OPEN ACCESS

University of BRISTOL

Davey Smith, G. (2023). Mendelian randomisation and vitamin D: the importance of model assumptions. *Lancet Diabetes and Endocrinology*, *11*(1), 14. https://doi.org/10.1016/S2213-8587(22)00345-X

Peer reviewed version

License (if available):
CC BY-NC-ND

Link to published version (if available):
10.1016/S2213-8587(22)00345-X

Link to publication record in Explore Bristol Research
PDF-document

This is the accepted author manuscript (AAM). The final published version (version of record) is available online via Elsevier at https://doi.org/10.1016/S2213-8587(22)00345-X. Please refer to any applicable terms of use of the publisher.

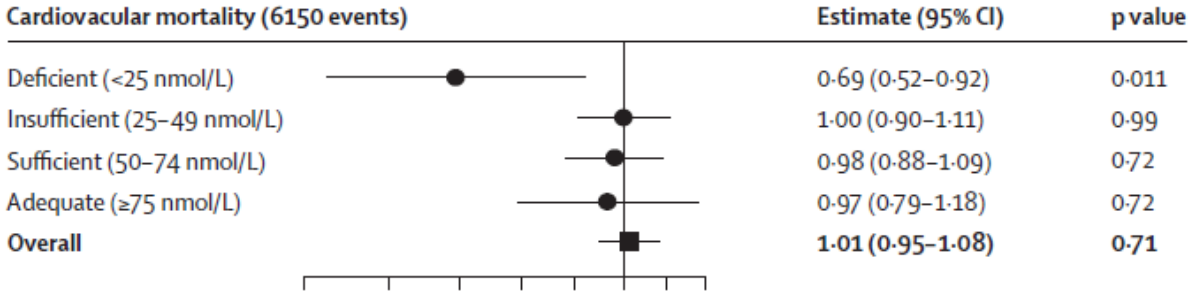
University of Bristol - Explore Bristol Research
General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/

The analyses presented in "Estimating dose-response relationships for vitamin D with coronary heart disease, stroke, and all-cause mortality: observational and Mendelian randomisation analyses", published in *Lancet Diabetes & Endocrinology*[1] raise issues of concern. One figure from the paper is reproduced below. Applying Mendelian randomization (MR)[2] techniques this purports to suggest there is a substantial causal preventive effect of vitamin D levels in those defined as being "deficient" in vitamin D, but little causal effect (although with central effect estimates in the protective direction or null) in the other three strata examined and a positive (but imprecisely estimated) direction of estimated causal effect in the overall study sample. Unfortunately, this has low plausibility. Combining a causal interpretation of Simpson's paradox[3] together with the intention of MR to estimate causal effects, it is difficult to envisage situations in which the key assumptions of the MR analysis are not violated and assumptions regarding other causal effects are consistent with what is known. The central finding of the paper – a detrimental effect of low levels of vitamin D at the lower end of the population distribution – was endorsed by the *Lancet Diabetes & Endocrinology* editorial[4], has been "replicated" within the same data set using the same analytical approach[5], and the method it is based on is being widely used. When considering findings from such analyses caution should be applied.

Mendelian randomisation estimates for primary outcomes in overall population and strata of residual 25(OH)D concentrations[1]

Estimates (95% CIs) represent odds ratios per 10 nmol/L increase in genetically-predicted concentration of 25(OH)D in strata of the population defined by residual concentration of 25(OH)D.



References:

1. Sofianopoulou E, Kaptoge SK, Afzal S, et al. Estimating dose-response relationships for vitamin D with coronary heart disease, stroke, and all-cause mortality: observational and Mendelian randomisation analyses. *The Lancet Diabetes & Endocrinology* 2021; **9**(12): 837-46.
2. Sanderson E, Glymour MM, Holmes MV, et al. Mendelian randomization. *Nature Reviews Methods Primers* 2022; **2**(1): 6.
3. Hernán MA, Clayton D, Keiding N. The Simpson's paradox unraveled. *International Journal of Epidemiology* 2011; **40**(3): 780-5.
4. Butler-Laporte G, Richards JB. Targeting of vitamin D supplementation to individuals with deficiency. *The Lancet Diabetes & Endocrinology* 2021; **9**(12): 803-4.
5. Sutherland J, Zhou A, Hyppönen E. Vitamin D Deficiency Increases Mortality Risk in the UK Biobank. *Annals of Internal Medicine* 2022.

George Davey Smith, FRS
Director, MRC Integrative Epidemiology Unit, University of Bristol
Email: kz.davey-smith@bristol.ac.uk