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Editorial

Adiposity and Cardiometabolic Outcomes
What Can Meta-analyses of Mendelian Randomization Studies Contribute?

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In the study by Riaz et al,[1] evidence was presented for a potential causal role of obesity (determined by body mass index [BMI]) on increasing the risk of type 2 diabetes (T2D) and coronary artery disease (CAD) in over 800 000 individuals in a meta-analysis of 5 studies. Specifically, authors screened over 2500 articles and conducted a systematic review of 7 studies and meta-analysis of 5 studies (including a total of 881 269 individuals) that used Mendelian randomization (MR) methodology to assess the potential causal role of any measure of adiposity in the incidence of cardiovascular events, including T2D, CAD, and stroke.

The association between obesity (or, indeed, any measure of adiposity) and cardiovascular outcomes has been assessed primarily with large-scale observational studies, which have limitations such as confounding (external factors that associate with both obesity and cardiovascular outcomes), reverse causation (where disease leads to increased adiposity), and many forms of bias (especially, in this context, selection bias). Furthermore, interventions and trials that aim to lower BMI are inherently difficult and many have proven unsuccessful in achieving sustained weight loss of a magnitude and duration that could be expected to reduce cardiovascular events or mortality. Increasingly, studies have used an alternative approach—MR—to overcome these limitations and help strengthen causal inference (**Figure**),[2,3] particularly within the field of cardiometabolic health. The MR methodology exploits the properties of genetic inheritance to mimic a randomized clinical trial to improve causal inference (see the 2-minute primer on MR methodology for a basic description and for further details[3,4]). Many MR studies have provided evidence of higher adiposity increasing the risk of adverse cardiovascular outcomes, with some inconsistencies, possibly owing to low statistical power.

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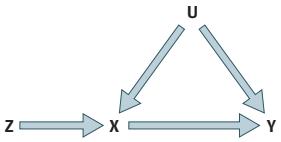
Figure. Mendelian Randomization Methodology to Assess the Association Between Obesity and Cardiovascular Outcomes



Genetic variants (Z) is used as an instrumental variable for an exposure (X) to assess its causal role on an outcome of interest (Y). Mendelian randomization methodology relies on the following 3 key assumptions: (1) Z is associated with X, (2) Z is independent of measured or unmeasured confounders—U, and (3) Z only influences Y through its effect on X. In a 1-sample setting, individual-level data on genetic variation, exposure, and outcome are present in 1 sample of individuals. In a 2-sample setting, summary-level estimates of the genotype-exposure association and the genotype-outcome association are obtained from 2 independent samples usually from genome-wide association studies, and individual-level data are not needed.

Riaz et al[1] searched both MEDLINE and Scopus for studies (up to January 2018), retrieving articles that performed MR analyses to assess the association between any measure of obesity (BMI or waist to hip ratio) and cardiometabolic outcomes (CAD, stroke, and T2D), and provided appropriate summary statistics for performance of systematic review and meta-analysis.

Of the 2511 studies that remained after initial screening, 7 studies met a priori criteria for inclusion in their systematic review and 5 studies met inclusion criteria in the meta-analysis for the association of obesity with T2D, CAD, and stroke. Results provided evidence for an effect of obesity (specifically, each 1-SD-higher BMI) on T2D (odds ratio, 1.67; 95% CI, 1.30-2.14; $P < .001$; $I^2 = 93\%$; n = 461 871) and CAD (odds ratio, 1.20; 95% CI, 1.02-1.41; $P = .03$; $I^2 = 87\%$; n = 570 261), but no evidence for an effect on stroke (odds ratio, 1.02; 95% CI, 0.95-1.09; $P = .65$; $I^2 = 0\%$; n = 228 816). The authors defined severe heterogeneity as an I^2 statistic of greater than 75%. While there was consistent and nonheterogeneous evidence regarding the lack of a clear effect of obesity on stroke, the evidence for the effect of obesity on T2D and CAD were considered severely heterogeneous by this definition. The authors state that this heterogeneity was anticipated given the variation in study methodologies, participants, localities, and selection of genetic variants. Additionally, while the authors initially searched for studies that assessed the impact of multiple measures of adiposity, only those that focused on BMI passed inclusion criteria. Future work focusing on multiple measures of adiposity (such as waist to hip ratio, fat mass, and lean mass indices) and methods such as multivariable MR may help decipher the effect of differential body composition on cardiometabolic outcomes.[5]

As the authors state, there are no standardized tools to ascertain the risk of bias of MR studies included in meta-analyses; thus, to assess the quality of studies included, Riaz et al[1] evaluated the heterogeneity between studies for each outcome and whether the 3 key MR assumptions had been met (Figure). However, 2 of these assumptions were grouped together but are different concepts and should be treated as such. Assumption 2 (as defined by the authors) says that the genetic instrument should be independent of confounders, while assumption 3 says that the genetic instrument should affect the outcome only through the exposure (otherwise known as horizontal pleiotropy). In a 1-sample setting with rich individual-level data, it is possible to test the presence or absence of an association with measured confounding factors, which provides some evidence regarding assumption 2 (although, of course, unmeasured confounders could be associated with the genetic variants even if the measured confounders are not). With the drive toward using 2-sample MR methods, it is increasingly difficult to examine this important assumption, even in the incomplete way it can be interrogated in 1-sample settings. However, with this same move toward 2-sample MR analyses, there are increasing methods of subjecting the third assumption—absence of horizontal pleiotropy—to sensitivity analyses, which may require less stringent assumptions to hold. In addition to the referenced weighted median method they discuss, there are other approaches that aim to assess and/or account for horizontal pleiotropy, including the weighted mode[6] and MR-Egger[7] analyses.

As part of their criteria to be included within their qualitative systematic review, the authors required that a minimum of 2 studies reported an association between a measure of adiposity and cardiovascular events in nonoverlapping data. In the case where 2 or more studies used data from the same source or biobank, only the larger one was included in the quantitative meta-analysis. However, it is worth noting that, by the definition of these criteria, there was some study overlap in the articles contributing to the qualitative systematic review. Specifically, 2 articles used over 110 000 participants from UK Biobank and 2 articles used studies from the European Network for Genetic and Genomic Epidemiology Consortium. While there was no explicit overlap in the studies that contributed to the current meta-analysis, it is worth noting that as MR studies become larger, the likelihood of contributory articles including overlapping individuals becomes greater and will lead to overprecise estimates. The UK Biobank, for example, will contain individuals in some of the other UK cohorts that are included in the meta-analysis, illustrating that double counting of some

participants will already be occurring. Methods such as linkage disequilibrium score regression[8] will be important in estimating the extent of bias that such overlap could induce.

Future considerations of studies using MR methodology include the involvement of low- to middle-income countries, testing linearity of associations and identifying risk factors for disease progression (other than solely disease onset). First, a majority of MR studies include solely or largely individuals of European ancestry but, as the authors wrote, cardiovascular diseases are increasingly the leading cause of morbidity and mortality in the developing world. Therefore, future research should consider including data from low- to middle-income countries to ensure relevance to those settings.[9]

Second, MR studies typically assume linearity in all associations (ie, the genotype-exposure and exposure-outcome relationships), which may be inappropriate in some cases. With recent methodological developments, linearity can be assessed in an MR context[10] as in a recent study estimating the possible effect of BMI on all-cause and cause-specific mortality (including cardiovascular diseases) in the UK Biobank.[11] Such methods can also challenge the so-called "obesity paradox", whereby overweight individuals have the lowest mortality, risk of certain diseases, or adverse outcomes of disease compared with those who are within the normal weight range or obese, which the authors mention but cannot investigate directly.

Third, the authors state the importance of identifying novel risk factors for primary and secondary prevention of cardiovascular diseases. Most MR studies have focused on understanding primary risk factors for disease owing to the lack of availability of genome-wide association studies that focus on phenotypes that are directly related to disease progression and the complexities of using MR methodology in case-only contexts.[12]

An additional consideration relates to the use of categorical and/or binary variables as the exposure in MR studies. While in the current meta-analysis, the authors attempted to assess the effect of obesity on cardiovascular outcomes, the results presented relate to studies that estimated the continuous effects of BMI on cardiovascular outcomes. By dichotomizing BMI into obese and nonobese, in this instance, it is difficult to directly infer whether obesity itself causes variation in the risk of cardiovascular events or merely that the underlying liability to obesity influences this risk. Although in this case it is highly plausible that obesity has the effects ascribed to it, in other cases such as using MR to assess whether schizophrenia risk influences cannabis use,[13] the interpretation that this shows "a causal influence of schizophrenia" is not justified (and is highly unlikely given the low prevalence of schizophrenia). In this situation, interpretation is limited to underlying liability to schizophrenia, not to schizophrenia itself. The MR sensitivity analysis approaches remain useful tools for indicating whether this association reflects liability in general or relates to specific genetic variants.

The study by Riaz et al[1] presents the first meta-analysis, to our knowledge, of MR studies assessing the association between obesity and cardiovascular outcomes, reporting compelling evidence that each 1-SD-higher BMI increased the risk of T2D by 67% and CAD by 20% but no strong evidence for an effect on stroke. These results support a global effort to lower the increasing population trends for excess weight and suggest that in most cases, any reduction in BMI is likely beneficial.

ARTICLE INFORMATION

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