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COMMENTARY

Integrating Publicly Available Genome-Wide Association Data to Study the Genetic Basis of Metabolically Healthy Obese and Metabolically Obese but Normal-Weight Individuals

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An estimated 2.1 billion adults and children worldwide are obese (1), imposing a substantial burden on people's personal health and on society as a whole, as excess adiposity is associated with a number of cardiometabolic complications. These include insulin resistance, dyslipidemia, and hypertension, each of which is a risk factor for type 2 diabetes (T2D) and cardiovascular disease (CVD) (2,3). However, a sizeable proportion of obese individuals does not have these cardiometabolic complications. These individuals have favorable glucose, lipid, blood pressure, liver enzyme, hormone, and inflammation levels, despite their excess adiposity. Conversely, not all normal-weight individuals are healthy, as some demonstrate one or more cardiometabolic risk factors. Although there is no consensus on the criteria to define these obese and normal-weight subtypes, an estimated 15–45% of obese individuals are considered "metabolically healthy obese" (MHO) and 5–30% of the normal-weight population is considered "metabolically obese of normal weight" (MONW) (4–10).

While interest in MHO and MONW populations is growing rapidly, it remains unclear which factors determine why some obese individuals are protected, and why some normal-weight individuals are at elevated risk. Age, sex, ethnicity/race, physical activity, smoking, and alcohol intake have been identified as important correlates of MHO and MONW (6–10). However, even after accounting for these factors, the MHO population continues to be protected (longer) from the development of cardiometabolic disease compared with other obese individuals, and the MONW population remains at greater risk than healthy people of normal weight (9–15). These observations suggest that innate physiological mechanisms underlie at least part of one's predisposition to be MHO or MONW. Indeed, based on data from studies that were conducted mainly in rodent models, pathways implicated in adipogenesis, adipose tissue expandability, adipocyte differentiation, fat distribution, ectopic fat accumulation, lipid storage capacity, lipoatrophy, macrophage density, adipose inflammation, and responsiveness to endocrine secretions have been proposed to—at least in part—contribute to the cardiometabolic diversity observed among obese and normal-weight individuals (7,16). Studies that examine these mechanisms in humans are sparse and often limited by sample size and the lack of noninvasive methods to accurately assess activity in key physiologic pathways (7,16).

A study published in this issue of *Diabetes* by Yaghootkar et al. (17) used genetic association data from publicly available genome-wide association studies (GWAS) to gain insight into the mechanisms that link adiposity, insulin resistance, and other cardiometabolic risk factors. Nineteen genetic variants, previously shown to robustly associate with fasting insulin level (18), were examined for their association with eight adiposity and cardiometabolic traits and six disease outcomes (Fig. 1*A*). A cluster analysis was used to examine whether the genetic variants could be grouped based on their association signature

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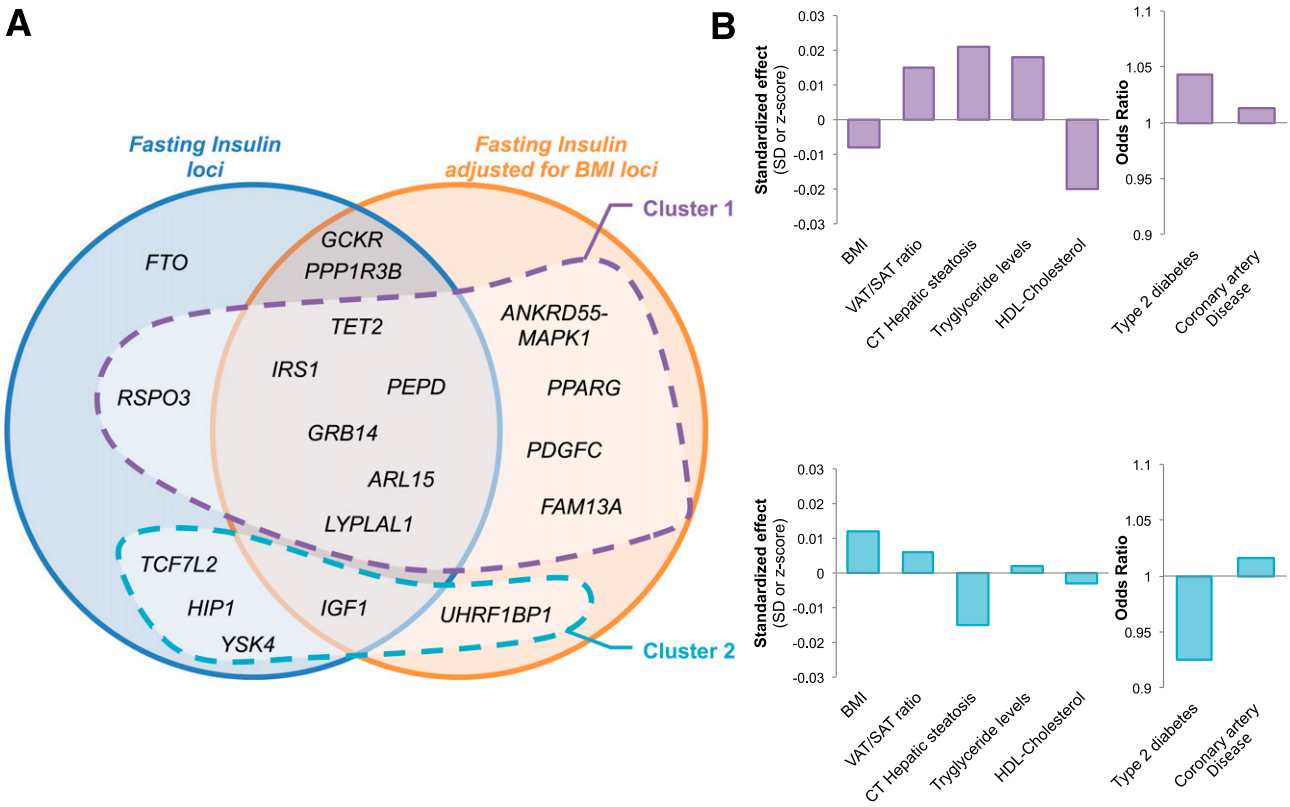

Figure 1—*A*: The 19 insulin-associated loci determined according to the association model by which they were identified in large-scale GWAS (18). For 5 of the 19 variants, the association with insulin was abolished or attenuated after adjusting for BMI, suggesting that BMI likely mediates the association between the variant and insulin (left). Five other variants were associated with insulin only after adjusting for BMI (right), indicating that BMI levers the association with insulin, possibly because the insulin-increasing allele is associated with lower BMI. The remaining nine variants were associated with insulin irrespective of BMI (middle). *B*: Association between the GRS of the insulin-increasing alleles of cluster 1 and cluster 2, respectively, with adiposity and cardiometabolic outcomes. The per-allele effects for continuous traits are expressed in SD or *z*-score. CT, computerized tomography.

with the eight traits, thereby providing insight into the potential mechanisms linking these traits. The first cluster grouped 11 variants (Fig. 1*A*), and, as expected, a genetic risk score (GRS) based on the insulin-increasing alleles of these 11 variants was associated with a poorer cardiometabolic profile. This profile was characterized by increased triglyceride levels, decreased HDL cholesterol levels, greater hepatic steatosis, and lower adiponectin levels, as well as increased risk of T2D and CVD. Interestingly, despite the well-known positive phenotypic correlation between increased BMI and fasting insulin levels, a higher GRS was associated with lower BMI and less subcutaneous adipose tissue (SAT), but not with less visceral adipose tissue (VAT). The authors concluded that this cluster of 11 variants provides genetic evidence for a lipodystrophy-like or MONW phenotype. The GRS can also be interpreted as a function of the insulin-decreasing alleles. Thus, a lower GRS is associated with higher BMI and more subcutaneous fat, but also with a favorable cardiometabolic risk profile. This combination of factors is consistent with the MHO phenotype. Five of the eight traits had been transformed to standardized normal distributions, allowing the comparison of genetic effects across the traits. Of interest is that the GRS was more strongly associated with the VAT-to-SAT ratio than with BMI (Fig. 1*B*), suggesting that preferential fat storage in visceral versus subcutaneous fat depots, rather than just overall adiposity, is a more important contributor to MHO and MONW phenotypes. Furthermore, the association was much more pronounced for T2D than for CVD risk (Fig. 1*B*), an observation that is likely due to the fact that insulin-associated variants were selected as part of the study design.

Support for a genetic basis of the MHO and MONW has been reported before. Adiposity-decreasing alleles near *IRS1* and in *PPARG* (Pro12Ala) have each been associated with an unfavorable cardiometabolic risk profile (19,20), both of which were also part of "cluster 1." That the GRS based on cluster 1 in the current study supports the apparent paradoxical link between adiposity and cardiometabolic traits is no surprise given that 10 of the 11 insulin-associated variants reached genome-wide significance in BMI-adjusted models. This indicates that BMI does not mediate the association between the variants and insulin (Fig. 1*A*). Indeed, 5 of the 10 insulin-increasing alleles were nominally associated with lower BMI (21).

As elegantly demonstrated by Yaghootkar et al. (17), data from large-scale publicly available GWAS provide a powerful resource to gain insight into the genetic basis of more comprehensive phenotypes, such as the MHO and MONW, which are not captured with traditional single-trait GWAS. Nevertheless, publicly available data come with some limitations. For example, the user has no control over the analysis model or the way outcomes are transformed. In the current study, some of the genetic consortia reported only BMI-adjusted GWAS results, a methodological issue that complicates the interpretation. This is particularly relevant in the context of MHO and MONW phenotypes. Furthermore, some traits were not transformed, whereas others were log transformed or standardized. While genetic associations with standardized traits can be easily compared, this is much harder for nonstandardized traits. Using *P* values to compare the strength of association across traits might be misleading because sample sizes across the different GWAS vary widely. For example, the effect of the GRS of cluster 1 is largest for hepatic steatosis and smallest for BMI (Fig. 1*B*). However, due to the much larger sample size, the association with BMI was more significant.

To integrate genetic association data across multiple traits, the authors applied a hierarchical clustering analysis method that has been used to study gene expression profiles. This method clusters genetic variants that show similar association signatures across multiple traits. While each cluster might point to a common mechanism underlying the genetic associations, follow-up studies will be required to examine whether these genetic loci are indeed part of the same physiological pathway. Sometimes clusters represent variants for which the biological commonality is not immediately obvious. For example, in the study by Yaghootkar et al. (17), the GRS based on the insulin-increasing alleles of the five variants of "cluster 2" are associated with a substantially reduced risk of T2D, but an increased risk of CVD (Fig. 1). This unexpected pattern may be driven by the presence of the *TCF7L2* variant, which has been notable for its complex relationship with adiposity and insulin sensitivity, depending on the presence or absence of T2D. This observation highlights that caution should be taken when making mechanistic inferences based on these clusters.

Taken together, the study by Yaghootkar et al. (17) demonstrates the value of large-scale GWAS data that have been made publicly available by genetic consortia. By integrating these data and carefully accounting for their limitations, the authors confirmed evidence for a genetic basis for the MHO and MONW phenotypes, which points to a role for adipose tissue storage and expandability. Future studies, based on variants that are associated with, for example, HDL cholesterol or blood pressure may reveal alternate mechanisms that underlie the apparent paradoxical relationship between adiposity and cardiometabolic risk factors.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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