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Using advanced genomics to bring behavior to the table

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Overweight and obesity affect ~2.1 billion adults worldwide, and are associated with increased risk of cardiovascular morbidity and mortality compared with normal BMI (1). Obesity has contributed to accelerate the epidemiological transition toward noncommunicable chronic diseases globally, and this change should prompt research on specific vulnerabilities, screening, and access to evidence-based preventive interventions. Despite efforts to revise health policy and develop more effective therapeutic options, the United Nations' goal to reduce premature mortality from noncommunicable diseases by one-third by 2030 appears unrealistic, considering that the leading cause of global poor health is attributed to dietary risks (2). In this context, there is an urgent need to understand how eating patterns and preferences are formed, allowing the creation and implementation of better targeted prevention strategies. Yet, we have a very limited knowledge about the causes of the heterogeneity in the behavioral processes involved in weight gain in humans.

In this issue of *The American Journal of Clinical Nutrition*, Masip et al. (3) combine the use of polygenic risk scores (PRSs) and twin modeling in a sample of almost 4000 healthy young adults from the FinnTwin16 study to explore whether eating behavior patterns mediate the effects of genetic susceptibility to obesity on BMI and waist circumference. They demonstrate that "snacking behavior" is associated with the PRS and both obesity measures in men and women. A more modest relation was seen with "infrequent and unhealthy eating" behavior, especially in men. Moreover, "emotional and external eating" behaviors were associated with PRS and BMI, but not waist circumference. In the twin modeling, the authors show that the relation between snacking and emotional and external eating behaviors with obesity is largely explained by genetic factors. Despite being limited by the cross-sectional nature of the study, the need of future replication, and the focus on a sample from 1 country in Europe, the use of advanced genomic tools to understand the underlying genetic background linking eating behavior and obesity is an important contribution that Masip et al. (3) bring to the field.

The use of methods of genomic risk profiling is consistent with the idea that the genetic contribution to a certain condition is derived from a combination of small effects from many genetic variants. A PRS is calculated for each subject in the target sample as a sum of the risk alleles count, weighted by the effect size described in a discovery genome-wide association study (GWAS) (4). In general, PRSs are calculated by combining variants that reach a certain threshold *P* value in the discovery GWAS, which limits the number of variants included in the score and hence considers only a very small fraction of the genome as responsible for the genetic susceptibility to complex diseases, bearing oversimplification. Some studies have already demonstrated mediation effects of eating behaviors in the association between these threshold-limited PRSs and obesity measures (5, 6). Masip et al.'s (3) contribution uses a novel approach to calculating PRSs, centered on Bayesian probabilities, that incorporates all the available information from ≤2.1 million common genetic variants from the genome (7), likely increasing the precision to capture genetic risk of obesity.

It is important to highlight that polygenic scores are but important research tools at the moment. Complex phenotypes are the result of multiple and additive genetic effects but also of nongenetic environmental effects and interactions that occur over time. A strong example is seen in the study from Khera et al. (7). They used the same genome-wide polygenic score approach as Masip et al. (3), integrating all available common variants into a single quantitative measure, to identify risk of obesity. Despite the strength of the described associations between the PRS and obesity, almost 20% of the individuals characterized as having a high genetic risk of obesity had a normal BMI (7), suggesting that polygenic risk is probabilistic and not deterministic, and should be considered in the broader context of past as well as current environmental variation. Understanding behavioral heterogeneity can certainly inform the development of targeted prevention strategies, because the classic one-size-fits-all approach is largely known to fail (8). But to move toward precision medicine, the tailored clinical decisions should apprise both biological as well as environmental factors—and mainly their interactions—that affect disease outcomes (9).

The new generation of studies using advanced genomic tools to improve our comprehension of individual differences in behaviors involved in disease vulnerability, like that of Masip et al. (3), can illuminate the delineation of interventions to prevent or reverse weight gain. Other efforts should also be focused on deciphering the biological processes involved in

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the development of these behaviors (10). Some genes that are relevant to obesity risk likely modulate the way individuals respond to environmental challenges or cues, and these discrete and differential gene × environment interactions might not be readily captured in simple association studies (11), so complex statistical models are warranted. Decoding this complexity will help us convey the proper tools for more effective and efficient therapies, policies, and practices for promotion of long-term health and well-being.

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