EDITORIAL

A Mendelian Randomization Approach for Assessing the Relationship Between Physical Activity and Depression

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There is a large and growing need to better manage the burden of major depression. Antidepressants are not universally effective, and many patients undergo a trial-and-error process to find the right regimen. Psychological therapies are about equally effective and can be expensive and difficult to access. Reducing the number of individuals who develop depression would be ideal, but identifying robust protective factors that are modifiable has proven challenging. Physical exercise has emerged as a key opportunity. In large cross-sectional studies,[1] individuals who exercise report significantly better mental health. In large prospective cohort studies,[2] individuals who exercise are less likely to develop depression. In randomized clinical trials,[3] people who were assigned to exercise groups had greater depressive symptom reduction than those who were not. Individuals with depression who are taking antidepressants and exercise more are significantly more likely to recover than those who exercise less.[4] Case closed, perhaps?

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Not quite. Observational studies may not identify causal mechanisms because of confounding, selection biases, and reverse causation. Randomized controlled designs are often small and expensive, can lack external validity, and primarily focus on people who are already depressed. Studies have reported bidirectional effects between exercise and mental health,[5] and the relationship depends on the specific type, duration, frequency, and intensity of exercise.[1] In this issue of *JAMA Psychiatry*, Choi and colleagues[6] help us triangulate the complex association between exercise and mental health using a statistical genetics approach called *mendelian randomization* (MR). Their study design offers clarity on 4 specific issues. First, does physical activity have a causal relationship with the risk of developing depression? Second, can we rule out potential confounding factors that are known to be associated with depression and exercise, such as body mass index, educational attainment, and income? Third, what about the reverse direction—does depression lead to reduced physical activity? Finally, does it matter whether exercise is measured according to the participant's self-report vs a more objective measure (eg, based on a wristwatch accelerometer)?

Mendelian randomization is a research method that offers insight into possible causal relationships between modifiable risk factors (eg, exercise) and health outcomes (eg, depression) by using genetic variation as a natural experiment. (Interested health care professionals might enjoy an excellent primer on MR designs by Davies et al[7] and a recent *JAMA* Guide to Statistics and Methods on MR[8]) The central idea is that gene variants can be used as instrumental variables, and because these variants are allocated randomly before birth, they are relatively independent of environmental factors (which mitigates the risk of residual confounding) and established before disease onset (which mitigates the risk of reverse causation). Put simply, if exercise causally reduces the incidence of depression, then people who carry gene variants that increase exercise should proportionally be less likely to get depressed.

Drawing on summary genetic data from approximately 300 000 adults of European ancestry, Choi et al[6] showed this to be the case. Across 10 gene variant instruments for accelerometer-based physical activity, they found a meta-analytic odds ratio of 0.74 (95% CI 0.59-0.92) for risk of major depressive disorder per 1-SD unit increase in activity (Figure 2B in the original article). Bringing these statistics back into practical terms of energy expenditure or step counts is challenging, but roughly speaking, the authors suggest that an individual replacing sedentary behavior with 15 minutes of vigorous activity (eg, running) or 1 hour of moderate activity (eg, fast walking) is approximately 26% less likely to be depressed (shown in eFigure 7 in the Supplement).

This estimate is remarkably consistent with previous observational findings, but has additional benefits. A meta-analysis of prospective cohort studies (N = 267 000) found that adults with higher levels of activity were about 22% less likely to be depressed than those who had lower levels[9]; and a large-cross-sectional study (N = 1.2 million) found that individuals who exercised experienced 43% fewer days of poor mental health per month than those who did not exercise.[1] However, because the gene variant instruments are inherited before birth and stable through life, the estimate by Choi et al[6] estimate is not affected by the usual confounders that arise throughout life (eg, social determinants of health, medical, or psychiatric events) and must be addressed in observational designs.

The 2-sample MR design is also well placed to evaluate the issue of reverse causation. Choi et al[6] can use this same logic to examine the effect of gene variants related to depression on exercise. They did not find evidence of a causal relationship between depression and self-reported or accelerometer-based activity.

Research is never simple, and the MR design depends critically on a number of assumptions. First, the design assumes that there is no separate pathway by which a gene variant might affect depression (ie, the exclusion restriction assumption). For example, if the exercise gene variants also relate to low energy, and low energy relates to depression, this relationship would represent another path through which exercise gene

variants might affect depression risk (known as *horizontal pleiotropy*). This possibility is a major concern for MR inference, and Choi et al[6] used the most up-to-date statistical methods (eg, the MR Egger intercept test) to demonstrate that their findings are robust to this issue. Moreover, when the authors took even greater precaution and removed all instrument variants that could be mapped to genes linked to relevant traits (eg, educational level, neuroticism, or body mass index), the pattern of results remains unchanged (shown in eTables 6 and 7 in the Supplement). In sum, the authors focused carefully on known weaknesses of the MR design to ensure their findings were not susceptible to potential sources of pleiotropic bias.

This study found discrepant relationships between self-reported vs accelerometer-derived activity and depression, and it is worth considering why. One should note that the MR analysis is better suited to stronger genetic instruments. That is, if the gene variants are more related to the exposure, then the MR analysis will have greater statistical power, which likely occurred in this study. The heritability of accelerometer-based physical activity is almost 3 times higher than for self-reported activity,[10] and so accelerometer-based activity may be better instrumented by gene variants than self-report activity. The definitions of activity were clearly different, too. Self-report estimates were for minutes per week of moderate to vigorous activity, whereas accelerometer measurements were mean accelerations in milligravities during a 72-hour period. Of course, self-reported exercise may simply be a poor measure of true physical activity, or individuals with mental illness may make particularly inaccurate estimates.

Where do we need to go in the future? The reality is that more findings linking exercise and mental health offer diminishing marginal returns. Given that exercise is beneficial, the key clinical question is how we increase the uptake and adherence to exercise and help individuals to measure and monitor their mental health alongside their exercise efforts. From a policy perspective, when is the most valuable time across the lifespan to implement exercise-promoting initiatives? One might target individuals of working age (given the high costs of depression on productivity and absenteeism), but many individuals experience their first depressive episode from 10 to 21 years of age, when financial incentives are less clear (ie, who would pay?). In any case, the data have told us—over and over—that exercise is a viable plan to minimize the burden of mental illness. The question is how we execute against this plan.

ARTICLE INFORMATION

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