are much more likely to have obese children, and routine antenatal healthcare should be seen as an opportunity for education with regard to healthy lifestyle choices for the whole family. Particular risks are associated with obese mothers who have gestational diabetes, and also gestational hypertension. As these conditions are increased in obese mothers, particular efforts should be made to screen, monitor and intervene early in these individuals.

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