The Use of Mendelian Randomization to Determine the Role of Metabolic Traits on Urinary Albumin-to-Creatinine Ratio

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COMMENTARIES

Urinary albumin-to-creatinine ratio (ACR) has both genetic and environmental influences. Previous studies have identified a number of genetic loci associated with ACR (1–3). Metabolic traits such as obesity and dyslipidemia also exhibit both genetic and environmental influences, and these measures have been associated with ACR (4). Previous studies indicate pleiotropic effects of metabolic genetic variants on ACR; however, it is not clear whether these metabolic traits have a causal relationship with ACR (5). In this issue of *Diabetes*, Casanova et al. (6) use Mendelian randomization (MR) to examine a putative causal relationship between metabolic traits and ACR.

An illustration of the potential relationship between metabolic traits and ACR is shown in Fig. 1. The association between single nucleotide polymorphisms (SNPs) identified through genome-wide association studies and metabolic traits should be established and strong; this relationship is noted by the arrow from the instrument variables (i.e., SNPs) to the metabolic trait of interest. Epidemiologic literature can be used to support the association of each metabolic trait with ACR; however, these relationships may be confounded. MR can be used to establish the relationship between the metabolic trait and ACR (this relationship is noted by the arrow from the metabolic trait to ACR in Fig. 1) by assessing the instrument variables. However, most MR methods assume that there is no direct effect of the SNPs on ACR and that there are no alternate pathways from the SNPs to ACR other than through the specific metabolic trait of interest (Fig. 1) (7).

Three of the most common MR approaches are the inverse-variance weighted (IVW) method, MR-Egger, and the weighted median method (7). These three MR methods make several key assumptions. The IVW method assumes that all SNPs are valid instrumental variables for the trait and the only path from the SNPs to the outcome is through the exposure (i.e., no pleiotropy) (8). The MR-Egger method is more robust to potential violations of the standard instrumental variable assumptions, and this method is less prone to confounding from possibly pleiotropic SNPs, which could have stronger effects on outcomes compared with the effect on the exposure (9). The weighted median method improves precision and is also more robust to potential violations of the standard instrumental variable assumptions (10). While MR offers a simple way to distinguish causation from correlation, a recent article in *Nature* has argued that scientists may be overusing or misusing MR methods (7).

Casanova et al. (6) used these three MR approaches to consider the role of 11 metabolic risk factors on ACR. The 11 metabolic risk factors were diastolic blood pressure, systolic blood pressure, HDL cholesterol, LDL cholesterol, triglycerides, BMI, waist-to-hip ratio (adjusted by BMI), fasting glucose, fasting insulin, type 2 diabetes liability, and favorable adiposity, which represents higher adiposity but lower metabolic disease risk using genetic variants previously identified (11). Using IVW as the primary method, all of these traits except for four (HDL cholesterol, BMI, fasting glucose, and fasting insulin) had a P value <0.05.

It is a strength of the study by Casanova et al. (6) that it implemented all three popular MR approaches including the MR-Egger and weighted median methods that, as mentioned previously, are more robust to potential violations of the standard instrumental variable assumptions and potentially less prone to confounding due to pleiotropy. Pleiotropy is not uncommon when examined across the genome and is a concern in the study. For example, one variant, rs2276936 [*FAM13A*], an instrument variable for favorable adiposity, and a second variant, rs3822072 [*FAM13A*], an instrument variable for HDL cholesterol, are in linkage disequilibrium ($r^2 = 0.94$). Given that the MR-Egger approach is less prone to confounding

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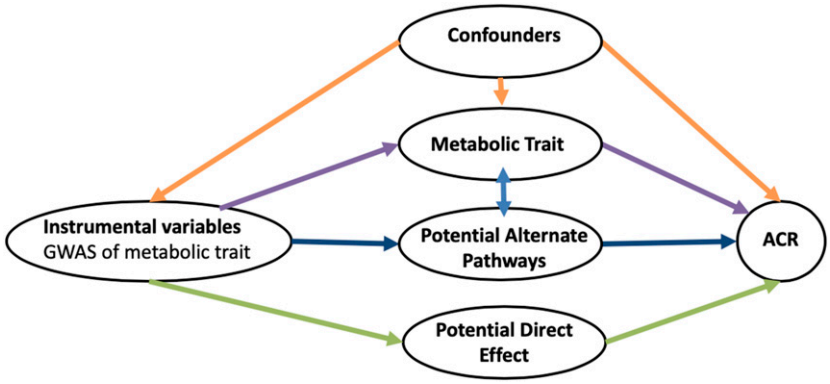

Figure 1—Causal diagram of the potential relationship among instrument variables (i.e., SNPs), the metabolic trait of interest, and ACR. MR tests the association between the exposure (i.e., metabolic trait) and the outcome (i.e., ACR) using the instrument variables (SNPs derived from a genome-wide association study [GWAS] of the metabolic trait). Depicted are potential alternate pathways and direct effects of the SNPs on ACR. The metabolic trait may also be correlated with alternate pathways.

due to pleiotropy than the IVW approach, the MR-Egger approach would be a more valid primary method than the IVW approach for examining the role of these 11 metabolic traits on ACR when pleiotropy is likely to exist. Using the MR-Egger method, five of the metabolic traits (triglycerides, waist-to-hip ratio, BMI, fasting insulin, and type 2 diabetes liability) are significantly associated with ACR (P value <0.05), although these results would be further reduced in number if a Bonferroni correction was used to account for the multiple testing correction of the 11 metabolic traits.

Casanova et al. (6) observed a complex relationship between multiple metabolic pathways and ACR. However, given concerns over the assumptions regarding pleiotropy, the primary method used should best meet the assumptions of the given research question in that particular scenario. Their article also demonstrates the importance of directly assessing the model in Fig. 1. Future directions could examine other pathways in Fig. 1. Mediation analysis, for example, can estimate the indirect effect of a SNP in *FAM13A* on ACR through favorable adiposity or HDL cholesterol as well as the direct effect of that SNP on ACR. Mediation analysis may contribute to our understanding of the relative importance of these pathways on ACR and microvascular disease. Understanding the biological pathways that lead to clinically relevant outcomes is crucial in designing successful interventions. Mediation analysis can specifically test these biological pathways recognizing pleiotropic effects on these complex metabolic traits and ACR.

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