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EDITORIAL

Mendelian Randomization Supports a Causal Effect of Depression on Cardiovascular Disease as the Main Source of Their Comorbidity

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Depression and manifestations of cardiovascular disease (CVD), including coronary artery disease (CAD), myocardial infarction (MI), ischemic stroke, heart failure, and atrial fibrillation, are strongly comorbid.[1] Given their high prevalence and the many years lost to disability caused, establishing the causality underlying their comorbidity is of huge public health value. This is not a simple mission. Apart from chance, which is non-negligible with 2 highly prevalent conditions, several mechanisms could underlie the co-occurrence of depression and CVD, ranging from biological (inflammatory processes, dysfunction in the hypothalamic-pituitary-adrenal and autonomic nervous systems, and endothelial and platelet dysfunction) and behavioral mechanisms (physical inactivity, poor eating habits, smoking, and drinking) to a shared genetic vulnerability or chronic stress linked to socioeconomic status, both of which could independently affect the risk of developing depression and CVD. Of note, these mechanisms are not mutually exclusive, and the depression-CVD comorbidity is likely a composite of all of them. The exact mixture may differ across people and possibly be symptom specific.[2]

In the era of evidence-based medicine, questions of causality are typically addressed in randomized controlled trials (RCTs). These have, for example, tested whether the treatment of depression can prevent new incidents in patients with MI or stroke.[3,4] In general, these RCTs showed little effect of pharmacological or behavioral antidepressant therapy on cardiac outcomes, the exception being a positive effect of antidepressant treatment on glycemic control in those with diabetes mellitus.[5] However, the efficacy of the interventions on depression in these trials was often small, so causal downstream effects on CVD may have been hard to detect. In the trials that did successfully reduce depressive symptoms, the duration of the beneficial intervention effects may have been too short to undo the longer running impact of depression on atherosclerosis progression.

To resolve causality in the comorbidity of depression and CVD, additional methods are needed. Of these, the mendelian randomization (MR) technique has gained by far the most popularity in the past years as the method of choice for causal inference in observational data.[6] MR is the experiment of nature that comes most close to an RCT in that participants are randomly allocated at birth to different DNA variants (the label "MR" honoring Mendel's laws of segregation and independent assortment during meiosis). If these DNA variants cause the exposure (eg, depression), participants in different genotype groups can be considered to be randomly allocated to prolonged

See Article by Lu et al.

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exposure levels. The association between the DNA variant ("the genetic instrument") influencing the exposure and the outcome (eg, CVD) estimates the causal effect independent of confounders. A further strength of MR is that it captures lifetime exposure rather than the weeks or months of exposure within an RCT. Moreover, if a genetic instrument is also available for the outcome (eg, a DNA variant causing CVD), a bidirectional variant of MR can explicitly test a possible reciprocal causal relationship between exposure and outcome. Finally, MR does not always need new data collection. The genetic instruments for both exposure and outcome can be extracted from the summary statistics of genome-wide association meta-analyses on the exposure and outcome that are made widely available in the spirit of open science by international GWAS (genome-wide association study) consortia.

Using a bidirectional MR design, 2 recent articles, with the main authors respectively based in Hong Kong[7] and Hangzou,[8] used the MR approach to resolve causality of depression-CVD. Both articles used largely, but not completely, the same publicly available GWAS resources[9–11] and followed a broadly similar series of analytical steps. *Prima facie* this may sound alarming and journals demanding strict originality could have rejected either one of these "copies" for publication. This would have been a mistake and fortunately did not come to pass (that the articles were submitted in the same time frame to different journals may have helped). Strict replication by independent groups should be considered an inevitable but also highly valuable consequence of open science and public data sharing. Furthermore, although generally following the same path, slightly different analytical choices were made by the 2 articles, which serves to create greater confidence in their (strongly) convergent conclusions.

Lu et al, in this issue of the *Journal of the American Heart Association* (*JAHA*),[8] report that a genetic doubling of the odds of depression was causally associated with a 14% increased risk of CAD and a 21% increased risk of MI. Genetic liability to depression was also associated with a 36% risk for small-vessel stroke. Directionally consistent, but nonsignificant, increases in the risks for heart failure, large-artery stroke, or cardioembolic stroke were seen, whereas the risk for atrial fibrillation was not increased. No reverse causal effect of genetic liability for CVD on lifetime depressive risk was detected despite substantial power to find a mere 5% increase in depression risk. Absence of evidence for reverse causation was robustly found across both bidirectional MR studies.[7,8] Depression, in short, appears to be the driving force behind the well-established comorbidity of depression and CVD. This is in line with their age of onset. Depression often starts in adolescence or early adulthood, whereas CVD generally starts much later.

To dissect the mechanisms in the causal pathway from depression to CVD, multivariable MR analysis was performed in which the direct causal effects of depression were tested after keeping the potential mediator constant. Attenuation of the causal estimates in multivariable MR (direct effect) compared with the univariable (total effect) implies that causal effect acts at least in part via the potential mediator (indirect effect). Across the 2 MR studies, attenuation of the effect of depression on CAD and MI was found for smoking status, type 2 diabetes mellitus, blood lipid levels, body mass index, and blood pressure. These are all well-known risk factors for atherosclerosis, suggesting that causality might be substantially mediated by these factors. Lu et al[8] found the effects of type 2 diabetes mellitus and smoking to be of particular importance. The proportion of the depression-CAD comorbidity mediated by type 2 diabetes mellitus was 41.2%, and the mediated proportion by smoking was 30.5%. For the depression-MI comorbidity, the mediated proportions by smoking and type 2 diabetes mellitus were 24.9% and 24.1%, respectively. Apart from demonstrating a causal effect of depression on CVD outcomes, Lu et al[8] therefore suggest smoking and cardiometabolic risk as 2 important mechanisms along the causal path from mental to cardiac disorders.

Past meta-analyses of large prospective studies reported an increase in the risk for CAD and MI of 30%[12] (ie, about twice that found in the 2 recent MR studies by Lu et al [2020][8] and Li et al [2020][7]), where the odds were increased by 14%/10% for CAD and by 21%/14% for MI, respectively. Combining the results from "classic" epidemiology with those from the newer genetically informed methods, 2 overarching conclusions stand out. First, some residual (genetic) confounding is present in prospective studies even when they rigidly control for known confounders. Second, more complete correction for confounding in MR still fully supports a causal effect of depression on CVD.

An important caveat with these conclusions is that GWAS used, whether on exposure, outcome, or mediators, were almost entirely based on participants of European ancestry. This reinforces the need for multiethnic GWAS consortia to ensure more equitable coverage of and generalizability to the world population. Methodological concerns about MR also remain. As with all methods, MR has to make some assumptions that, when violated, constitute a serious threat to deriving reliable causal effect sizes. MR assumes that the genetic instruments are strong (ie, they explain substantial variance in the exposure), that there is no horizontal pleiotropy, and that intergenerational transmission through the shared (family) environment can be ignored. Weak instrument bias can be partly amended by (inverse variance

weighted) averaging across multiple single-nucleotide polymorphisms, but this increases the risk of violating another important assumption of MR, the "no horizontal pleiotropy" assumption. Horizontal pleiotropy occurs when single-nucleotide polymorphisms are used as genetic instruments that have an effect on both exposure and outcome, other than through their causal path. For instance, a single-nucleotide polymorphism could influence a trait like neuroticism, which can independently affect depression and CVD. Several sensitivity analyses were used by Lu et al[8] to ensure that their findings were robust to invalid instrument bias attributable to pleiotropy. Ruling out the shared (family) environment, however, would require large-scale within-family GWASs[13] for both depression and CVD, which are not yet available.

Notwithstanding these limitations, the genetic predisposition to depression can be considered a causal risk factor of CAD and MI. This supports the idea that early diagnosis of depression may help prevent CVD, and it reinforces the need for greater investments in the prevention of depression.[14] It also suggests that strategies to alleviate depression cannot turn a blind eye to the risk it poses for developing CVD comorbidity. Already, recommendations for antidepressant medication suggest to avoid those that impact negatively on the heart and heart rhythm generators.[15] Taking this a step further, one might not just avoid potentially cardiotoxic treatments altogether, particularly in patients with cardiac conditions. Instead, deployment of antidepressant treatments that *enhance* cardiovascular health is preferable. Engaging patients in regular exercise ("running" therapy) is such a treatment.

The multifold cardiovascular benefits of regular exercise are firmly established. Many well-conducted RCTs further testify to the potential therapeutic effects of exercise in psychiatric settings.[16] Apart from being a good choice as a treatment modality, increasing physical activity levels is even more valuable in the *prevention* of depression.[17] Physical activity guideline committees around the world have stated with great confidence that a beneficial effect of physical activity on mental health is real.[18] This confidence is based on well-wrought triangulation across prospective studies, well-conducted RCTs, and genetically informed designs.[19,20] Given the evidence in this issue by Lu et al[8] for a causal role of depression in the cause of CVD, a strategy for the prevention of depression that deals an additional blow to CVD risk seems the obvious choice.

ARTICLE INFORMATION

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Disclosures

None.

REFERENCES

1. Gold SM, Kohler-Forsberg O, Moss-Morris R, Mehnert A, Miranda JJ, Bullinger M, Steptoe A, Whooley MA, Otte C. Comorbid depression in medical diseases. *Nat Rev Dis Primers*. 2020;6:70.
2. Kappelmann N, Arloth J, Georgakis MK, Czamara D, Rost N, Ligthart S, Khandaker GM, Binder EB. Dissecting the association between inflammation, metabolic dysregulation, and specific depressive symptoms: a genetic correlation and 2-sample Mendelian randomization study. *JAMA Psychiatry*. 2020:e203436. [Epub ahead of print].
3. Berkman LF, Blumenthal J, Burg M, Carney RM, Catellier D, Cowan MJ, Czajkowski SM, DeBusk R, Hosking J, Jaffe A, et al. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. *JAMA*. 2003;289:3106–3116.
4. Zuidersma M, Conradi HJ, van Melle JP, Ormel J, de Jonge P. Depression treatment after myocardial infarction and long-term risk of subsequent cardiovascular events and mortality: a randomized controlled trial. *J Psychosom Res*. 2013;74:25–30.
5. Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with diabetes mellitus and depression. *Cochrane Database Syst Rev*. 2012;12:Cd008381.
6. Davies NM, Holmes MV, Smith GD. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ*. 2018;362:k601.
7. Li GH, Cheung CL, Chung AK, Man-Yung Cheung B, Chi-Kei Wong I, Lei Yee Fok M, Chun-Ming AUP, Sham PC. Evaluation of bi-directional causal association between depression and cardiovascular diseases: a Mendelian randomization study. *Psychol Med*. 2020;9:1–12.
8. Lu Y, Wang Z, Georgakis MK, Lin H, Zheng L. Genetic liability to depression and risk of coronary artery disease, myocardial infarction, and other cardiovascular outcomes. *J Am Heart Assoc*. 2020;9:e017986. DOI: 10.1161/JAHA.120.017986.
9. Howard DM, Adams MJ, Clarke TK, Hafferty JD, Gibson J, Shirali M, Coleman JRI, Hagenaars SP, Ward J, Wigmore EM, et al. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nat Neurosci*. 2019;22:343–352.
10. Nikpay M, Goel A, Won HH, Hall LM, Willenborg C, Kanoni S, Saleheen D, Kyriakou T, Nelson CP, Hopewell JC, et al. A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. *Nat Genet*. 2015;47:1121–1130.
11. Malik R, Chauhan G, Traylor M, Sargurupremraj M, Okada Y, Mishra A, Rutten-Jacobs L, Giese A-K, van der Laan SW, Gretarsdottir S, et al. Multiancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes. *Nat Genet*. 2018;50:524–537. DOI: 10.1038/s41588-018-0058-3.
12. Gan Y, Gong Y, Tong X, Sun H, Cong Y, Dong X, Wang Y, Xu X, Yin X, Deng J, et al. Depression and the risk of coronary heart disease: a meta-analysis of prospective cohort studies. *BMC Psychiatry*. 2014;14:371. DOI: 10.1186/s12888-014-0371-z.
13. Davies NM, Howe LJ, Brumpton B, Havdahl A, Evans DM, Davey SG. Within family Mendelian randomization studies. *Hum Mol Genet*. 2019;28:R170–R179. DOI: 10.1093/hmg/ddz204.
14. Patel V, Burns JK, Dhingra M, Tarver L, Kohrt BA, Lund C. Income inequality and depression: a systematic review and meta-analysis of the association and a scoping review of mechanisms. *World Psychiatry*. 2018;17:76–89. DOI: 10.1002/wps.20492.
15. Beach SR, Kostis WJ, Celano CM, Januzzi JL, Ruskin JN, Noseworthy PA, Huffman JC. Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. *J Clin Psychiatry*. 2014;75:e441–e449. DOI: 10.4088/JCP.13r08672.
16. Schuch FB, Vancampfort D, Richards J, Rosenbaum S, Ward PB, Stubbs B. Exercise as a treatment for depression: a meta-analysis adjusting for publication bias. *J Psychiatr Res*. 2016;77:42–51. DOI: 10.1016/j.jpsychires.2016.02.023.
17. Hu MX, Turner D, Generaal E, Bos D, Kamran Ikram M, Arfan Ikram M, Cuijpers P, Penninx BWJH. Exercise interventions for the prevention of

depression: a systematic review of meta-analyses. *BMC Public Health*. 2020;20:1255. DOI: 10.1186/s12889-020-09323-y.

18. Stubbs B, Vancampfort D, Hallgren M, Firth J, Veronese N, Solmi M, Brand S, Cordes J, Malchow B, Gerber M, et al. EPA guidance on physical activity as a treatment for severe mental illness: a meta-review of the evidence and Position Statement from the European Psychiatric Association (EPA), supported by the International Organization of Physical Therapists in Mental Health (IOPTMH). *Eur Psychiatry*. 2018;54:124–144. DOI: 10.1016/j.eurpsy.2018.07.004.
19. Choi KW, Chen CY, Stein MB, Firth J, Veronese N, Solmi M, Brand S, Cordes J, Malchow B, Gerber M, et al. Assessment of bidirectional relationships between physical activity and depression among adults a 2-sample Mendelian randomization study. *JAMA Psychiatry*. 2019;76:399–408. DOI: 10.1001/jamapsychiatry.2018.4175.
20. Schuch FB, Stubbs B. The role of exercise in preventing and treating depression. *Curr Sports Med Rep*. 2019;18:299–304. DOI: 10.1249/JSR.0000000000000620.