Methodological issues in designing and reporting of systematic reviews in assessing association between vitamin D supplementation and COVID-19 severity

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Keywords: Methodological quality, Meta-analysis, Vitamin D supplementation, PROSPERO, PRISMA reporting guidelines, COVID-19 severity

We have read with interest the article of Shah et al. 'Does vitamin D supplementation reduce COVID-19 severity?: a systematic review'.[1] Systematic reviews (SRs) and meta-analysis are critical in policy and clinical decision-making for the welfare of patients to minimise burden of a disease or health condition. The authors argue that vitamin D supplementation is effective in reducing the COVID-19 severity, but we identified several methodological issues related to planning (no information on PRSOPERO (International Prospective Register of Systematic Reviews) registration), conduct (non-reproducible literature search), analytical methods (misleading and biased analysis plan), and its reporting (not following PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2020 checklist[2]) that limits the acceptability and generalisability of the findings from this study and could mislead clinical decision-making. Most COVID-19 SRs were poorly designed as outlined in a methodological review of 243 COVID-19 SRs that identified 87.6% reviews were of low quality or critically low quality.[3] Producing such low-quality evidence in SRs is clearly a research waste and misleading to policymakers.

One of the serious problems in this systematic review is combining all study designs in meta-analysis with unadjusted data. A recent SR of 16 studies showed inconsistent results when comparing vitamin D levels between the COVID-19 positive and negative patients when stratified by the study design (case-control: mean difference [MD] -4.08, 95% confidence interval [CI] -5.98 to -2.10; cohort: MD -0.39, 95% CI -1.62 to 0.84) which clearly indicate that findings can be heavily confounded by the factors controlled within the study design.[4] A large cohort study using the UK Biobank data with 307,512 participants has also found no evidence that vitamin D deficiency or insufficiency was associated with either hospitalisation or mortality due to COVID-19.[5] Using crude estimates from the observational studies in meta-analysis can introduce bias (such as selection and immortal time biases). Meta-analysis of observational studies is always challenging as not all studies report the adjusted estimate (to avoid possible confounding in meta-analysis) for the outcome of interest. Where possible, adjusted estimates should be used for pooling as recommended in the Cochrane handbook.[6] Several meaningful subgroup analyses (such as by study design, gender, and disease severity etc.) can also be helpful in exploring heterogeneity which will help in interpreting results.

Additionally, authors have conducted systematic review of systematic reviews (commonly known as 'overview' or 'umbrella review') without properly following its methodology as outlined in the literature and not mentioning it anywhere in the report which is misleading to researchers/readers.[7] For example, authors have used GRADE (Grading of Recommendations, Assessment, Development and Evaluations) for quality of evidence however, it is not useful in Overviews due to the overlapping of primary studies. Authors have completely ignored several key aspects such as the reporting of prediction intervals (PIs), choice of effect estimate, excess statistical significance, and evidence of small-study effects which are used in preparing a threshold of convincing associations (by combing multiple methodological criteria) in overviews.[8] Authors have reported high overlap (13.8%) of primary studies in the included systematic reviews which may have introduced bias due to the double-counting of influential primary studies. The most appropriate approach to include or not the primary studies may depend on the purpose (to answer a new review question about a subpopulation, or to present and

describe the current body of systematic review evidence on a topic) of the Overview and on the method of data analysis.

To conclude, it is a collective responsibility of the journal editorial office, reviewers, and authors to pay proper attention in future on the methodological aspects to improve the conduct and reporting of such studies to benefit the researchers at large.

COMPETING INTERESTS

The authors have no competing interests to declare.

ACKNOWLEDGEMENTS

Ram Bajpai is affiliated to the National Institute for Health and Care Research (NIHR) Applied Research Collaboration (ARC) West Midlands. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

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