Chapter 28
Infant Growth and Adult Obesity: Relationship and Factors Affecting Them

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Key Points

- An early life component is increasingly being recognised in the aetiology of obesity.
- Many epidemiological studies have shown that early weight gain, infant overweight and infant obesity are associated with overweight and obesity in later life.
- There is a prevailing diversity on the definitions of exposures which limits the interpretation of a postulated prognostic association between isolated infant size estimates and adult obesity.
- The available accumulated evidence in the field fails to answer important public health questions and support clinical decisions, the most important being the exact timing for overweight/obesity screening.

Keywords Infant growth • Obesity • Developmental origin of disease hypothesis • Birth size • Epidemiological methods

Introduction

Obesity reflects the energy imbalance between calorie consumption and expenditure leading to abnormal body weight with direct negative consequences on human health. Obesity is considered today a pandemic since its prevalence has more than doubled since 1980 worldwide [1]. It increases the risk of chronic diseases such as type 2 diabetes, cardiovascular disease, musculoskeletal disorders, and some cancers, and it is the fifth most important risk factor of death globally. The underlying causes

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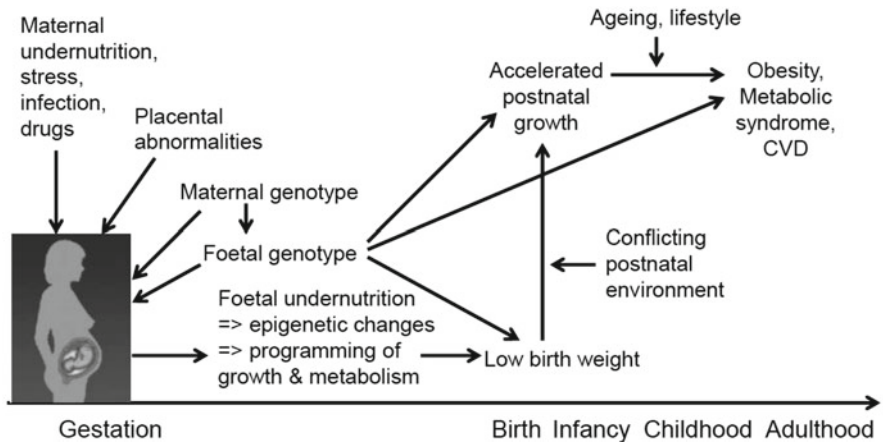

Fig. 28.1 Developmental Origins of Health and Disease (DOHaD) hypothesis. Adapted from Ozanne and Constancia [25]

contributing to the rising prevalence of obesity are complex and involve societal and environmental risk factors such as urbanisation and changing modes of work and transport as well as various individual risk factors. An early life component is increasingly being recognised in the aetiology of obesity [2, 3] being of major potential importance for public health strategies' guidance. Patterns of growth associated with low birth weight and increased weight gain in childhood, as well as low birth weight per se, have shown inverse associations with obesity and related disorders such as insulin resistance, diabetes, and cardiovascular disease in adulthood [4–7]. In addition to birth weight and childhood growth trajectories, immediate postnatal growth has received considerable attention in the medical literature. This is the period of the fastest growth in the entire life span and is a critical window of tissue and organ development wherein several regulatory mechanisms continue to develop after birth [8]. Thus, variations in this process may have long-lasting effects on health. Several studies have examined weight changes between birth and the first years of life; results have suggested that weight gain is associated with childhood, adolescent, and adult obesity and with higher levels of cardiovascular and metabolic risk factors [9, 10]. There is also evidence that increased growth velocity in first years of life is associated with obesity and metabolic outcomes in adulthood [3, 11]. However, the majority of those studies use different definitions of postnatal growth and obesity, as well as of surrogate metabolic outcomes, which poses challenges in synthesising the available evidence in order to draw firm conclusions. Here we attempt to summarise the biological basis, which may explain the association between postnatal growth with later onset of obesity. We also aim to present the main evidence from observational studies, which examine associations between postnatal growth and obesity and focus on the main methodological limitations associated with this research area. We will focus our description on human studies; however, there is a large body of literature examining early life programming in animal models.

Biologic Plausibility

The association between small size at birth and higher risk of adult disease, such as type 2 diabetes and cardiovascular, has been consistently reported [12]. The foetal origins of adult disease hypothesis was first introduced by Barker [13] and was later named Developmental Origins of Health and Disease (DOHaD) hypothesis [14] (Fig. 28.1). It can be placed within a wider framework of life course approaches to chronic disease epidemiology. In this framework, the DOHaD hypothesis has a close relationship with the critical period model that includes later life effect modifiers [15]. Here we describe hypothesis

that have been suggested to explain association between birth weight and early life growth with obesity and related disorders including type 2 diabetes and cardiovascular disease.

Hypotheses Explaining Inverse Association Between Birth Size and Adult Disease

There are two main hypotheses that have been put forward to explain the observed inverse association between small size at birth and adult disease: (1) foetal programming i.e. the thrifty phenotype hypothesis and (2) genetic susceptibility hypothesis, which proposes pleiotropic genetic effects for foetal and adult phenotypes or traits [16]. The idea of programming induced by foetal undernutrition was originally implied as an explanation behind the statistical associations between small size at birth and adult disease [13] and it is often included in the definition of the Barker or DOHaD hypothesis. The foetal programming hypothesis emphasises the environmental and the foetal insulin hypothesis the genetic influences behind the association between foetal growth and adult disease. The environmental effects may include maternal undernutrition and other maternal or placental abnormalities leading to foetal undernutrition, hormonal effects such as increased administration of natural glucocorticoids from the mother to the foetus during stress, and/or accelerated postnatal growth followed by restricted foetal growth. The foetal programming hypothesis proposes that the adaptive response of the foetus to the in utero environment at "critical periods" of development leads to permanent changes in its body structure, physiology and metabolism [13]. As an alternative mechanism, it has been suggested that pleiotropy may explain at least part of the association between the foetal and adult phenotype. In particular, the foetal insulin hypothesis proposes an insulin-resistant genotype which leads to both smaller size at birth and to an insulin-resistant phenotype in adulthood, increasing the risk of T2D and related diseases [16].

Foetal Undernutrition

The hypothesis of foetal programming due to undernutrition postulates that the adverse conditions in the intrauterine environment cause the foetus to optimise the use of energy to guarantee its survival. This kind of adaptation, allowed by developmental plasticity [17], has short-term benefits (survival of the foetus) but detrimental permanent effects to the growth and function of the tissues, which later increase the risk of obesity, type 2 diabetes and cardiovascular disease [18, 19]. However, maternal undernutrition is not common in Western societies [20] where most of the research on this topic has been done. In these countries, the function of placenta plays a more important role. However, the associations between absolute or relative measures of placental weight and type 2 diabetes and cardiovascular disease have been inconsistent [18]. Pre-eclampsia as an extreme form of placental dysfunction seems to be associated to cardiovascular disease in the mothers and a higher blood pressure in the offspring; however, the potential role of genetic factors in this association remains unclear. In their review, Jaddoe and Witteman [18] conclude that there is no strong evidence for the foetal programming hypothesis by foetal undernutrition from the existing studies.

Maternal Stress and Glucocorticoids

An increasing problem among pregnant women especially in the Western societies is social stress due to career demands, financial uncertainty and a low level of support from family [20]. Glucocorticoids belong to steroid hormones and the most important one of them in humans is cortisol. Stress during

pregnancy causes plasma glucocorticoid levels to rise in the mother. It is also known that administration of glucocorticoids during pregnancy leads to lower birth weight of the baby. The babies with decreased birth weight have increased cortisol levels throughout life, which may be explained by the programming of the function of the hypothalamic-pituitary adrenal axis (HPA), which is sensitive to glucocorticoids [21]. In particular, placental 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2) enzyme inhibits glucocorticoids by converting maternal cortisol to inactive cortisone. Reduced placental 11βHSD2 is associated with both lower birth weight and higher blood pressure in later life in the offspring [22]. Studies in knockout mice support these findings [23]. It has been suggested that the molecular mechanism that underlies the programming may include epigenetic changes which could be passed on to subsequent generations without further exposure [24].

Epigenetic Modifications

In the recent years, increasing amount of research has focused on the role of epigenetics in DOHaD [25, 26]. Epigenetic modifications, including DNA methylation and histone modifications, regulate gene activity without affecting the DNA sequence. For example, in mammals, parent of origin effects on gene expression and X-chromosome inactivation in females can be observed. The early foetal period after conception has been identified as a critical window for the establishment of DNA methylation patterns, and at a later stage, tissue-specific patterns of epigenetic modifications have been shown in organisms [27]. There is an increasing body of evidence, mainly from animal models, suggesting that epigenetic changes due to early environmental factors have an important role in later disease susceptibility (see reviews of these studies in Ozanne and Constancia [25] and Gluckman et al. [26]). Imprinted genes, whose effect on gene expression is parent-specific, provide good candidates for the search for genes involved in developmental programming through epigenetic modifications. Some evidence already suggests the involvement of imprinted genes in growth and metabolism [25].

Growth Acceleration

The growth acceleration hypothesis postulates that the foetal growth restriction relative to genetic growth potential could result in compensatory postnatal growth acceleration which is responsible for the higher risk of adult disease [27]. Accelerated growth is often linked to the nutritional environment during infancy [28]. Animal studies, in which the perinatal environment can be manipulated, have reported that early life nutritional experiences different in quantity or quality of nutrition are associated with obesity and a higher metabolic rate in adulthood [8] as a result of tissue remodelling, changes in cell differentiation, organ growth, and cell signalling [3, 29–31]. Postnatal nutritional excess, has been shown associations with chronic increase in leptin levels, which is further associated with obesity [32].

Genetic Susceptibility

The foetal undernutrition, glucocorticoid and growth acceleration hypotheses all imply foetal or postnatal programming. The genetic susceptibility hypothesis has recently gained some support as an alternative hypothesis for the mechanism underlying the association between birth size and adult disease. The foetal insulin hypothesis, which specifically postulates a genotype producing small, thin

babies and insulin-resistant adults, relies on the importance of foetal insulin secretion as a key factor in foetal growth particularly in the third trimester of pregnancy [16]. The evidence for this hypothesis at the time it was presented came from studies on rare monogenic variants that were associated with both low birth weight and altered insulin secretion or resistance later in life. Twin studies examining this hypothesis have overall been inconclusive and population-based genetic association studies conducted before the genome-wide era have produced conflicting results [18]. However, recent studies have indicated that at least part of the association between low birth weight and type 2 diabetes in particular may be explained by common genetic effects [33, 34]. An age-dependent association between variation at the FTO locus which is associated with obesity and type 2 diabetes, and body mass index (BMI) in children has also been suggested [35].

Synthesis and Future Research

It remains still unclear which of the suggested mechanisms has the best explanatory power for the association between birth size and early growth and adult obesity and disease. It is likely that none of them is adequate in itself but several mechanisms operate simultaneously [16]. The role of different mechanisms may vary between different adult trait or diseases studied. Therefore, further studies on these mechanisms are warranted. It is important to design epidemiological studies in a way that allows the examination of these mechanisms in conjunction with each other. Such study design would be a prospective, population-based cohort study on a large number of subjects with a follow-up of their growth and health frequently from pregnancy until adulthood [18].

Methodological Challenges in Examining Early Life Effects on Adult Obesity

The research agenda of early life effects on adult obesity and its consequences is a complex system of associations exhibiting a spectrum of interactions ranging from completely independent to highly correlated associations. Each association represents an individual research question that is typically approached through observational studies, birth cohort studies in their majority. Delineating fundamental aspects of this system of associations will eventually lead to specific clinical research questions which have been and will be pursued through intervention-based hypothesis-testing under rigorous clinical trials' designs with the ultimate goal of the effective prevention of the long-term detrimental consequences of obesity. Deciding upon the specific association that best addresses the research question under study is a complex endeavour involving serious considerations on all study design aspects, including and not limited to the population and outcome under study and definitions thereof, as well as the early life parameters investigated and definitions thereof. Variations of a postulated identical research question can produce surprisingly different study results due to a number of reasons ranging from a different biological background to bias-proned outcome and exposure definitions. Examples of different obesity definitions are obese, overweight, BMI as a continuous outcome, other BMI trajectories, BMI combined with hip-to-waist ratio, BMI associated with metabolic syndrome, etc. comprising a long list of proposed approaches for a major public health issue. Similarly, examples of different exposure definitions include BMI at 2 years, BMI at 1 year, weight gain over the first 2 years, growth velocity, catch-up growth, etc. compromising a long list of exposures that might be tested in association with later overweight and obesity. In fact, postnatal growth itself has a long list of definitions with many studies using smoothing or regression cubic splines in order to model growth—such models are easy to fit but the interpretation of parameters poses challenges—while others have chosen standard parametric approaches to model longitudinal growth—this has the advantage of natural biologic interpretability of

the parameters [3]. Another considerable concern regarding this field is whether reverse causation issues prevail. Are the observed phenotypes related to early growth patterns a proxy of the final adult obesity phenotype—confounded by factors that influence both postnatal weight gain and later adiposity—and any intervention would actually simply suppress the presentation of the underlying disordered pattern of metabolism or modifying growth patterns associated with adult obesity would truly affect the natural history of the disease? Standard regression techniques, which have been used to address the aforementioned hypothesis, have limitations and are often inadequate in addressing these research questions. Reparameterisation of a multiple regression analysis can change the interpretation of the model's results while regression models are usually hindered by collinearity problems. Other techniques such as latent class and path analysis have been proposed to address many of these issues but still are infrequently used in the literature [32].

Overview of the Currently Available Evidence

Many epidemiological studies have examined associations between size at birth, infancy and growth with later measures of obesity in childhood adolescence and adulthood. Here we summarise the evidence from epidemiological studies focusing on studies, which examine association between early size and growth with overweight and obesity in adulthood. We retrieved information from the latest available systematic reviews as well as large (arbitrarily set as of a sample size larger than 1,000 participants) observational studies subsequently published in the field.

Birth Weight and Adult Obesity

Many studies have examined the association between birth weight and later BMI and have shown positive but weak associations between higher birth weight and higher BMI in adulthood [36]. For example, the Health Professionals Follow-Up Study collected self-reported information on birth weight and current height and weight for 51,829 middle-aged men [37]. The OR for being in the highest vs. the lowest age-adjusted BMI quintile was 2.08 (1.73–2.50) for men with a birth weight of over 4.5 kg, and 0.75 (0.66–0.84) for men with a birth weight between 2.5 and 3.1 kg compared to the reference category of 3.2–3.8 kg. A similar analysis was performed in the Nurses Health Study, which had information on 71,100 women aged 30–55 years and 92,940 women aged 25–42 years. Among women aged 30–55 years, the OR of having a BMI in the highest vs. the lowest quintile was 1.62 (95% CI 1.38–1.90) for those with a birth weight >10.0 lb, compared to those with a birth weight of 7.1–8.5 lb [38]. Some studies have also reported a J- or U-shaped relationship between birth weight and obesity but most support a linear relationship [10].

BMI is only a marker of body fat and does not inform on lean and fat mass or fat distribution. It is possible for example that positive associations between birth weight and BMI could result from increases in lean body mass rather than adipose tissue or vice versa [39]. Few studies have addressed this issue and those have reported positive associations between birth weight and subsequent lean body mass, and a negative association with relative adiposity [40]. In addition, other studies have shown inconsistent associations between birth weight and waist circumference [3, 38–40]. These results need to be interpreted with caution as accurate methods of measuring body fat distribution such as DXA scan or whole body MRI scan were not available. Recently, the population based ALSPAC study of 6,000 UK children aged 9–10 years showed positive associations between birth weight and total body lean mass index and fat mass index measured with a DXA scans; however, data on adults is not yet available [41].

Infant Size and Adult Obesity

Many epidemiological studies have examined the association between infant weight and adult obesity addressing the notions for early screening and prevention of obesity in childhood. In a recent systematic review [11], 18 studies which assessed the relationship between infant size and subsequent overweight or obesity were identified. Most studies showed that infants who were obese or overweight had higher risk of being overweight and obese in later life. Only seven of those studies examined the association between infant size and obesity in adulthood again showing consistent positive associations [11]. Despite the observed consistency across study results, a quantitative synthesis of the reported estimates was not possible due the large heterogeneity in the definitions of infant size and subsequent outcomes (obesity). The infant size for example has been defined as BMI at 6 months, as BMI at 1 year, as weight in 1 year, weight in 2 year, weight at 18 months, weight for height and skinfold thickness by various studies. In addition, results need cautious interpretation as risk of bias was high in 5 out of the 18 studies and medium in other 11 studies [11]. The prevailing diversity of exposure definitions in the field arises from lack of in-depth knowledge of the contribution of isolated infant BMI measurements in predicting future obesity [9]. The developmental pattern for BMI differs somewhat from the more-familiar patterns for height and weight; the normal pattern is for BMI to decrease from approximately 2 years of age until 5 or 6 years of age and to increase thereafter. Thus, infancy represents a time period of non-linear decrease and increase in BMI and poses considerable challenges in terms of methodology and interpretation of a postulated prognostic association between isolated infant size estimates and adult obesity. Hence, the available accumulated evidence in the field fails to answer important public health questions and support clinical decisions, the most important being the exact timing for overweight/obesity screening. Subsequent research reflects the difficulty of choosing an isolated infant size estimate and mainly focuses on growth velocity assessment discussed in detail later. The current guidance from the American Academy of Pediatrics recommends a staged approach towards obesity prevention starting the obesity screening at age 2 [41]. Alternatively, in 2010, the USPSTF recommends that clinicians screen children aged 6 years and older for obesity and offer them or refer them to comprehensive, intensive behavioural interventions to promote improvement in weight status [42]. The observed controversy regarding the exact time-point as to when to measure and start screening for obesity led to the alternative approach of involving a more inclusive growth parameter as presented by growth velocity.

Infant Growth and Adult Obesity

Sufficient weight gain is fundamental for a normal growth and development process during childhood. However, it remains unclear if weight gain above the expected or usual weight gain, regardless of its direct impact in crossing the overweight/obesity threshold in infancy, causes additional short-term or long-term benefits or harms. As mentioned in the previous section, several studies of obesity in early childhood have focused on cross-sectional evaluations of obesity prevalence, but, until recently, few have evaluated longitudinal changes in weight status for infants. The association between weight gain in infancy and obesity in childhood, adolescence, and adulthood has recently been widely recognised [2] and a better understanding of weight transitions early in childhood would likely inform future interventional work and policy focused on childhood obesity. In this section, we will discuss the available evidence regarding that research question; associations between catch-up growth patterns and adult obesity in pre-term or small-for-gestational-age born infants as well as in settings with high prevalent malnutrition lie beyond the scope of this section and will not be discussed further. In 2005, Baird et al. [11] published a systematic review of ten studies, which examined the relation

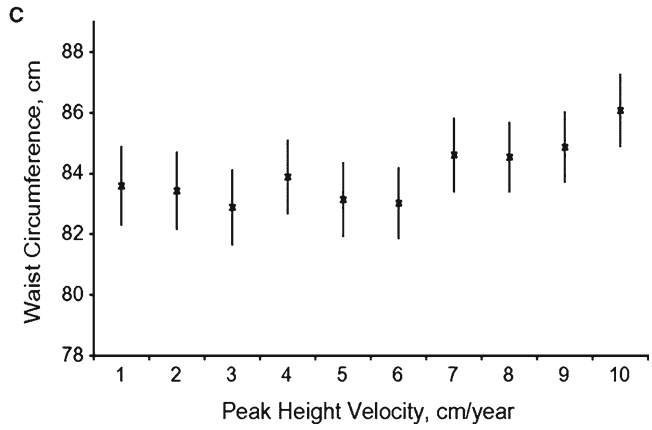

Fig. 28.2 Associations of waist circumference with deciles of peak height velocity in infancy, Northern Finland Birth Cohort 1966 Study [3]

between weight gain in infancy, assessed in various ways, and subsequent obesity, measured as body weight or BMI. Relative risks for subsequent obesity ranged from 1.2 to 5.7 among infants with rapid weight gain. However, in most of the articles reviewed, obesity was measured in childhood or adolescence, information on markers of obesity beyond weight or BMI was scarce, and few studies had repeated measures of growth at different time points. In a following systematic review [43], researchers reported that higher odds ratios were reported from studies with longer duration of the infancy weight gain exposure, younger age when the outcome was measured, and less or no adjustment for potential confounding factors; interestingly, after standardising the observed risk estimates, all studies reported associations of comparable magnitude. Subsequent research in the field, confirms the direction of the postulated association, but lacks again consistency regarding exposure and outcome definitions. In the Caerphilly Growth Study, McCarthy et al. [44] modelled detailed weight changes among 676 boys and girls over the first 5 years of life and reported variable, non-consistent associations between weight gain and adiposity in adulthood that were influenced by the time window of growth and the measure of adiposity used in adulthood. Results from the large Finnish Birth Cohort study, which had detailed and frequent measurements of growth over the first 2 years of life, showed that peak weight velocity (PWV) in infancy was significantly associated with adulthood BMI and waist circumference [3]. A 4-kg/year higher PWV was associated with a 1.87-cm (95% confidence interval: 1.08, 2.65) larger waist circumference in adulthood, after adjustment for potential confounders. In the same study, height velocity was also strongly associated with greater waist circumference independent of adult BMI, despite the high correlation between these two variables (Fig. 28.2). The associations of weight and height growth velocities with waist circumference highlight the fact that early growth might have an effect on later visceral obesity. This is of particular importance, since abdominal adipose tissue, an endocrine organ, secretes adipocytokines and other vasoactive substances and can influence the risk of developing metabolic traits [45].

Future Implications

Tackling obesity remains a public health priority for most developed and developing countries and interventions and policies are greatly needed to prevent and reduce obesity [46]. At the end of the pipeline, the research community is waiting for the emergence of randomised clinical evidence that will eventually validate hypotheses generated and refined through the observational epidemiology framework. These hypotheses are expected to form into community-based interventions that will adequately address the causes of excessive weight gain through different periods of child development, will define the risks and benefits of promoting growth in infancy and will be stringently assessed for causality, generalisability, safety and cost-effectiveness.

Results summarised here support the hypothesis that the first months of life, a period of development that is amenable to intervention, are important in the risk of later overweight and obesity—a major risk factors for cardiovascular disease and other chronic diseases. In future work, investigators need to replicate these results using robust methodologies including and not limited to conceptual standardisation of exposures and outcomes and elucidate potential mechanisms that might explain the reported associations. In addition, these results need to be placed in the context of other findings which have shown beneficial effects of early growth on later development of diabetes and other outcomes, including brain development [47]. Little is known about associations between early growth and other outcomes such as depression and cancer, which are other main causes of morbidity and mortality in adulthood [47, 48]. A better understanding of mechanisms throughout the life course that contribute to obesity, cardiovascular risk, and other health outcomes is important and would have important implications for prevention of chronic disease in adulthood [3].

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