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Alcohol Use and Mental Health: How Genetic Information Can Help Unravel Their Relationship

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Abstract

Background: Traditional epidemiological evidence suggests various associations exist between alcohol and mental/cognitive health outcomes. However, whether these reflect causal relationships remains unclear. Mendelian randomization (MR) – a kind of instrumental variable analysis using genetic variants to proxy for an exposure of interest – has the potential to improve causal inference from observational data. ***Summary:*** In the first part of this review, the challenges of causal inference in the field are discussed, and a theoretical and practical introduction to the technique of MR is given. Next, we report on literature searches performed to update a previous systematic review of MR studies evaluating alcohol-mental health relationships. Twelve relevant studies were identified and considered in the context of the 22 studies included in the previous review. While the reviewed MR literature suggests possible causal relationships/a lack thereof, for the most part, the nature of causal relationships between alcohol and mental health remains unclear. ***Key Messages:*** MR is beginning to yield valuable insights into the causal effects of (problematic) alcohol consumption on mental and cognitive health outcomes. Future studies must be mindful of the technique's underlying assumptions and should allow for potential nonlinearity in relationships. Triangulating across sensitivity methods within MR studies, as well as between MR studies and other methods for enhanced causal inference, will be crucial.

Introduction

Comorbidities between heavy alcohol use/alcohol use disorder and mental illness have been widely reported [1]. However, identifying the precise mechanisms underlying relationships between problematic alcohol use and mental illness is challenging because both are complex and multifactorial traits. There are different possible explanations for why problematic alcohol use is associated with a higher risk of mental illness: there are shared risk factors (e.g., stressful life events or shared genetic liability), causal effects where alcohol use increases the risk of mental illness, and/or causal effects where mental illness increases problematic alcohol use. For preventive efforts as well as treatment of problematic alcohol use or mental illness, causal relationships and their direction are of particular interest. Given that randomized controlled trials are not ethical or feasible for the relationships under study here, and the fact that conventional methods such as longitudinal cohort studies are subject to bias from confounding and reverse

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causality, advanced causal inference methods are required. In this mini-review, we (1) describe Mendelian randomization (MR), a genetic instrumental variable approach used to test causality in complex relationships such as between alcohol use and mental illness, (2) review all MR studies looking at any measure of alcohol use and any measure of mental health (including symptoms and cognitive outcomes) conducted so far, and (3) reflect on the current state of the field and provide recommendations for future research.

The Challenge of Causal Inference

There is a long history of epidemiological studies looking at alcohol use and health outcomes and finding a so-called "J-shaped" curve. Those who drink small to moderate amounts of alcohol on average often appear to have better health than those who drink no alcohol at all, with risk increasing again for very heavy alcohol users [2]. These types of studies are based on observational data (either cross-sectional or longitudinal), and while in most cases, potential confounders will have been corrected for in the analyses, there is still a very high risk of bias. First, bias from confounding can arise when not all relevant confounders have been considered or via measurement error [3]. For alcohol use, the most relevant and impactful confounders are socioeconomic status and related variables such as income and type of employment. Often, when socioeconomic status is rigorously accounted for, protective effects disappear. These variables are especially difficult to fully correct for because they drive much of a person's environment and experiences. Second, reverse causality is a major source of potential bias which cannot properly be accounted for with conventional observational methods. For instance, it has been suggested that the J-shaped curve between alcohol use and mortality appears because worsening health makes people stop drinking [4, 5], shifting more unhealthy people into the "abstinent" category. Work in recent years has helped elucidate the nature of many alcohol-health relationships, but for alcohol use and mental health, much less is known. There are clear associations between very heavy/disordered alcohol use and several mental health conditions [1], as well as J-shaped findings for particular outcomes (e.g., depression; [6]). However, given the aforementioned sources of bias, causality in these relationships is unclear.

Mendelian Randomization

The field of human genetics has seen major developments in the past decades, leading us to the current era of genome-wide association studies (GWASs; [7]). A GWAS tests the association between a trait of interest and millions of genetic variants, usually single-nucleotide polymorphisms (SNPs). Current GWAS sample sizes range from hundreds of thousands to over a million people. Large-scale GWASs are now available for alcohol use frequency, quantity, and dependence [8–10], as well as for major mental illnesses [11]. The main goal of a GWAS is to identify SNPs that are "genome-wide significant" (usually $p < 5E\text{-}08$) and are therefore assumed to play a role in the genetic etiology of the trait of interest. However, there are also numerous follow-up analyses that can be done by leveraging the "summary-level" data of a GWAS study. Summary-level data refer to the summarized effect estimates, across all study participants, of all included genetic variants. One of those follow-up analyses is MR, a method which allows for causal inference and has rapidly gained popularity.

MR is a method that uses genetic variants as instrumental variables, or proxies, for the exposure of interest and tests if there is a causal effect on an outcome of interest. MR relies on three core assumptions: (1) the SNPs are associated with the exposure ("relevance"), (2) the SNPs are *not* associated with confounders of the exposure-outcome relationship ("exchangeability"), and (3) the SNPs affect the outcome only via their effect on the exposure ("exclusion restriction"). For a complete overview of these and other crucial assumptions, caveats, and misconceptions around MR, please see Richmond and Davey Smith [12].

Initially, MR analyses were performed with data from a single sample ("one-sample" MR), using individual-level data. This involves using each individual's data on genotype, exposure, and outcome to estimate the SNP-exposure and SNP-outcome relationships. However, as large-scale GWAS findings have become increasingly available, two-sample MR – which involves combining the SNP -exposure estimates from one dataset and SNP-outcome estimates from another – has become the dominant method. See Figure 1 for a depiction of two-sample MR and the general MR assumptions.

Genetic instruments are almost always composed of multiple SNPs. The most common way to generate a single estimate is to first calculate all SNP-specific effects (ratio of SNP-outcome relationship to SNP-exposure relationship, also called the "Wald ratio") before meta-analyzing these with weights based on the inverse of the variance of the SNP-outcome relationship. However, the estimates of such inverse-variance weighted regression analysis will be biased if any of the core assumptions are violated – of particular concern is horizontal pleiotropy, where SNPs may be affecting the disease outcome via a path that does not involve the exposure of interest. As a

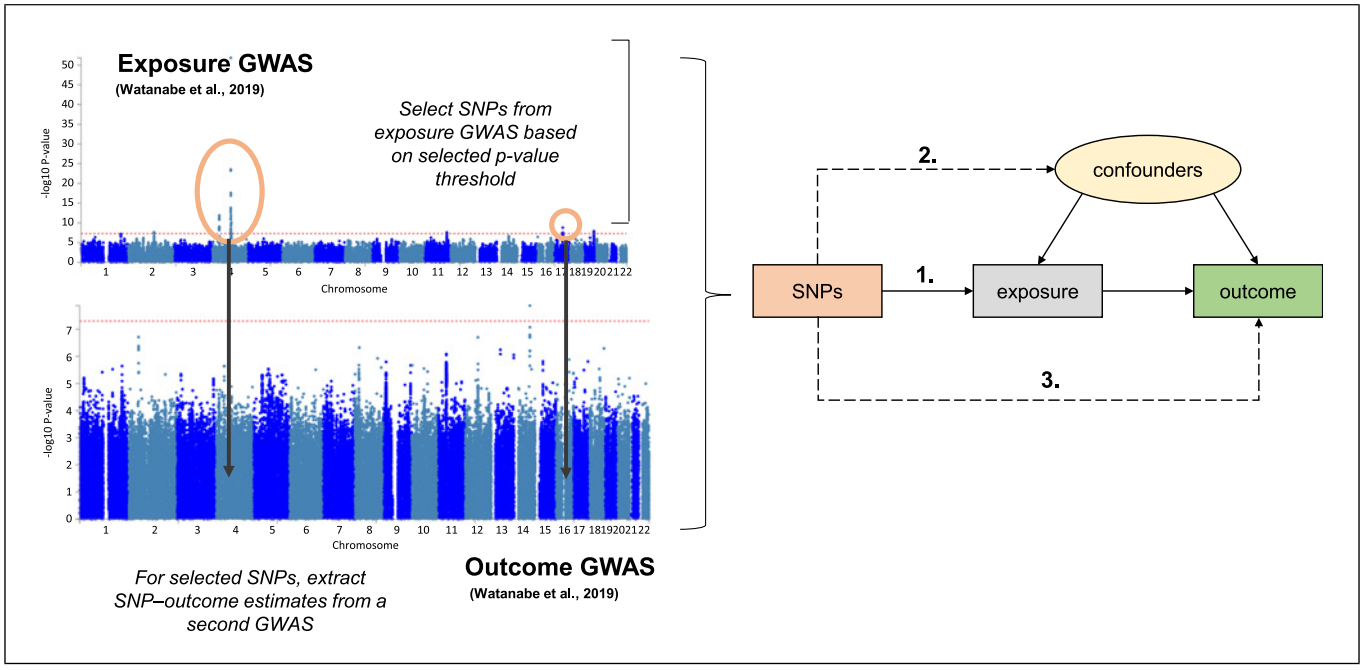

Fig. 1. Two-Sample MR using SNPs from an exposure GWAS (source Manhattan plot: amount of alcohol drunk on a typical drinking day [47] extracted from the GWAS atlas) as instrumental variables under the following assumptions: (1) the genetic instruments are robustly associated with the exposure, (2) the genetic instruments are independent of confounders, and (3) the genetic instruments are not associated with the outcome except indirectly through the exposure (outcome GWAS [47]: major depressive disorder, single episode, extracted from GWAS atlas).

result, it is best practice to perform multiple sensitivity methods that are robust to different kinds of bias. Concordance in findings across methods is crucial for confidence in results. In the context of one-sample MR, an alternative option is combining multiple SNPs into a single genetic risk score to be used as the instrument.

MR Studies on Alcohol and Mental Health

Search Strategy

We updated findings of a previous systematic review by Treur and colleagues [13], the search for which was conducted in April 2020. As such, we performed a literature search of Medline for published, peer-reviewed papers reporting on MR analyses of alcohol use or alcohol use disorder in combination with mental health (including diagnoses, subclinical symptoms, and cognitive functioning) that were published after April 2020 (search terms provided in online suppl. Table 1; for all online suppl. material, see https://doi.org/10.1159/000538454). Studies had to have examined potential causal effects from alcohol to mental health (studies investigating bidirectional effects were also included). We also searched preprint servers (bioRxiv and medRxiv). The search was performed on April 28, 2023, and restricted to English-language papers published from 2020 onward.

Quality

Based on criteria developed for the previous review (see online suppl. Table 2), key indicators of study quality were extracted including those related to phenotype measurement, sample size, instrument strength (e.g., *p* value threshold of selected SNPs, F statistic), main analytical methods, and use of sensitivity analyses to explore potential bias from violated assumptions. A total score of "–", "–+", or "+" was awarded based on these features, with "–+" requiring sufficient sample size and main analytical methods, and "+" further requiring extensive sensitivity methods.

Results

We identified 218 potentially relevant records for title and abstract screening, 12 of which met inclusion criteria for this review (10 peer-reviewed papers and 2 preprints; see Table 1). The outcomes spanned cognitive traits (educational attainment [EA], cognitive impairment, executive

Table 1. All MR studies included for qualitative synthesis with their identifying information, description of the exposure and outcome variable(s), whether the study used individual-level (1-sample) and/or summary-level (2-sample) data, the total quality rating, and a brief summary of their findings

First author (year)	Individual/ summary-level data	Alcohol variable	Mental health outcome	Quality	Methods used	Findings
Cui et al. [14] (2022)	Individual	1. Current drinking 2. Consumption frequency 3. Weekly volume consumed	A. MCI	"–"	2. SLS regression	1 ↑ A 2 ↑ A 3 ↑ A
Burton et al. [16] (2022)	Summary	1. Drinks per week 2. Alcohol dependence	A. Executive functioning	"–+"	IVW, MR-Egger, weighted median, simple mode, weighted mode, Steiger filtering	1 ↑↓ A 2 ↑↓ A
Yang et al. [21] (2020)	Summary	1. Drinks per week	A. Alzheimer's disease	"–+"	IVW, MR-Egger, weighted median, simple mode, weighted mode	1 ↑↓ A
Demange et al. [24] (2023)	Summary	1. Alcohol dependence	A. EA	"–"	IVW, MR-Egger, weighted mode, weighted median	1 ↑↓ A
Jang et al. [25] (2022)	Summary	1. Drinks per week	A. EA B. Schizophrenia C. Major depressive disorder D. Bipolar disorder	"–+"	Latent causal variable, Pickrell, IVW, weighted median, weighted mode, MR-Egger	1 ↑↓ A 1 ↑↓ B 1 ↑↓ C 1 ↑↓ D
Pasman et al. [28] (2020)	Summary	1. Drinks per week 2. Alcohol dependence	A. Insomnia	"+"	IVW, weighted median, weighted mode, MR-Egger, generalized summary-data-based MR, Steiger filtering	1 ↑↓ A 2 ↑↓ A
Chakravorty et al. [29] (2023)	Summary	1. Alcohol use disorder 2. Alcohol consumption level	A. Insomnia B. Shorter sleep duration	"–+"	IVW, MR-Egger, weighted median, simple mode, weighted mode	1 ↑ A 1 ↑↓ B 2 ↑↓ A 2 ↓ B
Bountress et al. [31] (2021)	Summary	1. Drinks per week 2. Alcohol use disorder	A. PTSD	"–+"	MR-RAPS	1 ↑↓ A 2 ↑↓ A
Cai et al. [32] (2022)	Summary	1. Drinks per week 2. Alcohol use disorder	A. Bipolar disorder B. Major depressive disorder C. Schizophrenia	"+"	IVW, MR-Egger, weighted median, weighted mode	1 ↑↓ A 1 ↑↓ B 1 ↑↓ C 2 ↑↓ A 2 ↑↓ B 2 ↑↓ C
Orri et al. [37] (2021)	Summary	1. Drinks per week	A. Suicide attempt	"–+"	IVW, MR-Egger, weighted median, MR-RAPS	1 ↑ A

Table 1 (continued)

First author (year)	Individual/ summary-level data	Alcohol variable	Mental health outcome	Quality	Methods used	Findings
Colbert et al. [38] (2021)	Summary	1. Problematic alcohol use	A. Lifetime self-harm	"–"	Cause	1 ↑↓ A
			B. Suicide attempt			1 ↑↓ B
			C. Suicide death			1 ↑↓ C
Villar-Ribo et al. [40] (2021)	Summary	1. Alcohol dependence	A. ADHD	"–"	IVW, MR-Egger, weighted median, MR-PRESSO, Steiger filtering	1 ↑↓ A

↑ indicates a significant positive causal effect, ↓ indicates a significant negative causal effect, and ↑↓ indicates no significant causal effects were found (for alcohol use on the outcome). IVW, inverse-variance weighted regression analysis.

function, Alzheimer's disease), sleep problems, internalizing disorders (depression, bipolar disorder, posttraumatic stress disorder [PTSD]), externalizing disorders (self-harm/suicide, attention-deficit/hyperactivity disorder [ADHD]), and psychotic disorders (schizophrenia). Regarding quality, 4 papers were awarded "–", 6 "–+", and 2 "+" (see online suppl. Tables 3, 4, and 5 for quality details of each study). These 12 papers add to the 22 studies published before 2020 reported in the previous review.

Cognitive Traits

Mild Cognitive Impairment

Cui and colleagues examined the causal effect of alcohol consumption on mild cognitive impairment (MCI) using one-sample MR in a rural Chinese sample [14]. In the study, the authors found that three alcohol consumption phenotypes (self-reported current drinking, self-reported total frequency of consumption of three kinds of alcohol drinks, and weekly ethanol consumption) were causally associated with a higher risk of MCI. However, given the very small sample size of the study ($N = 235$), its quality rating was "–", and replication of this finding in a larger sample is necessary before drawing strong conclusions based on these findings. The previous review by Treur et al. reported on one (low-quality) paper [15] that found no clear causal effects of alcohol use frequency on cognitive impairment.

Executive Function

Burton and colleagues examined causal relationships between mental health and substance use, among which were alcohol consumption (drinks per week) and alcohol dependence, as well as executive function [16] (rating "–+"). Using two-sample MR, the authors found no evidence for causal effects of the different alcohol phenotypes on executive function, but some evidence of a causal effect of increased executive function on decreased number of alcoholic drinks per week (no effect on alcohol dependence). While the previous review by Treur et al. found no papers on executive functioning, for cognitive function more generally, there was no clear evidence that alcohol consumption had a causal effect (although all studies were rated of low quality [17–20]).

Alzheimer's Disease

One relatively well-powered study by Yang and colleagues examined bidirectional causal associations between different types of risky behaviors, including drinks per week and Alzheimer's disease, using two-sample MR [21] (rated "–+"). There was no evidence for a causal effect of drinks per week on liability for Alzheimer's disease, but a weak causal effect of Alzheimer's disease reducing number of drinks per week. The previous review by Treur et al. summarized two prior studies examining alcohol's effects on Alzheimer's disease [22, 23]. Again, neither study found causal effects of drinks per week (nor problematic alcohol use) on risk for Alzheimer's disease diagnosis. One of the two also looked at time to onset, finding that increasing drinks per week caused an earlier onset but that alcohol use disorder caused a later onset (a possible product of survivor bias).

Educational Attainment

A preprint by Demange and colleagues examined causal relations between EA and different mental health outcomes (including alcohol dependence) using a triangulation design that included both sibling-control analyses and two-sample MR [24]. Alcohol dependence was not associated with EA, while higher EA was associated with a reduced risk of alcohol dependence across both the MR and sibling-control analyses. While this paper was awarded a rating of "–" due to small sample size, it performed well on other quality markers such as performing several sensitivity tests.

Jang and colleagues ([25]; rating "−+") similarly examined associations between drinks per week and years of education and found no evidence for a statistically significant effect. In the previous review by Treur et al., there was mixed evidence on the effect of increasing alcohol use on EA [26, 27], and evidence that liability to alcohol use disorder was found to negatively impact EA [9].

Sleep

Sleep/Insomnia

Two recent studies looked at the effects of alcohol on sleep outcomes. Pasman and colleagues found no evidence of a causal effect of drinks per week or alcohol dependence on risk for insomnia using two-sample MR [28] (rating "+" having performed many additional sensitivity analyses). Also using two-sample MR, Chakravorty and colleagues found weak evidence for a causal effect of AUD for insomnia but not for sleep duration [29] (rating "−+"). Alcohol consumption levels were also not found to causally affect insomnia, but weak evidence was found for a positive effect of alcohol consumption on sleep duration (i.e., greater consumption increases sleep). This latter finding concords with a (low-quality) study [30] included in the previous review by Treur et al. based on data from different cohorts. Both studies in the present review also tested for bidirectional effects, with Pasman et al. finding some evidence for insomnia causally increasing alcohol dependence (but not drinks per week), and Chakravorty et al. also finding causal effects of insomnia and sleep duration on risk for AUD.

Internalizing

PTSD

One recent two-sample MR study conducted by Bountress and colleagues [31] (rating "−+") looked at the effects of both drinks per week and AUD on risk for PTSD, finding no evidence of a causal effect of either exposure (however, bidirectional MR indicated some evidence of PTSD having a causal effect on AUD but not drinks per week). The previous review by Treur et al. identified no prior existing MR evidence on this relationship.

Bipolar Disorder

Jang et al. (rating "−+") examined causal associations for drinks per week with several mental health outcomes, including bipolar disorder [25]. There was no evidence for causal associations between the alcohol variables and bipolar disorder. A study by Cai and colleagues also examined potential causal associations between alcohol consumption per week and alcohol use disorder with bipolar disorder and also did not find evidence for a significant causal effect [32] (rating "+" with robust SNP filtering and sensitivity analyses). In the previous review by Treur et al., one study found no evidence of a causal effect of alcohol use disorder on bipolar disorder [9].

Major Depressive Disorder

Alcohol phenotypes were studied in relation to major depressive disorder using two-sample MR in both Jang et al. [25] (rating "−+", using drinks per week) and Cai et al. [32] (rating "+"; using alcohol consumption per week and alcohol use disorder). Neither of the studies found a statistically significant causal association. In the previous review by Treur et al., there was no clear evidence of a causal effect of alcohol consumption/disorder on depression [9, 33–36].

Externalizing

Self-Harm/Suicide

Two recent two-sample MR studies looked at the effects of alcohol on self-harm/suicide. Orri and colleagues found a causal effect of drinks per week on suicide attempt [37] (rating "−+"). Bidirectional MR did not indicate reverse causation. However, Colbert and colleagues found no evidence of a causal effect of problematic alcohol consumption on risk for lifetime self-harm, suicide attempt, or suicide death [38] (rating "−" due largely to poor methodological reporting and lack of sensitivity analyses). This latter finding is consistent with a study included in the previous review by Treur et al., which found no clear evidence of causal effects of alcohol use disorder on non-suicidal or suicidal self-harm [39].

ADHD

A recent two-sample MR study looked at the effect of alcohol dependence on risk for ADHD [40] (rated "-" due largely to small sample size for exposure GWAS and poor methodological reporting). It found no evidence of a causal relationship in either direction. This is at odds with a study included in the previous review by Treur et al., which found higher alcohol use frequency increased attention problems – although that study was small and also rated of low quality [35].

Psychotic

Schizophrenia

Both Cai et al. [32] (using alcohol consumption per week and alcohol use disorder; rated "+") and Jang et al. [25] (using drinks per week; rated "−+") examined associations between alcohol phenotypes and the liability for schizophrenia. Neither study identified statistically significant causal effects. This is in line with conclusions from a study included in the previous review by Treur et al. [9].

Conclusions and Future Directions

Several new MR studies have added to the limited evidence base on alcohol's causal effects on mental and cognitive health outcomes in the past 3 years. While for some relationships, evidence is still too sparse and/or contradictory, MR is beginning to generate valuable insights in this field. Despite the strong comorbidity between (problematic) alcohol use and mental ill health, both the previous and current reviews found little evidence for a causal effect of the former on the latter. Considering the papers included in both reviews, the most consistent findings to date (across at least two studies of sufficient quality) are a lack of causal effects of alcohol on depression, bipolar disorder, and schizophrenia. This appears true for both volume of consumption and alcohol use disorder, while for other conditions (e.g., sleep duration), it is possible these two phenotypes may have different causal relationships with the outcome. Below, we discuss key issues to consider for future MR research on relationships between alcohol and mental/cognitive health.

First, the assumptions of MR must be kept front of mind. In addition to violations of the core assumptions already discussed, other important sources of bias in MR studies are increasingly being acknowledged. These include assortative mating (when mate choice based on particular traits leads to biased exposure-outcome correlation in offspring), population stratification (when the gene-exposure relationship is biased by differences in frequency of gene and exposure distribution between ancestral subpopulations; [41]), and dynastic effects (when parental genotype influences offspring outcome via means other than offspring genotype).

While MR is now predominantly conducted in large, whole-population cohorts, initial proposals for MR emphasized that performing analyses within families was the only way to protect against the above-mentioned sources of bias [42]. Specifically, within-family MR, e.g., within-sibling pairs, avoids assortative mating (inheritance of variants by siblings is random), population stratification (siblings belong to the same ancestral subpopulations), and dynastic effects (likely to be similar between siblings) [43]. Additionally, multivariable MR, incorporating (genetic instruments for) multiple exposures, is a useful tool for adjusting for potential confounding e.g., if there are concerns that alcohol-related SNPs are also related to socioeconomic factors. Both methods should be considered for inclusion in future MR analyses of alcohol and mental health.

Additionally, while most studies were rated as of sufficient quality or better, almost all were conducted in European ancestry samples limiting generalizability – cross-ancestral comparison would strengthen the evidence base. Also, few studies tested for bidirectional effects – an important step in disentangling forward from reverse causation. Another limitation of the studies in the current review – reflecting the dominant methods used in MR analyses – is that they assume a linear relationship between alcohol and mental health outcomes. The lack of a causal relationship reported by several linear MR studies may be masking a nonlinear relationship. There is a need for application of nonlinear MR methods developed in the past 10 years, and still an active area of research [44]. However, because nonlinear MR involves the calculation of local average effects within strata of observed alcohol consumption before evaluating the (in) consistency of these effects, it requires individual-level data (not summarized) from very large cohorts.

Triangulation

While bias in MR studies can be mitigated by adhering to best practice guidelines (https://wellcomeopenresearch.org/articles/4-186), given its inherent limitations, MR alone is not sufficient for elucidating relationships between alcohol and mental health. The concept of triangulation – "the strategic use of multiple approaches to address one question" [45] – is a response to the fact that there is no single study, nor method, that is sufficient for causal inference. An extension of the consistency required across sensitivity methods within MR itself, triangulation refers to the comparison of findings across several separate kinds of analysis, where approaches used have different underlying assumptions/sources of bias and therefore complementary strengths and weaknesses [46].

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J.T. conceptualized the study. R.V. and M.W. undertook data extraction and curation. R.V., M.W., and J.T. contributed to, read, revised, and approved the final manuscript.

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