Challenges in Interpreting Mendelian Randomization Studies with Instruments of Diseases: Using COVID-19 Mendelian Randomization Studies as an Exemplar

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Background

Mendelian randomization (MR) studies using disease as exposures are increasingly prevalent[1] although there are challenges in interpreting any observed associations, including the presence of association in MR have various interpretations.[2-4] To highlight these challenges, we conducted a systematic review of MR studies which aimed to investigate the consequence of COVID-19, where we speculated majority of the outcome GWAS were conducted prior to 2019 and hence any observed associations in these studies were unlikely driven by COVID-19.

Objectives

To conduct a systematic review of MR studies which aimed to investigate the consequence of COVID-19 with quality evaluation.

Methods

We systematically searched PubMed, EMBASE and MEDLINE for all MR studies published between 2019 and 20 May 2023. Inclusion criteria included Mendelian randomization studies which used COVID-19 as the exposure and intended to explore the effect of COVID-19 in health outcomes. We extracted information including assessment of “relevance” assumption, main findings, how likely the outcome GWAS contained COVID-19 cases, and corresponding result interpretation. This review was registered at PROSPERO (CRD42023421079).

Results

This review included fifty-seven (57) MR studies. Forty-five (45) studies used outcome GWAS published prior to 2019 whilst the remaining studies likely used outcome GWAS containing data prior to 2019. Assessment of relevance assumption was mainly based on P values. Thirty-five (35) studies showed a possible association of COVID-19 liability with health outcomes. However, regardless of the presence/absence of associations, forty-five (45) studies attributed these as evidence (or lack of evidence) of COVID-19 consequence.

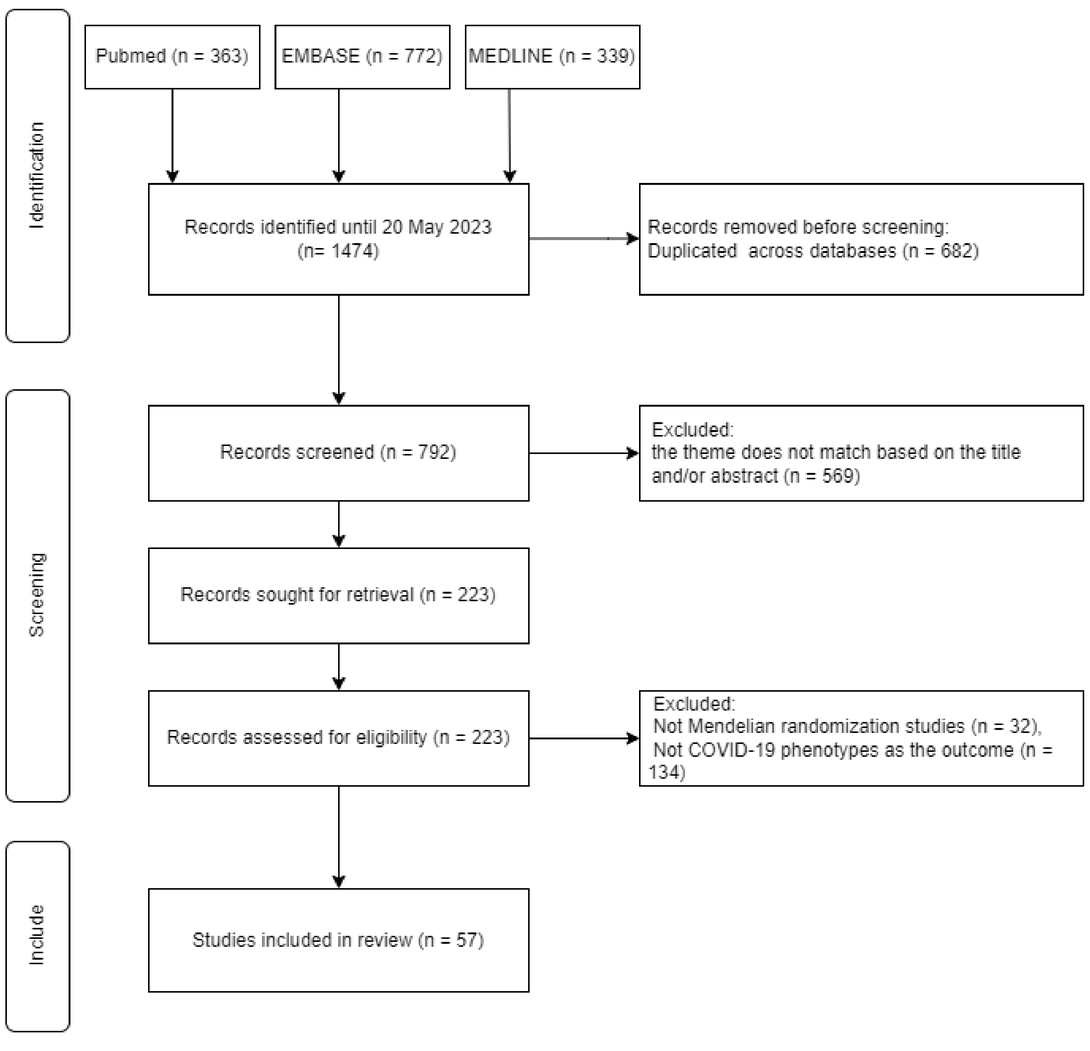

Figure 1. Selection process of this systematic review

	Number (Proportion)
Using outcomes GWAS published prior to 2019	45 (79%)
Outcome GWAS using data collected prior to 2019	57 (100%)
Selecting instruments based on P values	54 (95%)
Reporting F-statistics	26 (46%)
Showing possible association between genetic liability to COVID-19 with health outcomes	35 (61%)
Attributing the observed (or lack of) association as evidence of COVID-19 consequence, or absence of evidence of COVID-19 consequence	45 (79%)

Table 1. Summary of results in this review

Discussion

Multiple studies reported possible association of genetic liability of COVID-19 with disease outcomes such as coronary artery disease, type 2 diabetes, and hypertensive disorders, where these studies attributed the observed association as a consequence of COVID-19,[5-7] which is biologically implausible. It implicates the authors should be more cautious about the interpretation of association identified by MR and take into account the overall characteristics of populations, such as the prevalence of the disease in the outcome GWAS, where higher prevalence may increase the likelihood of the association being a reflection of consequence of the disease (the consequence of exposure in MR). Strength of this study included highlighting the possible hurdles of using disease status as an exposure in MR; However, this study had some limitations, including the variations of quality of included studies.

Conclusion

Better understanding of the relevance assumption would be important to improve the design of 2 sample Mendelian randomization studies using disease traits as exposures.

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Conflict of interest

None declared.