

Translating Developmental Genetic Findings Into Obesity-Related Clinical Practice

Are We There Yet?

FOR MOST INDIVIDUALS, REACHING OVER-weight or obesity status is the result of a process that is cumulative and progressive. Cross-sectional measurements of obesity-related traits are one-time indicators of an individual's historical trajectory of fat accumulation and, based on general scientific consensus, respond to continuous environmental, behavioral, and genetic factors. These factors individually and collectively act and interact in complex ways to lead to the progression of fat accumulation. A challenge confronted by the research community is the identification of statistically powerful samples and/or experimental designs to uncover the biological and nonbiological factors that affect changes in body composition parameters across the life span.

*See also pages 515
and 522*

Belsky and colleagues¹ were positioned to successfully address the longitudinal effect of biological factors on obesity by evaluating genetic information from 32 single-nucleotide polymorphisms that were combined into a genetic risk score. The investigators explored the association of the genetic risk score with longitudinal changes in obesity-related traits in a predominantly white sample from New Zealand. They found that a higher genetic risk score was associated with rapid growth during early childhood, a rapid rate of weight gain, and earlier adiposity rebound. By following up participants from birth to 38 years of age, Belsky and colleagues showed that genetic predisposition to obesity outcomes becomes detectable at about 3 years of age and continues to create a developmental trajectory that cumulatively has an effect on adult obesity. This study provides clear evidence regarding the role of biological risk attributed to the development of obesity and suggests that genetic risk for obesity affects fat accumulation through accelerated growth in early childhood. Further insights and implications of the study, however, cause concern as much as they fascinate. Given that the associations identified were independent of parental body mass index, the findings from Belsky et al may imply a degree of genetic determinism that challenges overall public health recommendations worldwide in a simple question: What about the role of the environment across the life span?

Insight regarding the role of environmental factors in the development of obesity is provided by the work of White and Jago,² who explored how environmental and behavioral factors influence obesity outcomes through-

out puberty. These investigators evaluated the role of physical activity in a sample of African American and European American adolescent girls from the US National Heart, Lung, and Blood Institute Growth and Health Study. White and Jago explored the contribution of physical activity to changes in body composition at 12 and 14 years of age after taking into account social and economic factors, caloric intake, and television watching. These authors demonstrate that higher levels of physical activity were associated with a lower risk of obesity in European American but not in African American girls, evidencing, once again, that in population research, the one-size-fits-all approach cannot be applied to different groups. The results presented by White and Jago² force us to question whether the results from the study by Belsky et al¹ could be applied to other populations.

A quantitative genetic measure of obesity predisposition can without doubt be a useful tool with *potential* clinical applications. However, the use of this resource in clinical practice is still limited by the fact that the genetic variants identified through genome-wide association studies explain less than 2% of the variation in body mass index, a trait that is roughly 50% heritable in Western society. The advances and findings in the genetics of obesity have been exciting (in its discovery) and frustrating (in its application). A quotation from Herodotus, "Tis the sorest of human ills to abound in knowledge and yet have no power over action," may apply in this scenario. Attempting to translate the findings from Belsky and colleagues¹ to clinical practice would be naive at this point when more research is clearly needed to fully understand the genetic basis of many complex traits. We should keep in perspective that for obesity-related outcomes the environment plays a pivotal role. Developing effective public health interventions to prevent obesity will require population-specific genetic studies that incorporate socially and culturally sensitive behavioral and environmental factors.

As scientists, we must remember that overgeneralization of findings is a tactic that must be carefully avoided because it can limit scientific discovery and generate stereotyping, which can be detrimental to disease prevention, particularly in obesity. White and Jago² raise an underlying message that should not be overlooked: the information we receive in population-based research—and the conclusions that we make—depend on the samples we obtain. In their study, those with favorable outcomes were more likely to provide valid physical activity data. This observation should make us wonder how the results of their study could have been influenced by

the inclusion of missing data from participants with less favorable outcomes, challenging researchers to overcome barriers to obtain full participation of subjects in research initiatives. Certainly the studies by White and Jago² and by Belsky and colleagues¹ provide a platform for some scientific reflection regarding genes, environment, their interaction, and their application to population research and the development of obesity-related preventive strategies. However, we must accept that until now in scientific discovery, regardless of what the genetic risk score might be, promoting healthy behaviors is the approach to take in preventing pediatric obesity.

We hope the gaps in understanding individual variability will be resolved by next-generation sequencing, the inclusion of diverse populations in biomedical research, and the identification of new molecular, methodological, and population approaches that will allow us to continue the advancement of knowledge regarding complex obesity-related traits. Until we know more, and perhaps after we know more, preventive behaviors should be each individual's priority so that we all achieve the best health possible regardless of genetic profiles. With-

out taking this approach, we might risk the mistake of allowing genetic predisposition to become genetic determinism.

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