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Review

Childhood obesity: rapid weight gain in early childhood and subsequent cardiometabolic risk

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Abstract. Dynamic changes in body weight have long been recognized as important indicators of risk for human health. Many population-based observational studies have shown that rapid weight gain during infancy, including a catch-up growth phenomenon or adiposity rebound in early childhood, predisposes a person to the development of obesity, type 2 diabetes, and cardiovascular diseases later in life. However, a consensus has not been established regarding which period of weight gain contributes to future risks. This review evaluates recent evidence on the relationship between early rapid growth and future obesity and cardiometabolic risk, with a focus on the differential significance of rapid weight gain in infancy and early childhood. Although there is a need for attention to childhood growth during early infancy before 1 yr of age as it may be related to future obesity, emerging evidence strongly suggests that toddlers showing an increase in body mass index (BMI) before 3 yr of age, a period normally characterized by decreased BMI, are prone to developing later cardiometabolic risk.

Key words: obesity, rapid weight gain, catch-up growth, adiposity rebound, cardiometabolic risk

Introduction

Obesity is a public health concern worldwide. The most common cause of obesity in children is a positive energy balance due to caloric intake higher than caloric expenditure combined with a genetic predisposition for weight gain (1). While the rate of increase in the overall prevalence of childhood obesity in the developed world has slowed or plateaued (2–4), the most severe and recalcitrant form of obesity has increased progressively (5). In the United States in 1999–2004, almost 4% of children and adolescents of 2–19 yr of age were classified as severely obese, and as recently as 2011–2012, the prevalence of severe obesity increased to approximately 6% in this age group (5, 6). Inokuchi *et al.* (7) suggested a generally recognized increased prevalence of central fatness in Japanese youth aged 6–17 yr, and central fatness associated with severe obesity is linked to adverse metabolic and cardiovascular complications. Therefore, childhood obesity has led to the emergence of multiple obesity-related comorbidities and future cardiovascular diseases (8–12).

The term cardiometabolic risk refers to the possibility of damage to heart and blood vessels when 1 or more risk factors, including obesity, dyslipidemia, high blood pressure, insulin resistance, and type 2 diabetes, are present (13). Cardiometabolic risk factors are associated with bodyweight: the greater the severity of obesity, the higher the risks of a low high-density lipoprotein (HDL) cholesterol level, high triglyceride and insulin levels, and high systolic and diastolic blood pressures (13, 14). A 55-yr follow-up in the Harvard Growth Study showed that being overweight in adolescence resulted in a 2-fold higher risk of coronary heart disease mortality, independent of adult weight (15).

There is increasing evidence that the path to obesity is established early in life, and several early risk factors for obesity have been identified in systemic reviews of observational studies (16–18). Recently, it was suggested that rapid childhood growth or rapid weight gain during infancy through mid-childhood was associated with the future risk of obesity (10, 20). In developing a strategy for prevention of obesity and cardiometabolic risk from early childhood, identification of the period of rapid weight gain (infancy or toddlerhood) is important because this process may constitute a risk factor for subsequent

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adiposity and metabolic complications (21, 22).

This review evaluates recent evidence on the relationship between early rapid growth and future obesity and cardiometabolic risk, with a focus on the differential significance of rapid weight gain in infancy or early childhood.

Assessment of Rapid Weight Gain

Rapid weight gain (rapid growth) in infancy and early childhood is thought to be a predictor of increased risk of obesity in later life (1, 19). On average, weight decreases within the first 7–14 d after birth; then, it increases rapidly until about 6 mo of age and thereafter, increases at a reduced rate. The body fat content of a healthy full-term infant rises sharply from 10 to 14% at birth to 25 to 30% at 6 mo of age. Length increases quickly in the first few months, and thereafter, the rate of increase reduces (23, 24). Body mass index (BMI) increases from birth to late infancy, after peaking at 6 to 12 mo of age (the so-called infant BMI peak), the BMI then normally declines to a nadir at 5–6 yr old and then "rebounds", rising progressively throughout late childhood and adolescence. This transition from a decrease in BMI to an increase is referred to as the adiposity rebound (AR), and an early or exaggerated AR portends an increased risk of obesity in later childhood and adolescence (1).

Most longitudinal studies on the later outcomes of early weight change use metrics to identify growth beyond that anticipated from growth charts. A common metric is a change in weight for age ≥0.67 SD seen in the first 1–2 yr of life (24, 25). This is referred to as the "upward crossing of the SD line or percentile line", "rapid infant weight gain", or "catch-up growth" (26). These changes can be visually confirmed on the growth chart for Japanese children (27).

Adiposity Rebound

Early adiposity rebound

The phenomenon of AR is described above. In 1984, a French study by Rolland-Cachera first noted that early rebounders (before 5.5 yr old) had substantially higher adiposity at 16 yr than those who rebounded later (28). This finding has been replicated in other studies (29, 30). In Japan, in 2003, the first population-based study on AR showed that a rapid increase in BMI from 4 yr of age onwards was associated with later obesity (31).

AR may represent a critical window of development or may simply be an epiphenomenon of early rebound of BMI occurring in children who were already in higher BMI percentiles (32–34). Previous studies have looked at the BMI pattern of the percentile curves constructed cross-sectionally, whereas studies using longitudinal data have shown that many children with early AR had a normal or even low BMI at or before the AR, independent of BMI at AR age, followed by an increased BMI after AR (29, 34–36).

Moreover, whether the later high BMI in early rebounders reflects high fat or high fat-free mass has been a matter of discussion. Evidence suggests that it is mainly attributable to high fat (37, 38), with early rebounders having a higher fat mass in adolescence as measured by dual-energy X-ray absorptiometry than late rebounders (39). In a review, Taylor *et al*. (40) concluded that changes in BMI during AR occur due to the high velocity of weight gain, which in turn is due to rapid deposition of fat rather than fat-free mass, with early rebounders gaining fat mass at around 3 times the rate of late rebounders.

In the ALSPAC study (16), the adjusted odds ratio for obesity at age 7 yr was 15 for children with very early AR (before 3.5 yr) compared to those with late AR (after 5 yr). In other studies, early AR has been linked to other components of metabolic syndrome, including insulin resistance (41, 42), type 2 diabetes (43), dyslipidemia (41, 44), and elevated blood pressure (44). Additionally, an early rebound was associated with early menarche in girls, suggesting that the timing of AR is an indicator of physical maturity (45).

Furthermore, there is evidence that AR currently occurs earlier than in the past, and it has been argued whether this shift is due to the obesity epidemic or a secular trend of accelerated growth and pubertal development (46, 47). The strongest determinant of AR onset appears to be maternal BMI, with early rebounders having heavier mothers (48). In others, excessive rebound results from dietary indiscretion and/or sedentary behavior at toddler age (35, 48, 49). Breastfeeding in infancy may delay and reduce the magnitude of AR (49), with some investigators postulating that the low protein content of breast milk (compared with infant formula) reduces circulating levels of insulin and insulin-like growth factor-I and thereby limits adipogenesis and fat deposition (50, 51).

A recent long-term study showed that age at AR was associated with nutritional status and metabolic syndrome in adulthood (20–60 yr old) (52). Therefore, the identification of factors that influence the timing of AR should improve our understanding of the early pathways for the development of obesity and impaired cardiometabolic health.

Late adiposity rebound

The phenomenon of early AR is well-documented, but the clinical significance of late AR is not fully understood. Recently, Moon (53) reported that late AR (≥7 yr) was significantly associated with a decreased risk of developing obesity in a representative national cohort that included 31,316 children, from early childhood longitudinal studies of kindergarten classes of 1998–1999 and 2010–2011. Moreover, in an analysis of 217 children aged 12 yr, the relationships among the timing of AR (early vs. late: <3 vs. ≥7 yr), the timing of puberty, BMI, and plasma lipid profiles were evaluated. The results

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showed that pubertal timing was approximately one year delayed in both sexes with late AR compared to those with early AR, and serum lipid profiles were less atherogenic in children with late AR than in those with early AR. Thus, late AR was associated with delayed pubertal maturation and reduced cardiometabolic risks (54).

Energy demand of the brain and adiposity rebound

Kuzawa and Blair (55) recently proposed a remarkable hypothesis linking the energy demand of the brain to obesity risk. The brain consumes about 40% of daily energy expenditure in early childhood (compared to 20% for adults), and glucose alone cannot supply this energy. Therefore, ketone bodies generated in the liver from body fat are used as an energy source for brain development. This means that brain energy expenditure is inversely related to body fat gain. Thus, this hypothesis states that brain energy expenditure helps to explain variation in the timing of AR (55, 56).

Infantile Obesity

Although the long-term health relevance of body composition in infancy has not been extensively studied, multiple longitudinal observational studies have shown that rapid weight gain in infancy is associated with an increased risk of obesity. In a systemic review of 21 studies, Ong and Loss (57) concluded that rapid weight gain during infancy (up to 2 yr) is consistently associated with subsequent obesity risk. Taveras *et al.* (58) found that upwards crossing of 2 major weight-for-length percentiles during the first 6 months of life was more predictive of obesity at age 5 and 10 yr than were crossings during later age intervals. Ekelund *et al.* (59) showed that the risk of metabolic syndrome was predicted by rapid weight gain during infancy (0–6 mo). These reports caused infant obesity to be perceived as a condition requiring countermeasures due to the risk of future obesity and metabolic disorders (60–62).

Against the views described above, the association between infant growth and overweight status in later life has been disputed by subsequent studies that extended the observation period for weight gain. To assess the predictive ability of infant weight gain on subsequent obesity, Druet *et al.* (63) performed a meta-analysis of individual-level data for 47,661 participants from 10 cohorts and concluded that weight gain from birth to 2 yr had a stronger association with the risk of obesity in schoolchildren than weight gain from birth to 1 yr (odds ratio 2.46 vs. 1.96, respectively). In a longitudinal cohort study, Liem *et al.* (64) found that large relative increases in weight from 2 to 7 yr were associated with adolescent adiposity and metabolic syndrome. Sovio *et al.* (65) showed that early AR was a risk factor for an adverse cardiometabolic profile independently of early growth or BMI at rebound.

In a study in Japan, in which Sugiura *et al.* (66) tracked infantile obesity, the weight gain velocity of patients with infantile obesity declined until the age of 6 mo and subsequently, was constant from 7 mo onwards, suggesting that early infantile obesity is less likely to lead to later obesity. In our birth cohort, we found no association between weight gain during infancy (0–12 m) and timing of AR. Therefore, we concluded that infantile overweight or obesity was not a risk for future obesity or metabolic syndrome (67).

The controversy over whether the risk for later obesity was associated with obesity during infancy or early childhood was ended by a report from Germany in 2018 (68). In a retrospective analysis of 34,196 children (0–18 yr), Geserick *et al.* (68) found that among the adolescents who were obese, the greatest acceleration in annual BMI increments occurred between 2 and 6 yr of age, with a further rise in BMI percentile thereafter. Therefore, it was concluded that the critical age for the development of sustained obesity is during early childhood, which includes the period of AR and not in infancy (68, 69).

Although infant obesity is unlikely to lead to future obesity, infants born as large for gestational age (LGA) due to maternal obesity or gestational diabetes should be considered as exceptions. These infants have difficulty losing weight during infancy, and there is a risk of infant obesity leading to early childhood obesity (70, 71).

Catch Up Growth

There is an increasing interest in the long-term adverse effects of the recovery phase of growth or "catch-up growth (CUG)". CUG was first defined as acceleration in growth in response to recovery from illness or starvation (72–74). This concept was extended to include children who were born small for gestational age (SGA) and showed rapid post-natal growth, a phenomenon assumed to be CUG due to recovery from undernutrition *in utero* (26, 75).

The benefits of CUG for later neurodevelopment favors the promotion of rapid growth in infants born preterm; however, CUG in infants born at term (normal or low birth weight for gestation) is likely to have adverse effects on long-term health (75). Children born with low birth weight or SGA have an increased risk for non-communicable diseases (NCDs) such as type 2 diabetes and cardiovascular disease later in life, as illustrated by the concept of Developmental Origins of Health and Disease (DOHaD) (76–80). Poor maternal nutritional status or smoking during pregnancy are major causes of intrauterine growth restriction (76, 77).

General mechanism of CUG

Weight recovery or CUG is primarily driven by energy conservation (thrifty) mechanisms operating via suppressed thermogenesis; in this case, the sympathetic nervous system is suppressed to reduce energy

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expenditure. Independent of the timing, the dynamic process of CUG is characterized by a disproportionately faster rate of fat deposition than that found in lean tissue. This phenomenon of preferential catch-up of fat is intimately associated with the development of insulin resistance and leptin resistance (72, 81). The resulting compensatory hyperinsulinemia serves to redirect glucose spared from oxidation in skeletal muscle toward *de novo* lipogenesis and fat storage in white adipose tissue (72, 81). Leptin resistance causes hunger and reduces energy expenditure by suppressing the sympathetic nerve activity (82).

CUG in SGA infants

Leunissen *et al*. (83) found that SGA infants with rapid weight gain in the first 3 mo of life had lower insulin sensitivity and HDL-cholesterol and higher triglyceride levels at age 18–24 yr, than SGA infants without CUG who had no adverse effects. Additionally, this was observed in animal models (84). Notably, catch-up weight gain in SGA children is associated with visceral fat deposition, insulin resistance, hyperinsulinemia, and hypoadiponectinemia (85, 86). Therefore, promoting CUG by nutritional supplementation in SGA infants from high-income countries is unlikely to have advantages for long-term health (75, 87).

Insulin resistance acquisition in SGA infants

In a prospective study, Soto *et al*. (88) found that the fasting insulin concentration at 1 yr was significantly higher in SGA infants with CUG than in those without CUG and with appropriate for gestational age (AGA) infants. These data indicate that the pathophysiological mechanisms linking prenatal growth and postnatal sensitivity to insulin are present as early as 1 year. Furthermore, in a recent prospective follow-up study, blood cord insulin levels at birth were lower in SGA infants than in AGA infants, but plasma insulin levels at 3 yr of age in SGA infants with CUG were higher than that in SGA infants without CUG and AGA infants, indicating that insulin resistance in SGA infants may develop after birth (89).

Optimal weight gain in SGA

The optimal weight gain pattern in the first 2 yr of life for term SGA infants has not been fully investigated (75). Data from a longitudinal, community-based cohort study on growth and development of SGA infants collected from 2004 to 2010 in Shanghai suggested that for term SGA infants, CUG crossing two centile levels (from <10th to the interval between 25th and 50th) in the first few months, along with on-track growth and maintenance at a median level by age 2, maybe the optimal CUG trajectory that minimizes the risk of adverse health outcomes in childhood (90). Monitoring and ensuring optimal CUG starting from birth may be the first step towards the prevention of childhood adverse outcomes (50, 92). Breastfeeding is recommended to achieve this moderate growth during infancy because breastfed infants are relatively undernourished and grow more slowly than those fed formula milk (50, 91).

Relationship between CUG and AR

In some SGA infants, the boundary between CUG and AR is indistinguishable (72). Maeyama *et al*. found that approximately 7% of SGA children developed AR before 3 yr (92).

Sexual Dimorphism

Sexual dimorphism may account for the effect of fat distribution during infancy on cardiometabolic risk factors (93, 94). A children's cohort study in Australia showed sex differences in the relationship between early childhood obesity and subsequent metabolic risk clustering in young adult life; females destined for higher metabolic risk as young adults show higher skinfold thickness from 1 yr of age than corresponding males in whom measures of growth and adiposity were not distinguishable until 3–5 yr old (95).

Gender may play a role in how childhood growth trajectories influence subsequent obesity. Some evidence suggests that girls tend to experience AR earlier than boys, particularly in the high BMI percentiles, whereas other studies have found negligible or nonexistent gender differences (96). In the analysis of our birth cohort, it appeared that girls with an increase in BMI before 3 yr were more prone to develop insulin resistance at 12 yr than boys. Therefore, an increase in adiposity during early growth periods might be of long term relevance for altered insulin sensitivity to adiposity, particularly in girls (97).

Studies on human fetal programming of metabolic risk factors indicate that low birth weight is associated with increased cardiovascular disease in males and females, but females show an additional association of high birth weight with subsequent cardiovascular risk. This suggests that males are more susceptible to low birth weight than females and females are more susceptible to high birth weight than males during fetal programming (98).

Early Prediction of Future Cardiometabolic Risk

Among various anthropometric indices of obesity (99), the waist-to-height ratio is thought to be the best predictor to identify adolescence with a cardiometabolic risk associated with excess visceral fat (100). However, this risk can be reversed if individuals attain a low level of adiposity by adolescence or avoid becoming obese. Identifying children at high risk of developing obesity would allow preventive and intervention efforts to be initiated at an early life-stage (101, 102).

In our cohort, we showed that, as compared to a stable or decreased BMI, a BMI increase from age 1.5 to 3.0 yr was related to increased insulin resistance at 12 yr of age, even if BMI is in the normal range just before this increase (103). These data were obtained during follow-up at 1.5 and 3.0 yr, which included weight and height measurements, as defined by the Ministry of Health, Labour and Welfare in Japan.

This finding suggests that children with a BMI increase before 3 yr, a period normally characterized by decreased BMI, are more prone to developing insulin resistance in adolescence (102, 103). Similarly, Aris *et al*. (104) reported that the risk of future obesity was increased if BMI did not decrease between the ages of 1 and 3. Another population-based longitudinal study in Japan showed that AR before 3 yr of age with low pre-rebound BMI increased the risk of obesity among preschool children (105).

Conclusions

This review considered the specific evidence for the developmental origins of obesity and related cardiometabolic risk and the mechanisms involved, with a focus on the relationship between rapid weight gain in early childhood and future cardiometabolic risk. There is a need for attention to early infancy before 1 yr of age as an element of childhood growth that is related to future obesity, especially for low birth weight infants who present with accelerated CUG. However, rapid weight gain (a growth pattern showing an increase in BMI) in toddlerhood from 1 to around 3 yr is significantly related to subsequent cardiometabolic risk. Recognition of these growth patterns may help to identify high-risk children at an early age and permit tailored intervention that may prevent future cardiometabolic diseases.

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