

Appetite for Prevention

Genetics and Developmental Epidemiology

Join Forces in Obesity Research

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The obesogenic environment does not affect all children equally. Diminished opportunities for physical activity in daily life and increasing availability and declining cost of calorie-dense foods are primary culprits in the obesity epidemic.



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But there is more to obesity than the environment. Even children raised together in the same family may experience diverging trajectories of body mass.¹ The fact that children confronted with similar environmental circumstances experience disparate outcomes has been attributed to genetic factors.² And family-based and molecular genetic methods indicate substantial genetic contributions to obesity etiology.³ But just what these genetic factors are and just how they contribute to individual differences in response to the obesogenic environment remains, if not entirely a mystery, an enduring puzzle.⁴

Solving this puzzle is a public health priority. There is no going back to a world in which calories are scarce and obtaining them is physically demanding. And governments and their publics have shown little enthusiasm for regulations restricting access to palatable, calorie-dense foods. Policies and public health messaging that reframe health-behavior decision making provide a population-level approach to promoting healthier diets and more active lifestyles.⁵ Complementary practices are needed that can more directly address the most vulnerable individuals, preferably early in life, before obesity develops.

Rapid growth in the first months and years of life is associated with increased obesity risk across the life course.⁶ Genome-wide association studies (GWASs) have discovered genetic variants that predispose to higher adult body mass index.⁷ These variants contribute to the etiology of obesity partly by increasing the rate of growth in childhood.⁸ The next step in translating these discoveries to develop interventions that can prevent obesity is to identify mediating mechanisms that connect the DNA sequence a child inherits with the rapid growth trajectory that places them at risk for obesity and its adverse health consequences. In this issue of *JAMA Pediatrics*, articles by van Jaarsveld and colleagues⁹ and Llewellyn and colleagues¹⁰ suggest one mechanism: individual differences in satiety responsiveness during childhood. Specifically, these studies suggest that diminished satiety responsiveness is a conduit through which genetic risk accelerates weight gain in early life, contributing to obesity pathogenesis.

The study by van Jaarsveld and colleagues⁹ examined longitudinal associations among infant satiety, food responsiveness, and weight gain in a sample of 228 same-sex dizygotic twin

pairs followed up from birth through age 15 months. Satiety and food responsiveness were measured for the first 3 months of life, when all children were exclusively breastfed. The twins were selected from a larger cohort on the basis of high within-pair discordance in appetite measures. The researchers then conducted a co-twin control analysis to test whether infant appetite phenotypes predicted the rate of weight gain. The co-twin control analysis asked whether the twin with the higher appetite gained more weight than their co-twin with the lower appetite. The co-twin design ruled out confounding by any factors that influence both appetite and weight gain and are shared by twins in a family. For example, the constitution of the breast milk, the feeding environment, and the maternal biases in reporting on appetite are all controlled. Within this design, the researchers found that the twin with the greater appetite—lower satiety responsiveness and higher food responsiveness—gained weight more rapidly. Appetite was not related to weight at birth. From birth, differences emerged quickly; by age 3 months, the twin with the higher appetite was already heavier. This finding parallels what has been observed for the genetic risks discovered in GWASs of obesity phenotypes. Those genetic risks show little influence on birth weight,¹¹ but they do influence the rate of growth during the first months of life.¹²

The study by Llewellyn and colleagues¹⁰ examined relationships among genetic risk for obesity, satiety responsiveness, and body mass index and waist circumference standard deviation scores in more than 2000 unrelated children selected from a larger twin cohort. Children were genotyped for 28 obesity-associated variants identified in previous GWASs of obesity phenotypes. These variants were combined to produce a continuous index of genetic risk for each child—their genetic risk score. Children with higher genetic risk scores exhibited reduced satiety responsiveness and higher body mass index and waist circumference relative to age peers with lower genetic risk scores. Statistical tests indicated that small portions of the genetic associations with adiposity measures were mediated through reduced satiety responsiveness. Intriguingly, the genetic risk mediated through satiety responsiveness was not fully explained by the *FTO* locus, which had previously been linked with appetite phenotypes.¹³ These findings argue for an expansion of the program of appetite and obesity research focused on the *FTO* gene to consider a polygenic approach¹⁴ examining profiles of genetic risks across the genome.

In suggesting infant and early childhood satiety responsiveness as a mediator of polygenic risk for obesity, these stud-

ies highlight an important translational application of genetic discoveries: To identify intermediate phenotypes in disease pathogenesis to serve as targets for intervention and/or provide guidance as to when in development and with whom to intervene.¹⁵ Findings suggest that a mother's report of her child's appetite may be informative in identifying children especially vulnerable to developing obesity. The link between appetite and polygenic risk for obesity suggests that children identified in this way may be responsive to preventive interventions that promote healthy lifestyle practices; observational studies indicate that polygenic risk for obesity is amplified by poor diet¹⁶ and can be mitigated by active lifestyle.¹⁷

Whether maternal reports of eating behaviors are sufficiently sensitive and specific to identify individuals who can benefit from preventive interventions and whether interventions prove as effective with genetically at-risk individuals as observational studies suggest are topics for further research. In parallel to exploratory intervention studies, a number of more basic questions should be answered to clarify the translational significance of findings for infant and childhood satiety responsiveness. First, what are the long-term consequences of individual differences in appetite in infancy and early childhood? Studies are needed that follow up children from early life into adolescence and adulthood to test whether appetite measured in infancy and childhood is predictive of later obesity. Second, at what point during development are individual differences in appetite established and how do changes in appetite relate to changes in obesity risk? Studies that include repeated measures of appetite and weight during infancy and childhood are needed to determine when differences in appetite first manifest, how stable these differences are over time, and whether diminishment or increase in

appetite predicts corresponding changes in weight. Third, do these findings generalize to non-European populations? Studies are needed to test replication of these findings in cohorts representative of other racial/ethnic groups.

Stepping back from the specific case of appetite and obesity, these studies highlight an interdisciplinary approach to pediatrics research that has potential to inform prevention and treatment not just for obesity, but for a range of common chronic health problems that begin to develop during childhood. The sequencing of the human genome unleashed a flood of genetic discovery research. These studies have mostly focused on taking increasingly sophisticated measurements of genomes in ever-larger samples of individuals, almost all of whom are adults. To realize the translational potential of these discovery studies, research is needed that applies genetic discoveries to investigate disease processes early in life. Many investigators have been disappointed by the small effect sizes observed for GWAS-discovered risk variants. And funders are drained from the high costs of generating the data to support the initial discovery studies. Both groups should take another look at the opportunities now available. The true effect sizes of GWAS discoveries cannot be known until we understand how genetic risks contribute to pathogenesis. And conducting the research to generate this understanding need not be cost-prohibitive. Measuring genomes gets cheaper by the day. Longitudinal studies of population-representative samples that capture high-quality measures of developmental phenotypes for conditions ranging from obesity and asthma to behavioral and emotional problems already exist. What is needed is the creativity, the will, and the resources to put these rich databases to work to achieve the next generation of advances in genetics and health science.

ARTICLE INFORMATION

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