

Air pollution and psychiatric outcomes - is Mendelian randomisation an appropriate analysis? [Correspondence]

REYNOLDS, Gavin <<http://orcid.org/0000-0001-9026-7726>>

Available from Sheffield Hallam University Research Archive (SHURA) at:

<https://shura.shu.ac.uk/36328/>

This document is the Accepted Version [AM]

Citation:

REYNOLDS, Gavin (2025). Air pollution and psychiatric outcomes - is Mendelian randomisation an appropriate analysis? [Correspondence]. *Journal of affective disorders*, 391: 120061. [Article]

Copyright and re-use policy

See <http://shura.shu.ac.uk/information.html>

Air pollution and psychiatric outcomes - is Mendelian randomisation an appropriate analysis?

Gavin P Reynolds

Biomolecular Sciences Research Centre

Sheffield Hallam University

Sheffield U.K.

and

Rotherham, Doncaster and South Humber NHS Foundation Trust.

Doncaster U.K.

Orcid: 0000-0001-9026-7726

Gavin.reynolds@shu.ac.uk

The recent paper by Zhou et al. (2026) adds to the many studies supporting a role for air pollution in the development of several psychiatric disorders. The authors attempt to demonstrate causal associations between exposure to air pollution and psychiatric diagnoses by employing Mendelian randomisation (MR). This valuable and powerful technique employs genetic variants associated with an environmental exposure as a proxy for that exposure to investigate a potentially causal influence of exposure on outcome. In this case the genetic instrument is generated from GWAS data associated with the air pollution measures ascribed to the residential address where the individual subject lives.

One might ask what the biological factor(s) might be for a genetic association with exposure to air pollution; Zhou et al. (2025) certainly do not do this. While it cannot be denied that genetic associations are reported, it is impossible to identify, or even perhaps to imagine, what a direct biological mechanism may be. Others have also identified this as a concern. Tellingly, the expert critique of MR from Burgess et al. (2024) uses air pollution as a key example of an environmental factor for which a genetic association is implausible, in which case the use of MR is inappropriate.

How then have the authors managed to generate genetic instruments for MR analysis if a genetic basis for exposure to air pollution is inconceivable? The UK Biobank, which Zhou et al (2025) interrogated for their study, does not provide a measure of individual exposure to air pollution but uses pollution levels at residential addresses of participants as a proxy measure. Further factors associated with residential address of Biobank participants include measures of socioeconomic deprivation - poor housing and living environment, low household income, health deprivation and disability etc. Importantly, such measures of deprivation, particularly in an urban environment, are associated with levels of air pollution in which higher pollution is related to more severe deprivation (The Health Foundation, 2024). Some of these factors are likely to have some biological plausibility for genetic association, relating as they do to educational attainment, health status and so on.

It seems likely, therefore, that the apparent genetic association with residential measures of air pollution is driven by biologically more plausible associations with other factors associated with socioeconomic deprivation and which, importantly, can include psychiatric illness (Qi et al., 2022). Thus high air pollution is associated with residential areas of socio-economic deprivation which may include relatively higher prevalence of psychiatric diagnoses. Hence a genetic association with these residential areas will reflect this demographic and will likely include genetic factors associated with psychiatric disease. Therefore it is fallacious to conclude that any genetic commonality between residence in areas of high air

pollution and psychiatric diagnosis relates to a causal relationship. The approach of Zhou et al (2025) would appear to violate a particular requirement of MR analyses, i.e. that the genetic instrument can only influence the outcomes (psychiatric diagnoses) through its effect on the exposure (air pollution).

Of course, these arguments do not disprove the important and increasingly-recognised relationship between air pollution and psychiatric illness; there is strong, if mainly circumstantial, evidence for pollution as a risk factor for psychiatric disorders which Zhou et al (2025) refer to. However a causal link is not established, and interrogating epidemiological databases such as the UK Biobank by using residential area as a proxy for air pollution exposure is inevitably flawed.

In conclusion, it is important to reiterate the point made by Burgess et al. (2024) to emphasise that one essential requirement for MR studies is for there to be a biological plausibility for an association of a genetic instrument with an exposure. This appears not to be the case for studies of the consequences of air pollution.

References

Burgess, S., Woolf, B., Mason, A.M., Ala-Korpela, M., Gill, D., 2024. Addressing the credibility crisis in Mendelian randomization. *BMC Med.* 22, 374. Published 2024 Sep 11. doi:10.1186/s12916-024-03607-5

The Health Foundation, 2024. Inequalities in likelihood of living in polluted neighbourhoods. <https://www.health.org.uk/evidence-hub/our-surroundings/air-pollution/inequalities-in-likelihood-of-living-in-polluted> (accessed 18th July 2025)

Qi, X., Jia, Y., Pan, C., et al., 2022. Index of multiple deprivation contributed to common psychiatric disorders: A systematic review and comprehensive analysis. *Neurosci. Biobehav. Rev.* 140, 104806. doi:10.1016/j.neubiorev.2022.104806

Zhou, J., Lu, Z., Xu, K., et al., 2025. Air pollution is the risk factor for psychiatric disorders: a two-step Mendelian randomization study. *J. Affect. Disord.* Published online May 26, 2025. doi:10.1016/j.jad.2025.119475