COMMENTARY

Socioeconomic Disparities Across the Spectrum of Genetic Burden in Type 2 Diabetes and Obesity Risk

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The once-prevailing notion that human characteristics are the consequence of either genes *or* environment has been replaced by recognition that neither acts independently of the other and that gene–environment interactions are ubiquitous features of phenotypic expression. Indeed, many complex diseases are the consequence of modifiable environment exposures, the effects of which are conveyed through a biological cascade where DNA is transcribed and then translated into proteins that are the constituents of measurable phenotypes like blood glucose or body weight (1).

Variations in the DNA sequence of target genes can impact the way in which a given environmental exposure expresses its phenotypic effects. In some diseases caused by gene mutations, the likelihood the disease will be expressed ("penetrance") may be moderate to high. This includes lactose intolerance predisposing mutations in *MCM6* (2) and phenylketonuria–predisposing mutations in *PKU* (3). Both cause inborn errors of metabolism and are autosomal recessive traits that induce serious health problems, but dietary modification can annul the phenotypic impact of these mutations. Hence, rather than the destiny of diabetes or obesity being written into our genes, it is more helpful to view genes as predisposing factors whose tendency to cause disease may be conditional on features of the modifiable environment.

In epidemiology, gene–environment interactions are often defined as either multiplicative or additive in nature. To assess the former, statistical tests are used to examine the extent to which the relationship between an environmental exposure and a disease outcome is conditional upon genetic variation. In lay terms, the test seeks to determine if the whole is greater (or less) than the sum of its parts. For quantitative traits like blood glucose and BMI, the test is used to quantify the extent to which the estimate of the effect between the environmental exposure and the trait (usually expressed as the β coefficient) differs in magnitude across the spectrum of the genetic variable (e.g., quantiles of a polygenic risk score). For categorical disease outcomes (e.g., type 2 diabetes or obesity), the test seeks to determine if the estimate of risk (e.g., odds ratio) differs in value by genetic strata. If the β coefficients or risk ratios are statistically different between quantiles, this may be interpreted as a multiplicative interaction. Additive interactions, on the other hand, help determine the level of overall risk attributable to the combination of environmental and genetic exposures on an additive scale.

In this issue of *Diabetes Care*, Cromer et al. (4) describe analyses that explore interactions between genetic and socioeconomic factors in relation to type 2 diabetes and obesity risk. Genetic exposure was defined using polygenic scores comprising established type 2 diabetes- or obesity-associated single nucleotide polymorphisms; the socioeconomic exposure was derived from census tract–level measures of educational attainment, income/poverty, employment, deprivation, and social vulnerability. Primary analyses were performed on data from the Mass General Brigham Biobank (26,737 participants of European ancestry and 3,468 participants of non-European ancestry), with replication analyses performed in the UK Biobank (223,843 participants of European ancestry and 7,459 participants of non-European ancestry). The polygenic score was evenly distributed across the socioeconomic gradient. The authors found no evidence of multiplicative interactions but determined that genetic and socioeconomic factors interact on the additive scale. For example, in primary analyses they found that in the lowest quintile of the polygenic score, moving from the lowest to highest quintile of socioeconomic risk corresponded to a 1.7% absolute increase in type 2 diabetes prevalence. In contrast, in the highest quintile of the polygenic score the same transition in socioeconomic risk corresponded to a 9.2% increase in type 2 diabetes prevalence. Results were consistent in replication analyses.

Quantification of gene–environment interactions may help optimize health recommendations relating to the

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environmental drivers of type 2 diabetes or obesity by focusing on high-risk subgroups defined by genetic characteristics. Detection of a statistically significant multiplicative gene–environment interaction indicates that the effects of environmental exposures on an outcome are more marked in one genetic subgroup than in others. In rare instances, the same environmental exposure might convey elevated risk in one genetic subgroup and protection in another (a crossover interaction) (5). Provided such observations are appropriately validated in an intervention setting, they might motivate early interventions in those at highest genetic risk—an example of precision prevention (6).

As is the case of the study by Cromer et al. (4), additive interactions are often assessed by estimating the relative excess risk attributable to the interaction. Because the genetic component is essentially nonmodifiable, one might then use evidence of additive interactions to estimate the likely benefits of modifying the environmental risk exposures in people at various levels of genetic risk. In some instances, interventions on environmental risk factors may reduce the overall level of risk to an acceptable level, even in people at high genetic risk. This may be especially relevant in the presence of risk thresholds, where the risk gradient is shallow below a given environmental exposure level and more precipitous above it, as is the case with blood glucose and retinopathy in some populations (7).

Like many epidemiological studies, the analysis by Cromer et al. (4) is limited by its cross-sectional, observational nature. Owing to this, one cannot be certain that there is only a unidirectional relationship between socioeconomic status and type 2 diabetes or obesity prevalence, as the relationships are likely bidirectional. This type of bias does not affect genetic risk, as variants in germline DNA do not change in response to environmental exposures. The consequence of this type of bias is that the magnitude of the interaction effect may be inflated or, less probably, an entirely false interaction might be detected. A second key limitation is confounding. Here, the expectation that the environmental exposures (socioeconomic factors) are the causal agent may be false if there are other unobserved causal exposures that correlate with socioeconomic factors. This can also drive false-positive discovery in interaction analyses.

Epidemiological studies can be powerful for hypothesis generation. However, clinical trials are often needed to derive results that can be translated into public health recommendations, especially when these focus on behavioral and/or societal change. To test the hypotheses established through the analyses of Cromer et al. (4), one might enroll people with contrasting polygenic scores (a recall-by-genotype paradigm [8]) and intervene on socioeconomic status. A study of this nature would be extremely challenging, as it would be very difficult to mask assignment to the active intervention and deliver a meaningful control intervention without bias. The intervention may also have off-target effects that elicit changes to unintended environmental and behavioral exposures. Moreover, because improvement in socioeconomic status is generally beneficial for people's health and well-being, denying those randomized to the control arm this opportunity would be difficult to justify.

In conclusion, Cromer et al. (4) report eloquent analyses performed within epidemiological cohorts that illustrate how socioeconomic factors convey risk of type 2 diabetes and obesity against the backdrop of genetic diversity. The results help emphasize the importance of considering a person's inherent biological predisposition to these diseases as well as the impact of potentially modifiable societal factors.

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