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"Mendelian randomization": using natural genetic variation to assess the causal role of modifiable risk factors in observational studies

Ian J. Neeland, MD[1,*] and **Julia Kozlitina, PhD**[2,*]

[1]Department of Internal Medicine, Division of Cardiology, University of Texas Southwestern Medical Center, Dallas, TX, USA

[2]The McDermott Center for Human Growth and Development, University of Texas Southwestern Medical Center, Dallas, TX, USA

"It is not in the stars to hold our destiny but in ourselves"

- William Shakespeare

Population-based cohort studies have established a consistent link between obesity and atrial fibrillation (AF)[1–3]. Whether this relationship is causal, though, remains a question. Associations observed in epidemiological studies could arise due to confounding by behavioral or socioeconomic factors, or as a result of obesity's common co-occurrence with hypertension, diabetes, and other established risk factors for AF. Although observational studies can adjust for known confounders using statistical techniques, the existence of unknown or unmeasured confounders and lack of precision in the measured variables can lead to residual confounding. Randomized controlled trials (RCTs) remain the gold standard for establishing the direct, causal effect of risk factor modification on the development of a disease related to that risk factor. However, RCTs are not always feasible due to the long follow-up time required to observe sufficient numbers of outcomes and the difficulties of maintaining complex intervention protocols. Indeed, no large-scale RCT of weight interventions for the prevention of AF have been reported to date. In this issue of Circulation, Chatterjee et al.[4] use the random assignment of genetic variants – an approach termed "Mendelian randomization" [5,6] – to provide support for a causal relationship between obesity and AF.

This method is founded on the principle that an individual's genotype is determined randomly at conception from his/her parental genotypes. Furthermore, according to Mendel's law of independent assortment, genetic variants governing variation in one trait are inherited independently of those influencing another trait. Therefore, genotype will in most

For Correspondence: Ian J. Neeland, MD, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Mail Code 8830, Dallas TX, 75390, Fax: 214-645-2480 Tel: 214-645-1267 ian.neeland@utsouthwestern.edu and Julia Kozlitina, PhD, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Mail Code 8591, Dallas, TX, 75390, Fax: 214-648-1666 Tel: 214-648-1446 julia.kozlitina@utsouthwestern.edu.

*Both authors contributed equally to this work.

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cases be unrelated to behavioral, dietary, and other factors that could confound the association between obesity and AF. Unlike observational studies, where obese individuals are likely to be different from those with normal weight with respect to many confounding factors, those with and without an obesity predisposing genotype are expected to be balanced with regard to measured and unmeasured confounders. For these reasons, Mendelian randomization studies have often been likened to natural randomized trials, in which genotype plays the role of random treatment assignment (Figure 1). The fact that genotype is determined before birth and stays constant throughout life also rules out the possibility of reverse causation. Hence, a difference in the outcome (AF) between the genotype groups is taken to be evidence of the causal effect of the exposure (obesity).

To perform a successful Mendelian randomization study, one needs to find a genetic variant that can reliably predict the exposure. Recent genome-wide association studies have identified multiple single nucleotide polymorphisms (SNPs) in dozens of genetic loci that are associated with increased body-mass index (BMI) and adiposity[7,8]. Because each of these variants typically exerts only a small effect on BMI, to obtain a more powerful predictor, one common approach is to combine multiple variants into a single genetic risk score, whereby all obesity predisposing alleles that a person carries are added up in a weighted sum, with weights proportional to their effect sizes. Chatterjee and colleagues used two genetic predictors of BMI: a variant in the fat mass and obesity-associated (*FTO*) gene and a BMI gene score comprised of 39 BMI-associated SNPs identified by previous genome-wide association studies[7,8]. They first confirmed that both genetic instruments were associated with increased BMI. In a meta-analysis of several prospective studies including 51,646 individuals of European ancestry, they showed that each unit increase in the genetic risk score was associated with an average increase in BMI of 1.05 kg/m^2. They next showed that the same one-unit increase in the genetic risk score was associated with an 11% increase in the risk of incident AF, lending support to the hypothesis that obesity is causally related to incident AF.

Although Mendelian randomization provides a powerful approach to strengthen the conclusions of observational studies, it has several limitations. First, as noted above, the validity of the method relies on the assumption that genotype is unrelated to any factors that could confound the exposure-outcome relationship. While this assumption is often untestable, empirical evidence suggests that it is plausible in many situations[9]. For example, a previous study[10] found no association between BMI-associated variants and several traditional risk factors of cardiovascular disease. On the other hand, an earlier study showed that a closely linked *FTO* variant was associated with blood pressure, and concluded that obesity was causally related to hypertension[11]. This alone does not invalidate the use of *FTO* variants as genetic instruments for testing the causal relationship between BMI and AF. On the contrary, this suggests that if hypertension is a direct consequence of obesity, rather than a correlate, adjusting for it could obscure the true causal role of obesity. Similar arguments may be made for other AF risk factors such as sleep apnea. Nevertheless, adjustment for hypertension and other risk factors did not alter the associations between genotype and AF in the current study. Conversely, the association between genetic variants and AF was completely attenuated after accounting for measured BMI, further supporting the notion that the relationship was causally mediated by BMI, rather than through alternate pathways, due

to pleiotropy (the effect of a particular gene on multiple risk factors) or linkage disequilibrium (statistical association between different genetic variants induced by the tendency of alleles that are close together on a chromosome to be inherited together). Second, weak genetic instruments, that explain too little variation in the exposure, could bias causal estimates or result in failure to establish causal relationships due do a lack of power. A recent article described this situation as analogous to interpreting the effects of a lipid lowering trial on coronary heart disease when the therapy studied (such as niacin or fibrates) has a weak effect on lowering LDL-cholesterol[12]. The large sample size and the use of a genetic score including multiple SNPs robustly associated with BMI partially alleviate this concern.

What are the implications of these findings? While the study provides strong support for the causal role of obesity in the development of AF, the estimate of causal effect size should be interpreted with caution and should not be extrapolated to other situations. Estimates from Mendelian randomization studies are likely to be different than the effects of weight-loss interventions for several reasons. First of all, Mendelian randomization estimates represent the effect of life-long differences in BMI, whereas most interventions are applied to individuals for a limited duration of time. In this respect, it is interesting to note that the causal effect of genetically determined BMI on AF (~10% increase in AF risk for a one-unit increase in genetically determined BMI) was larger in magnitude (but not statistically different) than the observational association between measured BMI and incident AF (5% increase in AF risk for a one-unit increase in measured BMI), suggesting that genotype may better reflect the effects of cumulative exposure to increased BMI compared with cross-sectional assessments. Second, causal effect estimates from Mendelian randomization studies can be thought of as a population-average effect (i.e., as if the intervention was applied to the entire population), and could be different than the effect of interventions applied to specific subgroups. For example, a recent analysis of the Swedish Obese Subjects (SOS) trial demonstrated that an average weight loss of 18% or nearly 50 pounds through bariatric surgery reduced the risk of AF by 29%[13]. Based on the current study, however, a similar reduction in risk should be achieved with only a ~3-point reduction in BMI, corresponding to a weight loss of 15–25 pounds (depending on one’s height). Furthermore, it is not known whether obesity-mediated risk for AF is affected by body fat distribution, which has recently been shown to be a strong determinant of cardiovascular risk, independent of BMI[14], or if it might be modified by behavioral factors, such as nutrition and physical activity. Only future RCTs can establish the true magnitude of AF risk reduction resulting from weight loss in different patient groups. Nevertheless, the data provided by Chatterjee and colleagues suggest that early prevention of obesity is likely to have a greater impact in reducing the risk of AF, and should be a focus of public health interventions.

It is important to note that while Mendelian randomization studies use genetic variants as a proxy for an exposure, their main goal is not to identify genetic determinants of disease, which might be used for genetic screening, but to provide an insight about the role of modifiable (non-genetic) exposures in disease etiology[5,6]. As has recently been demonstrated, improving one’s environment with lifestyle behaviors such as increased physical activity and a healthy diet can decrease risk of heart disease regardless of one’s inherent genetic risk[15]. Whereas genetic variants can contribute to inter-individual

differences in BMI, they cannot explain the expanding obesity epidemic over recent decades, as the genetic makeup of the population could not have changed over a span of two or three generations. Thus, lifestyle interventions directed at primary prevention of obesity may be the best way to reduce the growing prevalence of AF. Although our genetic predispositions for obesity are pre-determined at birth, they do not have to define our destiny for disease - it remains within ourselves to alter that destiny through a healthy lifestyle and avoidance of weight gain.

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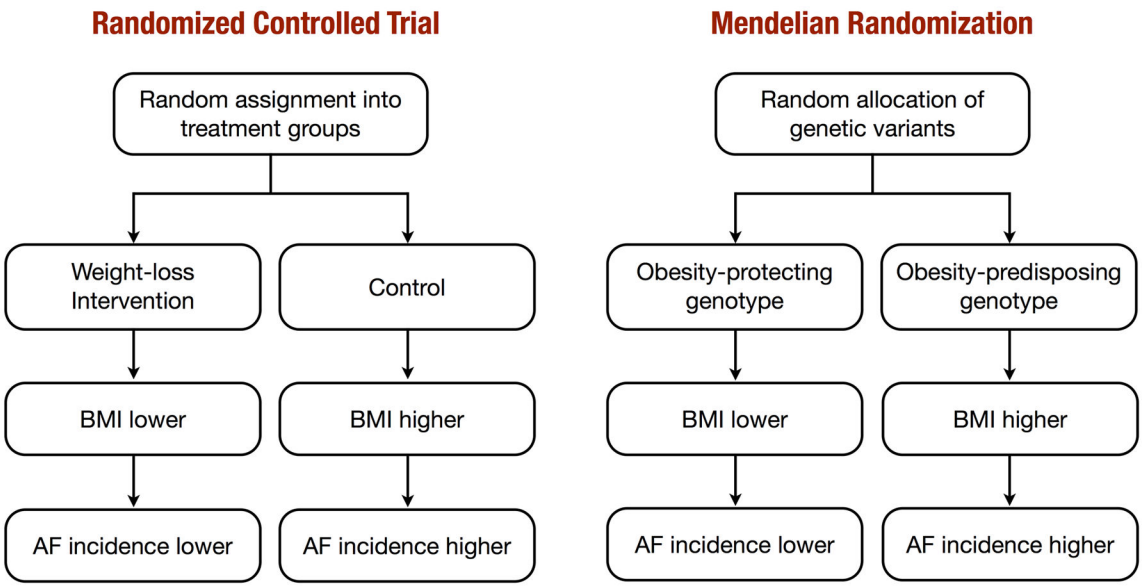

Figure 1.
Comparison of a randomized controlled trial and Mendelian randomization study