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PERSPECTIVE ARTICLE

Genetic pleiotropy between birth weight and adipose tissue regulation in determining the risk of childhood obesity

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Abstract

Although obesity primarily stems from an imbalance between energy intake and expenditure, recent research over the past years has highlighted the role of various other contributing factors, including fetal growth and birth weight. Although the link between birth weight and adult body mass index remains unclear, some genomic alterations are thought to influence both fetal growth and post-natal body mass. Specifically, potential involvement of gene variants and epigenetic modifications associated with both birth weight and adipose tissue regulation could be proposed, suggesting that a genetic pleiotropy may modify growth efficiency during the fetal stage, contributing to the development of diseases later in life and serving as a link between birth weight and obesity. Given the dual role of the insulin-like growth factor 1/insulin axis, insulin-like growth factor 2, and peroxisome proliferator-activated receptors in fetal growth and adipogenesis, the potential involvement of a pleiotropic genetic effect in the relationship between birth weight and obesity warrants further consideration. Understanding the genetic interplay between birth weight and adipose tissue regulation offers valuable insights into the developmental origins of childhood obesity. These findings highlight the critical importance of prioritizing both maternal and fetal health during pregnancy. Future research should aim to integrate genetic, epigenetic, and environmental factors to develop early, targeted interventions for high-risk populations, ultimately helping to alleviate the global obesity burden.

Keywords: Birth weight; Fetal growth; Adipose tissue; Adipogenesis; Childhood obesity

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1. Introduction

Obesity and related health issues have risen sharply in recent decades.[1,2] A particularly alarming trend is the rise in obesity among children, leading to conditions that were once primarily seen in adults.[3,4] In 2022, the World Health Organization reported that overweight affected 37 million children under 5 and 390 million aged 5 – 19, including 160 million with obesity.[1-4] As reported by the World Health Organization Europe report on the "Childhood Obesity Surveillance Initiative," in the European Region, one in three children suffers

from overweight or obesity (data collected in 33 countries and nearly 411,000 children aged 6 – 9 evaluated).[1-4] Data analyzed by the World Obesity Federation suggests a further surge in the prevalence of overweight and obesity, with an estimation of 206 million global cases among children and adolescents by 2025, and up to 254 million by 2030.[1-4]

Although obesity primarily stems from an imbalance between energy intake and expenditure, recent research over the past years has highlighted the role of various other contributing factors, including fetal growth and birth weight.[5-8]

2. Birth weight and childhood obesity

Inadequate birth weight has been associated with risk of obesity and cardiometabolic disease in adulthood if obesity develops at a young age.[9] Both high and low birth weights influence obesity risk and related health issues, forming a U-shaped pattern (Figure 1). Lower birth weight, in particular, is associated with increased visceral fat and a higher likelihood of cardiometabolic diseases like type 2 diabetes in adulthood.[10] Conversely, higher birth weight is associated with elevated body mass index in both childhood and adulthood.[11,12]

Birth weight serves as a reflection of the intrauterine environment, making it an important indicator of health at the time of birth.[13,14] The developmental origins of health and disease theory[15-17] link birth weight to obesity risk through fetal adaptations to adverse conditions, but it does not fully explain the association with metabolic issues.

Indeed, normal variation in size at birth seems to be influenced not only by the maternal uterine environment but also by the interactions between it and the fetal genetic factors.[18] Thus, although the link between birth weight and adult body mass index remains unclear, some genomic alterations are thought to influence both fetal growth and post-natal body mass.[19]

Specifically, potential involvement of gene variants and epigenetic modifications associated with both birth weight and adipose tissue regulation could be proposed, suggesting that a genetic pleiotropy may modify growth efficiency during the fetal stage, contributing to the development of diseases later in life and serving as a link between birth weight and obesity.[20]

In this context, genetic and epigenetic signals affecting the insulin-like growth factor 1 (IGF1)/insulin axis, insulin-like growth factor 2 (IGF2), and peroxisome proliferator-activated receptors (PPARs) may be highly relevant, as they play a dual role in fetal growth and adipocyte differentiation. IGF1 and IGF2 are key regulators of cell growth, differentiation, and metabolism. Their

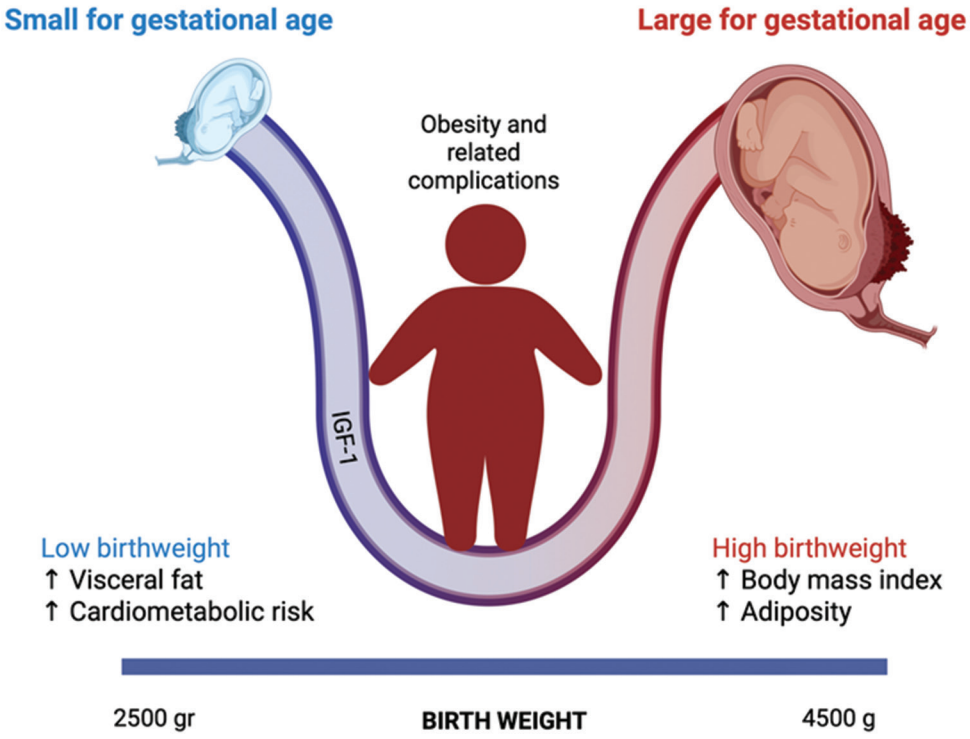

Figure 1. U-shaped relationship between birth weight and risk of obesity and related health issues. Both low and high birth weights are associated with increased risk, highlighting the link between prenatal development and future metabolic health. Image created by the author.

signaling pathways, primarily through the IGF1 receptor (IGF1R), activate downstream cascades such as PI3K-AKT and MAPK, which can influence the expression of various transcription factors, including PPAR gamma (PPARγ). PPARγ plays a crucial role in adipogenesis and lipid metabolism. Studies have shown that IGF1/2 signaling can upregulate *PPARG* expression, thereby promoting adipocyte differentiation and lipid accumulation. This functional link suggests a coordinated mechanism by which growth factor signaling and metabolic regulation are intertwined and highlights the potential for IGF signaling to modulate metabolic gene expression through *PPARG*.[21]

The IGF1 system plays a crucial role as an endocrine regulator of fetal growth.[21,22] While IGF2 contributes to fetal and placental development, evidence from direct measurements highlights IGF1 as the primary factor influencing fetal growth.[23] In the fetus, IGF1 and insulin, rather than growth hormone, serve as the primary drivers of growth.[24,25] Insulin promotes the production of IGF1, which facilitates a rapid response to nutritional changes through the glucose–insulin axis.[26] This mechanism is crucial during mid-to-late gestation when IGF1 levels typically increase to support the accelerated growth that occurs in the third trimester.[26,27] Notably, human fetal serum IGF1 levels from 15 to 37 weeks of gestational age are positively correlated with fetal weight.[28-31] Both IGF1 and IGF2 have been widely studied in umbilical cord blood. Cordonal IGF1 levels exhibit a strong positive correlation with growth indices, whereas IGF2 demonstrates a comparatively weaker positive correlation.[32]

On the other hand, IGF-1 and -2 and insulin gene expression showed a relevant role in adipose tissue and adipogenesis. Adipose tissue serves as a key target for both IGF1 and insulin, with these hormones playing a crucial role in the growth and differentiation of both white and brown adipose tissues.[33,34] Both white and brown adipose tissues begin to develop *in utero*. In human fetuses, adipose tissue first appears between 14 and 24 weeks of gestation (early second trimester) as fat lobules without lipid storage. The timing varies depending on fetal size, with larger fetuses developing distinguishable adipocytes earlier than smaller ones. By the third trimester (28 weeks), adipose tissue depots are established, while brown adipose tissue starts to form around week 20, peaks at week 26, and stabilizes by week 35. The growth of adipose tissue occurs through hypertrophy (increase in cell size) and hyperplasia (increase in cell number, known as adipogenesis). Adipose tissue remains partially expandable throughout life. The number of adipocytes is established during childhood and adolescence, and remains relatively stable throughout adulthood; in humans, approximately 8% of adipocytes are renewed each year.[35-38] Adipogenesis results from the differentiation of new adipocytes from precursor cells in adipose tissue, primarily regulated by the nuclear factor PPARγ, along with other proteins such as CCAAT-enhancer-binding protein, bone morphogenetic protein, and zinc finger protein. The functions of IGF1, IGF2, and insulin are mediated through insulin receptors and IGF receptors, which are closely related and share numerous overlapping downstream signaling pathways. In pre-adipocytes, IGF1R expression is higher than insulin receptor expression, whereas the opposite pattern is observed in mature adipocytes.[39,40]

Adipogenesis plays a crucial role in numerous physiological and pathophysiological processes including obesity. Moreover, the pathogenic mechanisms are not fully understood, and the exact role of adipocyte expansion, remodeling, and activity remains not unequivocal. As reported by Spalding *et al.*,[37] individuals with obesity have more adipocytes added per year than lean individuals, although the relationship between adipocyte morphology and production appears to be independent of body mass index. Obesity is associated with impaired white adipose tissue expansion and remodeling, which exacerbate ectopic fat deposition and metabolic disturbances.[41] On the other hand, according to Arner *et al.*,[42] adipocyte lipid storage and removal play a crucial role in maintaining health and the development of disease. While high triglyceride storage coupled with low removal favors fat accumulation and obesity, a reduction in both storage and removal impairs lipid buffering capacity, promoting lipid spillover into non-adipose tissues and contributing to dyslipidemia and metabolic dysfunction.

Studies on gene knockout animal models suggest that genes encoding IGFs, their receptors, and insulin play a crucial role in both regulating growth and controlling adiposity.[43,44] The association between birth weight and polymorphisms in genes related to IGFs and insulin expression have been also reported in humans.

Kentistou *et al.*,[45] using exome sequencing data from over 230,000 participants, identified nine genes influencing birth weight. Five out of nine associations (*ACVR1C*, *INHBE*, *NRK*, *NYNRIN*, *PPARG*) showed evidence of only fetal-genotype effects. *IGF1R*, *PAPPA2*, and *NOS3* were classified as both fetal- and maternal-acting, with rare variants in all three genes associating with a lower birth weight in both cases. However, among the identified genes, *IGF1R* and *PAPPA2* play a key role in the availability and signaling of IGF in fetal period, while *PPARγ*, *INHBE*, and *ACVR1C* are also involved in the regulation of adipose tissue and show associations with a favorable adipose profile in adults.[45]

Similarly, mutations in the *IGF1R* gene that affect the function or number of IGF1R can impair intrauterine

and post-natal growth, thereby influencing birth weight.[23] During childhood, *IGF1R* expression appears to be also linked to the metabolic profile. Specifically, reduced expression of IGF1R in adipose tissue contributes to early adipose tissue dysfunction and a worsening metabolic state in children with obesity.[46]

Concerning IGF2, as reported by Dunger *et al.*,[47] the common insulin (*INS*) variable nucleotide tandem repeat (VNTR) mini-satellite, which regulates INS and IGF2 expression, is been associated with size at birth. On the other hand, they has been also linked to childhood obesity, predisposing to post-natal fat deposition,[48] and to metabolic comorbidities.[49]

Osada[20] also described a connection between *IGF2* genetic polymorphisms and accelerated fetal growth, supporting that *IGF2* expression may play a role in the intrauterine programming of adipose tissue.[50] In addition, *IGF2* expression has been closely associated with weight and adiposity in children,[51] playing a key role in promoting adipogenesis and fat storage.[52]

Furthermore, the methylation status of the *IGF2* gene at birth has been linked to early childhood weight.[48] St-Pierre *et al.*[53] showed that genetic and epigenetic variations at the *IGF2*/*H19* locus could be key factors influencing birth weight in a normal pediatric population. On the other hand, a significant link between the *IGF2*/*H19* locus and obesity-related complications was also observed. Faienza *et al.*[54] identified an association between the *IGF2* polymorphism (6815A/T) and hypertension in children and adolescents with obesity; however, like other studies, they did not find a direct association with obesity.

All this evidence highlights the role of IGF1, IGF2, and insulin as key determinants of both birth weight and adiposity. In fact, while these factors predominantly regulate growth during fetal life, they play a significant role in controlling adipogenesis during infancy, childhood, and adult age, influencing obesity risk and related comorbidities.

Similarly to IGFs and insulin, PPARγ also plays a dual role in fetal growth and adipocyte differentiation.[55-60] PPARs are members of the nuclear hormone receptor subfamily, which comprises three distinct subtypes: PPARα, PPARβ/δ, and PPARγ. PPARγ is expressed in various tissues and plays a central role in processes such as adipogenesis, inflammatory response, and cell differentiation.[55] During pregnancy, PPARγ influences pre-term delivery and impaired fetal growth.[56,57] Exposure to adverse events in early life can profoundly impact the methylation patterns of *PPARs* in the organs of offspring, which may affect fetal development. Studies have reported that *PPARG* expression is low in the placentas of small-for-gestational-age fetuses and is positively associated with fetal and placental weights within this subgroup.[57-59]

On the other hand, PPARγ shows a relevant function in adipocyte differentiation and a deregulation of PPARγ has been reported in obesity Screening patients with obesity for *PPARG* expression indicated that levels of PPARγ increased in proportion to increased body mass index.[60] Reduced activity or dysregulation of PPARγ signaling is associated with impaired adipocyte function and may contribute to the pathogenesis of obesity,[61,62] confirming its plausible role in control weight control.

In addition, PPARγ is a key transcription factor not only in adipocytes but also in macrophages, where it modulates activation and inflammatory profiles. In obesity, macrophages infiltrate adipose tissue and contribute to a chronic low-grade inflammatory state, promoting obesity-related complications.[63] Activation of PPARγ in macrophages promotes an anti-inflammatory (M2) phenotype, reducing the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha and interleukin 6. Therefore, in this context as well, the expression and function of PPARs in macrophages represent a significant factor in the pathophysiology of childhood obesity and its associated metabolic complications.[63]

3. Conclusion

Given the dual role of the IGF-1/insulin axis, IGF-2, and PPARγ in fetal growth and adipogenesis, the potential involvement of a pleiotropic genetic effect in the relationship between birth weight and obesity warrants further consideration. Understanding the genetic interplay between birth weight and adipose tissue regulation offers valuable insights into the developmental origins of childhood obesity. These findings highlight the critical importance of prioritizing both maternal and fetal health during pregnancy. Future research should aim to integrate genetic, epigenetic, and environmental factors to develop early, targeted interventions for high-risk populations, ultimately helping to alleviate the global obesity burden.

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