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Coffee and health outcomes: a systematic review of Mendelian randomisation studies

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Abstract

Coffee is a widely consumed beverage, which has been extensively studied for its potential effects on health. We aimed to map genetic evidence for the effect of habitual coffee consumption on health. We searched PubMed, Embase, Cochrane Database of Systematic Reviews, CINAHL and two preprint repositories from inception to 30/09/2022, and included 59 studies, spanning 160 disease or biomarker associations. We evaluated the articles for certainty of evidence using a modified GRADE tool and robustness of the associations by comparing MR sensitivity analyses. Coffee consumption was associated with smaller grey matter brain volume in one study, and there was probable evidence for an increased risk of Alzheimer's disease and younger age of onset of Huntington's disease. MR studies provided probable evidence for an association with increased risk of esophageal and digestive cancers but protective effects for hepatocellular carcinomas and ovarian cancer. We found probable evidence for increased risk of type 2 diabetes mellitus, osteoarthritis, rheumatoid arthritis, menopausal disorders, glaucoma, higher total cholesterol, LDL-C and ApoB, and lowered risk of migraines, kidney disease, and gallstone disease. Future studies should aim to understand underlying mechanisms of disease, expand knowledge in non-European cohorts, and develop quality assessment tools for systematic reviews of MR studies.

Key words: coffee, caffeine, literature review, systematic review, Mendelian randomisation, MR

Systematic Review Registration: PROSPERO registration number CRD42021295323

Abbreviations:

MR	Mendelian randomisation
IVWMR	Inverse variance weighted Mendelian randomisation
MR-PRESSO	Mendelian Randomisation Pleiotropy RESidual Sum and Outlier
MVMR	Multivariable Mendelian randomisation
SNP	Single nucleotide polymorphism
GRADE	Grading of Recommendations, Assessment, Development and Evaluations

Introduction

Coffee is among the most commonly consumed beverages globally [1]. Roasted coffee has several biologically active compounds including caffeine, flavonoids, lignans, cafestol, and other polyphenols [2]. In particular, caffeine acts as a central nervous system stimulant and has short-term effects on cognitive functioning, heart rate, alertness, sleep regulation and emotional processing [3]. However, the potential long-term effects of its habitual consumption are not fully understood. In observational phenotypic studies, low to moderate levels of regular coffee consumption has been reported to lower risk of dementia [4], cardiovascular disease [5; 6], type 2 diabetes mellitus [7], Parkinson's disease [8] and all-cause and cancer mortality [9]. Conversely, high intakes have been associated with harmful long-term effects. High coffee consumption was found to be associated with increased risk of dementia [10] and cardiovascular disease [11].

Mendelian randomisation (MR) studies lie at the interface between observational and interventional research methods, allowing the estimation of causal effects using observational data [12]. This statistical approach relies on the use of genetic variants associated with the exposure of interest (coffee) to act as proxy markers or instruments and overall must comply with three core assumptions (Figure 1). Since genetic variants are randomly assigned at conception, MR overcomes the effect of unmeasured confounding and reverse causality. The variants can be selected based upon candidate genes known to affect the exposure or using results from genome wide association studies (GWAS) [13]. In the recent years, the use of the MR method has increased in popularity, with many papers utilising the availability of large-scale cohort data and genome wide association studies [14]. There have been several recent MR studies on coffee, spanning a broad range of health outcomes.

In this systematic review, we aimed to map the available MR studies examining the role of coffee consumption on health outcomes, and to evaluate the certainty and robustness of the evidence. The consolidation of this data allows us to summarise the potential benefits and harms of habitual coffee consumption on health and will help to guide and inform future research, policy makers and the public.

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Materials and Methods

Protocol and registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines, which is an update to the original 2009 statement [15; 16]. The protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) under ID CRD42021295323 on 9 December 2021.

This study is a review of previously published studies and does not involve the collection of original data from human or animal subjects. All data were sourced from publicly available studies and hence, no ethical approval was required.

Search strategy and data sources

We searched PubMed, Embase, Cochrane Database of Systematic Reviews, Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases and two preprint repositories – bioRxiv and medRxiv, from inception to 30/09/2022. We included the search terms "Mendelian" OR "Mendelian randomization", "Genetic instrument" OR "instrumental variable" and "Coffee" OR "caffeine", as both MeSH terms and keywords. We applied truncation and wildcard symbols to account for different variations, spelling, and plurals of each term. Pre-print repositories were searched using the medrxivr R package [17]. A summary of the search queries used for each database is provided in Supplementary Table 1.

Eligibility criteria

The criteria for inclusion and exclusion of studies were based on the PECOS (Population, Exposure/Intervention, Comparison, Outcomes and Study design) framework, as described in Table 1. Two reviewers (KP and NAK) independently screened the articles using Covidence [18] and any conflicts were resolved by a third reviewer (EH). The study selection process was documented using a PRISMA flow diagram template.

Data extraction

In the data extraction stage, two reviewers (KP and NAK) independently extracted key data using a custom template on Covidence. When any inconsistencies arose, a consensus was reached through discussion. For studies that included other analysis methods (e.g., phenotypic analyses), only data relating to the MR analysis were extracted. The minimum

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data to be extracted will include the title of the study, authors, year of publication, MR design, description of the exposure and outcome populations, description of the genetic instrument and effect estimates for at least one MR method. For most studies, inverse variance weighted MR was considered the main analysis. We also collected information on statistical power, replication cohorts, multiple testing corrections, statistical heterogeneity, and sensitivity/subgroup analyses.

Where multiple outcomes were investigated in a single study, each outcome-association was assessed independently to determine whether it met the inclusion criteria before extraction. In any studies that included results from multiple cohorts of the same ethnic group, we presented the pooled results or selected the analysis with the highest number of SNPs, largest outcome sample size or the main analysis as specified by the author. After data extraction, we further excluded studies that had overlapping outcome study samples. We chose to include the study with the largest sample size, or if sample sizes were similar, we chose the study with the most robust method of sensitivity analysis.

Meta-analysis

For any outcomes that had reported estimates in more than one non-overlapping sample, we meta-analysed the results using the STATA 'metan' command to provide a pooled estimate and presented them using forest plots. We did not include meta-analysis of outcomes which only had studies reporting null findings. Studies were also considered to be ineligible for meta-analysis if the SNP-exposure estimates were expressed in different units (e.g. cups/day and % increase in coffee) and conversion of the estimates was not possible given the available source information. In these cases, pooled estimates were shown separately for different units of coffee.

Evaluating certainty of evidence and robustness of the associations

To assess the certainty of evidence, we applied a modified version of the GRADE rating system [(19)]. Studies were ranked as high, moderate, low, or very low certainty to describe how likely it is that the reported estimate is similar to the true effect. MR studies start as high certainty and can be rated down based on risk of bias, imprecision, inconsistency, indirectness, and publication bias. Certainty can be rated up for large magnitude of effect, when a dose-response gradient is present and when the effect of any residual confounding would increase the magnitude of the effect (suggesting an underestimate of the effect estimate). We adapted the domains to be relevant for MR studies and created a checklist to

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improve ease and consistency of use [20]. Full description of the domains assessed in this study are given in Supplementary Table 2. Each included outcome was assessed using the GRADE rating system and reported individually. An overall study rating was also given, by taking the lowest quality of evidence rating from all outcomes. To aid with assessing whether pleiotropy was adequately addressed in each study, we summarised the potential pleiotropic associations using PhenoScanner V2 for coffee SNPs reported in the Coffee and Caffeine Genetics Consortium and UK Biobank GWAS studies and their proxies (r^2<0.8) (Supplementary Table 3) [21; 22; 23]. We firstly checked associations significant at genome wide significance level (p-value <$5x10^{-8}$), then checked for any additional associations significant at p<$1x10^{-5}$.

Robustness of the associations was assessed according to a ranking system previously established by Markozannes and colleagues [24]. The system ranks MR associations as robust, probable, suggestive, or insufficient evidence for causality based on the evidence provided by the main MR analysis and at least one sensitivity method (MR-Egger, weighted median, weighted mode, MR-PRESSO or multivariable MR). When statistical heterogeneity was detected, we considered the random effects model as the main analysis and did not include the fixed effects model in the assessment of robustness. A "robust" classification requires that all methods are statistically significant, and the direction of effects must be consistent. Both "probable" and "suggestive" evidence must have at least one method that is statistically significant – when the direction of effects was consistent, the association was categorised as probable and when the direction of effects was inconsistent, it was categorised as suggestive. In studies that applied multiple testing correction methods, the corrected p-value was used. We ranked the association as "insufficient" if all methods had statistically non-significant p-values, low statistical power, or wide confidence intervals. Studies that did not present any sensitivity analyses were assigned a "non-evaluable" ranking.

Results

Study selection

The search yielded a total of 462 studies, 163 of which were excluded due to duplication (Figure 2). We screened 299 articles in the title and abstract screening phase and excluded 201 that did not meet the inclusion criteria. A further 30 articles were excluded in the full-text screening phase. We extracted data from 67 studies, which contained analyses of 241 outcome associations. After data extraction, we excluded 44 outcome associations due to

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overlapping outcome sample populations from 14 studies. However, because some of these studies had other outcomes contributing to the review, the process resulted in the exclusion of only 8 out of the 14 studies. Details on excluded duplicate outcomes are described in Supplementary Table 4. Overall, we have presented results for 59 studies, covering 197 outcomes (of those, there are 160 unique outcomes).

Description of the study design and data sources

Most of the included studies used a two-sample MR design (84.7%, 50 studies), while only 9 studies (15.3%) used one-sample design (Table 2). The earliest study included in the review was published in 2015, however, nearly two thirds were published in 2021 or 2022 (66.1%, 39 studies). The UK Biobank (UKB) and The Coffee and Caffeine Genetics Consortium (CCGC) were the most common data sources for the exposure population, featuring in 37 (62.7%) and 15 (25.4%) studies, respectively. The outcome population data sources were more varied; however, population ancestry was mostly European. The studies similarly utilised large cohort databases such as the UK Biobank, FinnGen, PRACTICAL consortium, DIAGRAM consortium and the GIANT consortium. The outcomes spanned a broad range of health outcomes including cardiovascular traits, neurodegenerative diseases, metabolic disease, cancer, and mortality.

Description of the instrument selection

Although the genetic instruments were selected from similar GWAS studies or consortia, each study applied their own set of inclusion criteria for the SNPs. The median number of SNPs used was 11 (Table 2). In a majority of studies, all SNPs were associated with coffee consumption at a genome wide significance level ($p<5x10^{-8}$) and the clumping threshold was set to $r^2<0.001$ or $r^2<0.01$. IV-exposure estimates, where reported, were adjusted for at least age and sex, with most studies also adjusting for BMI, typical food intake, SNP array and 10-20 principal components (data not shown).

Assessment of potential pleiotropy

From the total 197 outcome associations, 134 (68.0%) included more than one MR analytical approach, with 130 (66.0%) of those analyses including two or more pleiotropy robust methods (Tables 2-9). In addition, 51 of 59 included studies (86.4%) conducted at least one method of formal pleiotropy assessment (MR-Egger test, MR-PRESSO outlier tests or leave-one-out analyses) and only 8 studies reported no formal pleiotropy assessment (Table 2).

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For most outcomes the associations were similar across different pleiotropy robust methods, however screening of the commonly used coffee SNPs and their proxies on PhenoScanner highlighted several potentially pleiotropic SNPs which should be considered when assessing the MR associations (Supplementary Table 3). SNP rs1260326 (GKCR) was most pleiotropic and was reported to be associated ($p<5x10^{-8}$) with serum lipid measures, cardiovascular disease risk factors, pulse rate, resting heart rate, gout, type 2 diabetes, markers of metabolic diseases, kidney disease, liver disease and alcohol intake. Serum lipid markers (rs1481012, rs7800944, rs34060476), coronary artery disease (rs66723169), gout (rs1481012, rs7800944, rs34060476), obesity and metabolic disease (rs1481012, rs4410790, rs7800944, rs6265, rs2470893, rs2472297, rs574367, rs10865548, rs66723169) or addictive behaviours such as smoking and alcohol consumption (rs4410790, rs6265, rs2470893, rs34060476, rs66723169), were all commonly flagged as potential pleiotropic associations. At $p<1x10^{-5}$, we identified further associations with diastolic blood pressure (rs2472297, rs10865548) and systolic blood pressure (rs10865548) and heart rate (rs597045, rs1956218), among others.

GRADE rating – certainty of evidence

When looking at the individual disease outcome associations, 136 of 197 (69.0%) had a high certainty of evidence and did not need to be downgraded in any domains, 37 (18.8%) had a moderate rating and 24 had a low or very low rating (Supplementary Table 5). Overall GRADE ratings for each study were also determined, with most studies (57.6%, 34 studies) ranked as high, nearly a third were ranked as moderate (30.5%, 18 studies), and only a small proportion of studies were downgraded to a low or very low rating (11.9%, 7 studies). We found that studies were most commonly downgraded in the risk of bias and imprecision domains, primarily due to issues regarding sample overlap between the exposure and outcome populations, violations of the core MR assumptions or insufficient statistical power (Supplementary Table 5).

Cardiovascular traits

MR studies reporting on cardiovascular outcomes were largely found to report null findings (Table 3). There was no evidence for an association between coffee consumption and coronary artery disease, peripheral artery disease, heart failure, atrial fibrillation, aortic valve stenosis, hypertension, aortic aneurysm (thoracic and abdominal), transient ischemic attack or pulmonary embolism [25; 26; 27; 28; 29; 30; 31; 32; 33; 34; 35]. There was also insufficient evidence to support an association with stroke, ischemic stroke (large vessel, small vessel and

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cardioembolic), intracranial aneurysm or subarachnoid haemorrhage [28; 29; 32; 34]. However, the findings on intracerebral haemorrhage were conflicting [27; 28; 32]. Meta-analysis of results from 3 non-overlapping studies were also inconclusive (pooled OR per 50% increase in coffee 1.09, 95% CI 0.71, 1.48; pooled OR per 1 cup/day increase in coffee 1.60, 95% CI 1.07, 2.13) (Figure 3).

There is a suggestive association with increased risk of venous thromboembolism and deep vein thrombosis, and a robust association with decreased risk of varicose veins (OR per 50% increase in coffee 0.78, 95% CI 0.67, 0.92) (Table 3) [28; 36]. There was a potential association with lower diastolic blood pressure [37]; however, out of the five variants used in the coffee instrument, one variant (rs2472297) is directly associated with diastolic blood pressure ($p<1x10^{-5}$), as identified in the GWAS by the International Consortium for Blood Pressure Genome-Wide Association Studies [38]. The same study did not report an association with systolic blood pressure.

Serum lipids

Our review identified four MR studies on serum lipids [35; 37; 39], including one still in the pre-print stage [40]. Genetically determined coffee consumption was consistently associated with higher total cholesterol, LDL-cholesterol, and apolipoprotein B (Table 4). There was no association between coffee and apolipoprotein A-1. As formal MR analyses were not conducted in Nordestgaard *et al.* [37] and the unit was not clearly described in Li *et al.* [40], we could only conduct meta-analysis between estimates from Zhou and Hyppönen [39] and Kwok *et al.* [35]. The pooled estimate supports an association with higher LDL-cholesterol (pooled beta per 1 cup/day increase in coffee 0.07, 95% CI 0.03, 0.11) (Figure 4). MR analyses in Zhou and Hyppönen [39] and Kwok *et al.* [35] both considered the impact of pleiotropy by excluding known pleiotropic SNPs.

Neurological diseases and brain morphology

A study on Alzheimer's disease reporting pooled estimates from the International Genomics of Alzheimer's Project (IGAP) and FinnGen cohorts found a positive association between coffee and Alzheimer's disease, while a later study in a smaller cohort found no association (Table 5) [27; 41]. Meta-analysis of these three estimates suggests that coffee consumption may be associated with increased risk of Alzheimer's disease (pooled OR per 1 cup/day increase in coffee 1.18, 95% CI 1.02, 1.33) (Figure 5). We also found probable evidence to support an association between coffee and younger age of onset of Huntington's disease [42]. Studies on

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cognition, amyotrophic lateral sclerosis (ALS), Parkinson's disease, epilepsy, attention deficit hyperactivity disorder (ADHD), and cerebral microbleeds all reported null findings [43; 44; 45; 46; 47; 48; 49]. While analysis using data from the International Headache Genetics consortium (IHGC) did not provide evidence for a relationship, meta-analysis incorporating data from the UK Biobank and FinnGen cohorts supported an association with decreased risk of migraines (pooled OR per 50% increase in coffee 0.73, 95% CI 0.63, 0.83, I2 87.5%) (Figure 5) [50; 51]. Heterogeneity in this analysis may reflect differences in how the migraine phenotype is defined and collected across the different studies; however, heterogeneity measures may be biased when there are a small number of studies in the meta-analysis [52].

There was one study reporting a robust association reported between coffee and lower grey matter volume (beta in SD per 1 coffee cup/day increase -0.371, 95% CI -0.596, -0.147) [44]. No associations were observed for other brain volume measures (total brain, white matter, hippocampus), white matter hyperintensity volume or MRI markers of small vessel disease (fractional anisotropy, mean diffusivity).

Cancer and neoplasms

Coffee consumption was not found to be associated with cancers of the brain, head and neck, breast, thyroid, lung, colon/rectum, stomach, liver, biliary tract, pancreas, kidney, bladder, cervix, endometrium, uterus, prostate, or testicles (Table 6) [53; 54; 55; 56]. There was also no association with overall cancer, lymphoma, non-Hodgkin's lymphoma, leukaemia, and melanoma. Carter *et al.* [53] identified a robust association between coffee consumption and increased risk of esophageal cancer in the UK Biobank cohort (OR per 50% increase in coffee 2.79, 95% CI 1.73, 4.5), however the results were not replicated in the FinnGen cohort. Similarly, this study found probable associations with increased risk of multiple myeloma and decreased risk of ovarian cancer, which were also not replicated in the FinnGen cohort. Meta-analysis of estimates from UK Biobank and FinnGen suggest that coffee consumption is associated with increased risk of esophageal cancer (pooled OR per 50% increase in coffee 2.67, 95% CI 1.40, 3.94). Given that epithelial ovarian cancer subtype accounts for most ovarian cancer cases [57], we conducted meta-analysis of ovarian cancer estimates including an estimate for epithelial ovarian cancer in the Ovarian Cancer Association Consortium [58] (pooled OR per 50% increase in coffee 0.86, 95% CI 0.74, 0.98) (Figure 6).

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Metabolic traits

In the largest available study, coffee drinking had a suggestive association with increased risk of type 2 diabetes mellitus (Table 7) [59]. Coffee was also associated with markers of increased risk of diabetes including higher fasting glucose, higher insulin resistance, increased risk of obesity and higher BMI, however robustness could not be assessed for most outcomes [35; 37; 60; 61]. There was insufficient evidence to support an association with glycated haemoglobin, fasting insulin, adiponectin, height, or plasma glucose. Meta-analysis could not be conducted for waist circumference since Nordestgaard *et al.* [37] did not include formal MR analysis, only regression of the coffee genetic risk score against the outcomes (common in early MR studies).

Autoimmune and inflammatory diseases

There was insufficient evidence to support an association between genetically determined coffee consumption and multiple sclerosis or systemic lupus erythematosus (Table 8) [62; 63]. Bae and Lee [63] suggested that there may be an association between coffee and increased risk of rheumatoid arthritis, however the findings were not replicated in a later study [64]. Results from these two studies could not be pooled as the SNP-exposure estimates were expressed in different units.

A probable association between coffee consumption and increased risk of osteoarthritis (OA) was identified in the UK Biobank cohort [61], while only a suggestive evidence was identified within the Arthritis Research UK Osteoarthritis Genetics (arcOGEN) consortium [65]. The association remained when restricting to knee OA cases, but not for hip OA [66]. Coffee was not associated with fracture risk or estimated mineral density measures [67]. The findings on gout were conflicting, findings from the Global Urate Genetics Consortium (GUGC) and Biobank Japan cohort reported decreased risk of gout [68], while a study in the UK Biobank reported no association [61]. Although meta-analysis of the three cohorts suggested a negative association (pooled OR per 1 cup/day increase in coffee 0.71, 95% CI 0.53, 0.88) (Figure 7), MR PRESSO distortion test conducted in the UK Biobank study, showed that the association was likely to be due to a three potentially pleiotropic outlying variants (rs1260326, rs1481012, rs7800944) [61]. No association was found between coffee and serum uric acid [68].

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Diseases of the digestive system and renal system

Null findings were reported for diverticular disease, gastroesophageal reflux disease, Crohn's disease, and ulcerative colitis (Table 9) [69; 70; 71]. There was a potential association between coffee and decreased risk of non-alcoholic fatty liver disease [72]. Coffee consumption had a protective effect on gallstone disease, but only after adjusting for BMI and smoking in a MVMR model, or in another study looking at only cases of symptomatic gallstone disease [73; 74]. We also found probable evidence for a protective effect of coffee on markers of kidney disease. Coffee consumption was associated with decreased risk of chronic kidney disease, higher estimated glomerular filtration rate, lower levels of albuminuria and decreased risk of kidney stones [75; 76]. Analyses on glomerular filtrate rate excluded potentially pleiotropic variants (rs1260326, rs9275576, and rs476828) [75; 77].

Mortality and other outcomes

Coffee consumption had no effect on all-cause mortality or cancer-specific mortality (Table 10) [34; 55; 78; 79]. There was no association with pregnancy loss [80], however coffee consumption had a probable association with decreased postmenopausal bleeding and menopausal disorders [61]. There was insufficient evidence to support an association with lower back pain [81], while a study on hearing showed a potential association with decreased risk of tinnitus [82]. For eye disorders, we found no association with intraocular pressure [83], however coffee had a potentially adverse association with senile cataracts and glaucoma [84; 85].

Discussion

Our review including 59 MR studies and 160 unique disease outcome associations supports some possible benefits and harms with habitual coffee intakes. Previous observational evidence (for umbrella reviews please see [86; 87]) has identified almost no harmful effects and deemed coffee drinking in moderation as safe, except during pregnancy and for women at increased risk of fractures. These reviews also highlighted many potential benefits of coffee consumption, including lowered risk of all-cause and cardiovascular mortality, cancers, metabolic conditions, liver conditions, Parkinson's disease, depression, and Alzheimer's disease. However, most of these benefits from observational associations were not supported by genetic studies identified in our review [35; 49; 53; 79; 88], and for Alzheimer's disease/dementia, two studies [27; 41] suggested potential increases in risk warranting further research. This suggests that the phenotypic associations reported for coffee are likely to be

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due to residual confounding or reverse causality, and not through a causal pathway [12]. However, our review did suggest potential benefits for some conditions that align with observational findings, and notably, the potentially lower risk of ovarian cancer, hepatocellular carcinoma, kidney disease, gallstone disease, and migraines are interesting and warrant confirmation in independent studies.

Our systematic review provides an important update to the existing body of knowledge on the health effects of coffee consumption. There is one previous narrative review which summarised the MR evidence on coffee and caffeine consumption [89]. However, this review included only 15 MR studies and found that coffee had no consistent effects on the included health outcomes. Over two thirds of the studies included in our review were published after this previous review. We used two methods of quality assessment, and we adapted the processes for use with MR studies. Authors in the previous review provided valuable insights into the methodological issues of MR, including insufficient power, pleiotropy, and collider bias. We found that these methodological issues were still present but often improved in more recent studies with the increased availability of larger scale individual-level and summary-level data. Overall, we noticed a marked increase in the quality and standardisation of reporting MR studies, which coincides with the release of the STROBE-MR guidelines (pre-print 2019, published 2021) [90].

Our review found only a handful of studies reporting associations that could be assessed as "robust", and even these were not independently replicated. The association between coffee consumption and smaller grey matter volumes is well supported by prior observational studies and randomised controlled trial evidence, providing strong evidence that the association may be causal [10; 91]. However, the mechanisms of effect are yet to be fully understood. Considering that higher habitual coffee intakes are typically linked to higher circulating levels of caffeine [92], the competitive antagonist binding of caffeine to the adenosine receptors may be a potential pathway underlying these associations [93; 94]. Caffeine molecules are structurally similar to adenosine molecules, which allows them to competitively bind to adenosine receptors and pass through the blood brain barrier. It is possible that this disrupts adenosine homeostasis or alters the expression of adenosine receptors, which has been implicated in Alzheimer's disease [95]. Another theory to explain the association between coffee and brain diseases is that caffeine intake impacts blood brain barrier permeability and hence, allows entry of toxins and pathogens into the brain. However, a recent MRI study found that caffeine ingestion had no effect on blood brain barrier

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permeability [96]. Interestingly, a recently published MR study found an association between coffee and delayed age-of-onset of Parkinson's disease [97], supporting a protective effect of coffee for neurodegeneration. No association was found with Parkinson's disease risk, suggesting that coffee may influence the onset of Parkinson's symptoms not the main disease pathway. Coffee may impact Alzheimer's and Parkinson's uniquely, despite their similar neurodegenerative symptoms and overlapping affected brain regions.

The observed effects of coffee on esophageal cancer risk may reflect the association between hot beverage consumption and esophageal cancer. Meta-analysis of studies on tea drinking found that participants who drunk tea at higher temperatures had higher risk of esophageal squamous cell carcinomas [98]. It is possible that the consumption of hot beverages causes damage to the esophageal cell mucosa, which may increase cell turnover rates and risk of cancerous mutations [99]. This explanation is supported by a recent MR study which found that the association between coffee and esophageal cancer was attenuated in multivariable models additionally adjusting for hot beverage consumption [100].

Our review did not find strong evidence to support associations between coffee consumption and other types of cancer, except for potential protective associations with hepatocellular carcinoma and ovarian cancer and increased risks for multiple myeloma. More recent evidence provides further support for the association with multiple myeloma, including replication in an independent outcome cohort [101]. Mediation analyses from the same study suggested that three plasma metabolites acted as mediators in the association, possibly via the glutathione metabolism pathway. Dysregulation of this pathway impacts antioxidant defence and immune response modulation and has been implicated in the pathogenesis of several diseases [102]. Meanwhile, the protective association with hepatocellular carcinoma may only be present in Europeans, as later studies in East Asian populations found no association between coffee and hepatocellular carcinoma or other digestive system cancers [103; 104]. Similarly, recent literature suggests that coffee may associate with increased risks of endometrioid ovarian cancer, opposing previous studies that support protective associations [105]. Epidemiological evidence on coffee and ovarian cancer remains conflicting so further investigation is required to disentangle these associations.

MR studies do not support the cardiovascular benefits suggested by observational studies. While excessive intake of caffeine (toxicity) is known to lead to adverse cardiovascular symptoms such as tachycardia and increased blood pressure [106], MR studies in this review

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found no evidence for harm. It is important to note that MR studies examine the effects of habitual (rather than excessive) coffee intakes, and there is evidence to suggest that the patterns of coffee consumption are in part driven by individual differences in the function of the cardiovascular system, as reflected by blood pressure and heart rate [107]. Indeed, this type of natural self-moderation in consumption levels may help to protect those individuals who are susceptible to possible caffeine-related cardiovascular symptoms from any serious harm. More recent MR studies including a broader set of instrumental variables (37 SNPs vs. 9-14 SNPs) have reported probable associations between coffee and increased risk of coronary artery calcification, myocardial infarction, atrial fibrillation, and heart failure [108; 109; 110], which could in part relate to the observed increases in serum LDL cholesterol by higher habitual intakes [39]. Mediation analyses suggested that the association with heart failure may involve segmental/global circumferential strain and left ventricular volume [110]. Circumferential strain contributes to arterial wall thickening [111], which aligns with the theory that competitive adenosine receptor binding stimulates acute increases in blood pressure and arterial thickness that may induce ventricular modelling and cardiac strain over time [112].

Many of the instruments used to reflect habitual coffee intakes may be pleiotropic, and this was reflected in the varied conclusions on the association between coffee and gout. As noted in the analyses using MR PRESSO by Nicolopoulos and colleagues [61], estimates were influenced by the effect of pleiotropic outlying SNPs and when removed from the coffee instrument, no association was observed in the UK Biobank or the Global Urate Genetics Consortium cohorts. Estimates in the Biobank Japan cohort remained significant after the removal of pleiotropic SNPs (rs671, rs1260326, rs13234378); however, we observed a large drop in the precision of estimation, suggesting that the pleiotropic SNPs had a large contribution to the instrument strength [68]. It is also possible that the varied findings are due to ethnic differences between Asian and European populations.

It is important to acknowledge potential limitations of our review. Although we aimed to cover all health outcomes associated with coffee, our search may have missed relevant studies, particularly when the MR analyses were not described in the title or abstract or conducted only as a supplementary analysis. At the time of this review there are no formal data extraction or quality assessment tool established for MR studies, so our templates and tools had to be adapted from general tools for observational studies or previous publications. Additionally, the GRADE system for assessing certainty of evidence is known to be a very

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subjective process [19]. We aimed to standardise the process between reviewers using a checklist format [20], however there is naturally a level of subjectivity to each decision which should be taken into account. We found that most studies identified in this review were in European populations, and therefore not directly generalisable to other ethnic populations or lower to middle income countries. In particular, many studies utilise the UK Biobank as the exposure or outcome data source, which is known to be a non-representative sample and subject to a healthy volunteer bias [113]. There is evidence to suggest that the association between *CYP1A2* and coffee intake may differ between Caucasian and Asian populations, implying that one of the best genetic instruments for coffee intake may be influenced by ethnicity[114]. All included studies implemented linear MR analyses, and uncertainties exist in the ability to use MR in evaluating non-linear effects [115]. Our review focused on MR studies that approximate differences in habitual coffee intake using genetic variants. Although some variants included in the instruments of these MR studies are directly involved in caffeine metabolism, associations may not reflect circulating caffeine concentrations or be applicable to the effects of other caffeinated drinks [116]. We observed evidence for pleiotropy for many of the instruments used in the MR analyses. However, some of the earlier studies were published before sensitivity analysis methods for MR were developed preventing assessment of robustness of the evidence [117]. Similarly, a reporting standard for MR studies has only been recently established, so earlier studies lacked standardisation of methodology[90]. Lastly, several studies identified in the review were underpowered, so caution should be exercised with null associations as small effects may have been missed.

Our systematic review of MR studies did not support observational evidence for broad benefits of coffee intake, aside of potential associations with decreased risk of migraines, hepatocellular carcinoma, kidney disease, gallstone disease, and ovarian cancer. We also did not observe any strong evidence for harm, although more research is needed to assess possible effects on esophageal cancer and dementia/Alzheimer's disease. However, the genetic variants used to instrument coffee intake approximate modest differences in average coffee intakes, and as they may not directly reflect caffeine concentrations in the blood, these studies may not have captured effects seen with excessive intakes. Overall, evidence from MR studies published to date suggests that moderate consumption of approximately 1-3 cups per day is generally safe. There is a need for creation and validation of data extraction protocols and quality assessment tools for systematic reviews of MR studies. Future studies

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should also aim to understand the underlying mechanisms of any causal associations and expand upon knowledge in non-European cohorts and cross-ethnic studies.

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Table 1: PECOS criteria for inclusion of studies.

Parameter	**Inclusion criteria**	**Exclusion criteria**
Population	Adults, with no restriction based on sex, ancestry, country, history of illness, or pregnancy.	Studies in children (aged <18 years).
Exposure/ Intervention	Genetically predicted coffee consumption.	Studies where the exposure is not genetically predicted coffee intake, or where the genetic instrument relates to decaffeinated coffee only, or caffeine from an unspecified source.
Comparator	Linear associations by cup per day or 50% increase in consumption	
Outcomes	Any disease or biomarker health outcome.	Studies on health or other behaviours and where the outcome was not directly health related.
Study design	Mendelian randomisation studies.	Studies which did not include a MR analysis, or studies without sufficient original data (e.g., abstracts, conference presentations, reviews, and editorials) and any duplications across the databases.

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Table 2: Summary of the characteristics of 59 Mendelian randomisation studies on coffee consumption included in the review.

Study	PMID	Method	Outcome (s) included in this review	Coffee unit	Ancestry	No. of SNPs	Exposure sample	Outcome sample	Pleiotropy assessed*
Zhou 2022	36003339	TSMR	Aortic aneurysm	cups/day	European	4	CCGC	UKB & FinnGen	Yes
Zheng 2022	35369049	TSMR	Brain volume measures; fractional anisotropy; mean diffusivity	cups/day	European	12	UKB	CHARGE, UKB, ADNI, MGH-GASROS & CROMIS-2 AF	Yes
Zhang 2022	35254179	TSMR	Amyotrophic lateral sclerosis	50% increase in cups/day	European	12	UKB	2 GWAS studies (PMID 29566793)	Yes
Zhang 2022	35334809	TSMR	Epilepsy	50% increase in cups/day	~86% European	12	UKB	ILAE & FinnGen	Yes
Yuan 2022	33418132	TSMR	Gallstone disease	50% increase in cups/day	European	9	UKB	UKB & FinnGen	Yes
Yuan 2022	34139333	TSMR	Diverticular disease	50% increase in cups/day	European	12	UKB	UKB & FinnGen	Yes
Yuan 2022	34690004	TSMR	Kidney stones	50% increase in cups/day	European	12	UKB	UKB & FinnGen	Yes
Yuan 2022	35013517	TSMR	Senile cataract	50% increase in cups/day	European	12	UKB	UKB & FinnGen	Yes
Yuan 2022	35029599	TSMR	Migraine	50% increase in cups/day	European	12	UKB	UKB & FinnGen	Yes
Yuan 2022	35119566	TSMR	Gastroesophageal reflux disease	50% increase in cups/day	European	11	UKB	UKB & Qskin	Yes
Yuan 2022	35488966	TSMR	Non-alcoholic fatty liver disease	50% increase in cups/day	European	12	UKB	eMERGE, UKB, Estonian Biobank, FinnGen & 11 clinics (PMID 32298765)	Yes
Shirai 2022	35348303	TSMR	Gout risk; serum uric acid	days/week of drinking coffee | cups/day	Japanese | European	up to 10 | 5	BioBank Japan | CCGC	Biobank Japan | GUGC	Yes
Pu 2022	36172525	TSMR	Rheumatoid arthritis	1SD increase in	European	27	UKB	18 studies (PMID	Yes

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				cups/day				24390342)	
Nordestgaard 2022	35405480	OSMR	Dementia outcomes	cups/day	European	2	CGPS & CCHS		No
Narayan 2022	35166314	TSMR	Obesity outcomes; anthropometric measures	cups/day	European	10	CCGC	GIANT	Yes
Lv 2022	36114324	TSMR	Low back pain	50% increase in cups/day	European	13	UKB	FinnGen	Yes
Li 2022	35537532	TSMR	Primary open-angle glaucoma	cups/day	European	6	CCGC	18 studies (PMID 33627673)	Yes
Li 2022	36071939	TSMR	Renal cell carcinoma	50% increase in cups/day	European	12	UKB	FinnGen & IARC	Yes
Hoek 2022	35929454	TSMR	Peripheral artery disease	50% increase in cups/day	~72% European	14	UKB	MVP	Yes
Domenighetti 2022	34633332	TSMR	Parkinson's disease	ln(cups per day)	European	11	UKB	Courage-PD	Yes
Deng 2022	35670026	OSMR	Hepatocellular carcinoma	days/week of drinking coffee	East Asian	6	Biobank Japan		Yes
Creswell 2022	34108397	OSMR	Current tinnitus	cups/day (caffeinated coffee)	European	6	UKB		Yes
Chen 2022	35145549	TSMR	Migraine outcomes	50% increase in cups/day	European	9	UKB	IHGC	Yes
Carter 2022	36067583	TSMR	Cancer outcomes	50% increase in cups/day	European	12	UKB	UKB	Yes
Zhou 2021	33487505	TSMR	Serum lipid measures	cups/day	European	4	CCGC	UKB	Yes
Zhang 2021	34459406	TSMR	Alzheimer's disease; intracerebral haemorrhage	50% increase in cups/day	European	14	UKB	IGAP, ISGC & FinnGen	Yes
Zhang 2021	34858340	TSMR	Osteoarthritis outcomes	1% increase in cups/day	European	11	UKB	UKB	Yes
Yuan 2021	34187701	TSMR	Pregnancy loss	50% increase in cups/day	European	12	UKB	UKB & FinnGen	Yes
Yuan 2021	34203356	TSMR	Cardiovascular disease	50% increase in	European	12	UKB	UKB & FinnGen	Yes

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			outcomes	cups/day					
Yuan 2021	34666504	TSMR	Varicose veins	50% increase in cups/day	European	12	UKB	UKB & FinnGen	Yes
Wang 2021	34371827	TSMR	Prostate cancer	1% increase in cups/day	European	12	UKB	PRACTICAL & FinnGen	Yes
Wang 2021	34656958	TSMR	Huntington's disease (age of onset)	50% increase in cups/day	European	14	UKB	GeM-HD	Yes
van Oort 2021	33107078	TSMR	Longevity	50% increase in cups/day	European	14	UKB	20 studies (PMID 31413261)	Yes
Treur 2021	31733098	TSMR	Attention deficit hyperactivity disorder	cups/day	European	4	CCGC	iPYSCH & PGC	Yes
Li 2021	medRxiv	TSMR	Serum lipid measures; body mass index	cups/day	European	38	UKB	14 cohorts (PMID 27005778)	Yes
Kim 2021	33333105	TSMR	Intraocular pressure	cups/day	European	8	CCGC	UKB	No
Karhunen 2021	34729997	TSMR	Aneurysmal subarachnoid haemorrhage; intracranial aneurysm	50% increase in cups/day	European	10	UKB	ISGC	Yes
Georgiou 2021	32628751	TSMR	Crohn's disease; ulcerative colitis	cups/day	European	8	CCGC	UKIBDGC & UK10K	Yes
Ellingjord-Dale 2021	33465101	TSMR	Breast cancer outcomes	cups/day	European	33	UKB	BCAC	Yes
Yuan 2020	32895727	TSMR	Type 2 diabetes mellitus	50% increase in cups/day	European	12	UKB	DIAGRAM	Yes
van Oort 2020	32682105	TSMR	Heart failure	50% increase in cups/day	European	14	UKB	HERMES	Yes
van Oort 2020	33131310	TSMR	Hypertension	50% increase in cups/day	European	14	UKB	UKB & FinnGen	Yes
Qian 2020	32034791	TSMR	Stroke outcomes	high vs infrequent/no consumption and cups/day	European	up to 8	CCGC	MEGASTROKE & 6 studies (PMID 24656865)	Yes
Nordestgaard 2020	31486166	OSMR	Symptomatic gallstone disease	cups/day	European	2	CGPS & CCHS		No

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Nicolopoulos 2020	32284183	TSMR	Gout outcomes; obesity outcomes; menopausal disorders outcomes; osteoarthritis outcomes	cups/day	European	8	CCGC	UKB	Yes
Lu 2020	32590313	TSMR	Multiple sclerosis	1% increase in cups/day	European	9	UKB	IMSGC	Yes
Kennedy 2020	31837886	TSMR	Kidney function outcomes	cups/day	European	25	UKB	CKDGen	Yes
Yuan 2019	31482193	TSMR	Fracture risk, estimated mineral density measures	50% increase in cups/day	European	15	UKB	UKB & GEFOS	Yes
Yuan 2019	31558414	TSMR	Atrial fibrillation	50% increase in cups/day	91% European	9	UKB	AFGen	Yes
Ong 2019	31412118	OSMR	Cancer outcomes	cups/day	European	35	UKB		Yes
Zhou 2018	29760501	OSMR	Global cognition; memory cognition	cups/day	European	2	1958BC, ALSPAC-M, NFBC1966, YFS, HBCS, PIVUS, ULSAM, STR & TwinGene		Yes
Ong 2018	29186515	TSMR	Ovarian cancer outcomes	cups/day	European	4	CCGC	OCAC	No
Noyce 2018	bioRxiv	TSMR	Parkinson's disease	cups/day	European	4	CCGC	IPDGC	Yes
Lee 2018	30076541	TSMR	Osteoarthritis	categories (0-2, 3-4, 5-6, 7-9 and ≥10 cups/day); cups/day	European	4	CCGC	arcOGEN	Yes
Bae 2018	30167974	TSMR	Rheumatoid arthritis; systemic lupus erythematosus	categories (0-2, 3-4, 5-6, 7-9 and ≥10 cups/day); cups/day	European	3	CCGC	6 studies (PMID 20453842) & GWAS (PMID 18204098)	Yes
Taylor 2017	27741566	OSMR	Mortality outcomes	cups/day	European	2	PRACTICAL		No
Nordestgaard 2016	28031317	OSMR	Ischemic stroke; ischemic vascular disease; all-cause mortality	cups/day	European	5	CGPS, CCHS, CIHDS & CARDIoGRAMplusC4		No
Kwok 2016	27845333	TSMR	Ischemic heart disease; depression; body mass	cups/day	mostly European	5	CCGC	CARDioGRAMplusC4D, PGC, GLGC, GIANT,	No

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			index; serum lipid traits; glycaemic traits					MAGIC, ADIPOGen & SSGAC	
Nordestgaard 2015	26002927	OSMR	Metabolic syndrome; obesity; anthropometric measures; serum lipid measures; cardiovascular disease mortality	cups/day	European	5	CGPS, CCHS & DIAGRAM		No

OSMR: one-sample Mendelian randomisation study; **TSMR:** two-sample Mendelian randomisation study

*at least 1 method of formal pleiotropy assessment was performed (e.g. MR-Egger intercept test, MR-PRESSO outlier test, leave-one-out analysis)

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Table 3: Summary of MR studies related to cardiovascular traits.

Author	Outcome	Outcome population	Cases	Controls		Sensitivity analyses	Robustness
Yuan 2021	Coronary artery disease	UKB	35,979		–	MR-E, MVMR	Insufficient
Kwok 2016	Coronary artery disease	CARDIoGRAMplusC4	63,746	130,681	–		Non-evaluable
Hoek 2022	Peripheral artery disease	UKB	31,307	211,753	–	MR-E, WM, MR-P, O	Insufficient
Yuan 2021	Peripheral artery disease	MVP	4,593		–	MR-E, WM, MVMR	Insufficient
Nordestgaard 2016	Peripheral artery disease	CARDIoGRAMplusC4	21,695	112,509	–		Non-evaluable
Yuan 2021	Heart failure	UKB	10,560		–	MR-E, WM, MVMR	Insufficient
van Oort 2020	Heart failure	HERMES	47,309	930,014	–	MR-E, WM, MR-P	Insufficient
Yuan 2021	Atrial fibrillation	UKB	23,882		–	MR-E, WM, MVMR	Insufficient
Yuan 2019	Atrial fibrillation	AFGen	65,446	522,744	–	MR-E, WM	Insufficient
Yuan 2021	Aortic valve stenosis	UKB	3,528		–	MR-E, WM, MVMR	Insufficient
van Oort 2020	Hypertension	UKB & FinnGen	70,228	482,997	–		Non-evaluable
Zhou 2022	Aortic aneurysm	UKB & FinnGen	5,032	645,503	–	MR-E, WM, MR-P	Insufficient
Yuan 2021	Thoracic aortic aneurysm	UKB	601		–	MR-E, WM, MVMR	Insufficient
Yuan 2021	Abdominal aortic aneurysm	UKB	1,660		–	MR-E, WM, MVMR	Insufficient
Yuan 2021	Transient ischemic attack	UKB	4,813		–	MR-E, WM, MVMR	Insufficient
Yuan 2021	Stroke	UKB	12,036		–	MR-E, WM, MVMR	Insufficient
Qian 2020	Stroke	MEGASTROKE	40,585	406,111	–	MR-E, WM, MR-P	Insufficient
Yuan 2021	Ischemic stroke	UKB	6,566		–	MR-E, WM, MVMR	Insufficient
Qian 2020	Ischemic stroke	MEGASTROKE	34,217	406,111	–	MR-E,	Insufficie

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						WM, MR-P	nt
Nordestgaard 2016	Ischemic stroke	CARDIoGRAMplusC4	4,589	112,509	–		Non-evaluable
Qian 2020	Large vessel ischemic stroke	MEGASTROKE	4,373	406,111	–	MR-E, WM, MR-P	Insufficient
Qian 2020	Small vessel ischemic stroke	MEGASTROKE	5,386	406,111	–	MR-E, WM, MR-P	Probable
Qian 2020	Cardioembolic ischemic stroke	MEGASTROKE	7,193	406,111	–	MR-E, WM, MR-P	Insufficient
Yuan 2021	Intracerebral haemorrhage	UKB	1,504		–	MR-E, WM, MVMR	Insufficient
Zhang 2021	Intracerebral haemorrhage	ISGC & FinnGen	2,556	126,436	↑		Non-evaluable
Qian 2020	Intracerebral haemorrhage	6 cohorts	1,545	1,481	–	MR-E, WM, MR-P	Probable
Karhunen 2021	Intracranial aneurysm	ISGC	6,252	59,544	–	MR-E, WM, WMode	Insufficient
Karhunen 2021	Subarachnoid haemorrhage	ISGC	4,196	59,544	–	MR-E, WM, WMode	Insufficient
Yuan 2021	Subarachnoid haemorrhage	UKB	1,292		–	MR-E, WM, MVMR	Insufficient
Yuan 2021	Venous thromboembolism	UKB	16,412		↑	MR-E, WM, MVMR	Suggestive
Yuan 2021	Deep vein thrombosis	UKB	10,386		↑	MR-E, WM, MVMR	Suggestive
Yuan 2021	Pulmonary embolism	UKB	7,733		–	MR-E, WM, MVMR	Insufficient
Yuan 2021	Varicose veins	UKB & FinnGen	22,691	506,382	↓	MR-E, WM, MVMR	Robust
Nordestgaard 2015	Systolic blood pressure	CGPS, CCHS & DIAGRAM	n total < 93,197		–		Non-evaluable
Nordestgaard 2015	Diastolic blood pressure	CGPS, CCHS & DIAGRAM	n total < 93,197		↓		Non-evaluable

↑ positive association (main analysis); ↓ negative association (main analysis); − null association (main analysis).
MR-E: MR-Egger; **WM:** weighted median; **WMode:** weighted mode; **MR-P:** MR-PRESSO; **MVMR:** multivariable MR, **O:** Other method.
UKB: UK Biobank; **CARDIoGRAMplusC4:** Coronary Artery Disease Genome-wide Replication and Meta-analysis + Coronary Artery Disease (C4D) Genetics consortia; **MVP:** Million Veteran Program; **HERMES:** Heart failure Molecular Epidemiology for Therapeutic targetS; **AFGen:** Atrial Fibrillation Genetics; **ISGC:** International Stroke Genetics Consortium; **CGPS:** Copenhagen General Population Study; **CCHS:** Copenhagen City Heart Study; **DIAGRAM:** DIAbetes Genetics Replication And Meta-analysis.

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Table 4: Summary of MR studies related to serum lipids.

Author	Outcome	Outcome population	Sample size			Sensitivity analyses	Robustness
Zhou 2021	Total cholesterol	UKB	n total 370,882	<	↑	MR-E, WM, WMode, MR-P	Probable
Li 2021	Total cholesterol	14 cohorts	n total 21,491	=	↑		Non-evaluable
Nordestgaard 2015	Total cholesterol	DIAGRAM	n total 93,179	<	↑		Non-evaluable
Zhou 2021	LDL-cholesterol	UKB	n total 370,882	<	↑	MR-E, WM, WMode, MR-P	Probable
Li 2021	LDL-cholesterol	14 cohorts	n total 21,559	=	↑		Non-evaluable
Kwok 2016	LDL-cholesterol	GLGC	n total 188,577	<	–		Non-evaluable
Zhou 2021	HDL-cholesterol	UKB	n total 370,882	<	–	MR-E, WM, WMode, MR-P	Insufficient
Li 2021	HDL-cholesterol	14 cohorts	n total 21,555	=	↓		Non-evaluable
Kwok 2016	HDL-cholesterol	GLGC	n total 188,577	<	–		Non-evaluable
Nordestgaard 2015	HDL-cholesterol	DIAGRAM	n total 93,179	<	–		Non-evaluable
Zhou 2021	Triglycerides	UKB	n total 370,882	<	–	MR-E, WM, WMode, MR-P	Insufficient
Li 2021	Triglycerides	14 cohorts	n total 21,545	=	↑		Non-evaluable
Kwok 2016	Triglycerides	GLGC	n total 188,577	<	–		Non-evaluable
Nordestgaard 2015	Triglycerides	DIAGRAM	n total 93,179	<	–		Non-evaluable
Zhou 2021	Apolipoprotein B	UKB	n total 370,882	<	↑	MR-E, WM, WMode, MR-P	Probable
Li 2021	Apolipoprotein B	14 cohorts	n total 20,690	=	↑		Non-evaluable
Zhou 2021	Apolipoprotein A-1	UKB	n total 370,882	<	–	MR-E, WM, WMode, MR-P	Insufficient

↑ positive association (main analysis); ↓ negative association (main analysis); − null association (main analysis).

MR-E: MR-Egger; **WM:** weighted median; **WMode:** weighted mode; **MR-P:** MR-PRESSO; **MVMR:** multivariable MR, **O:** Other method.

UKB: UK Biobank; **DIAGRAM:** DIAbetes Genetics Replication And Meta-analysis; **GLGC:** Global Lipids Genetics Consortium.

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Table 5: Summary of MR studies related to neurological diseases and brain morphology.

Author	Outcome	Outcome population	Cases	Controls		Sensitivity analyses	Robustness
Nordestgaard 2022	Alzheimer's disease	CGPS & CCHS	2,152		–		Non-evaluable
Zhang 2021	Alzheimer's disease	IGAP & FinnGen	20,068	210,993	↑		Non-evaluable
Nordestgaard 2022	All dementia	CGPS & CCHS	3,784		↑		Non-evaluable
Nordestgaard 2022	Non-Alzhiemer's disease (vascular dementia proxy)	CGPS & CCHS	1,584		–		Non-evaluable
Zhou 2018	Global cognition	10 cohorts	n total = 300,760		–	MR-E	Insufficient
Zhou 2018	Memory cognition	10 cohorts	n total = 301,804		–	MR-E	Insufficient
Kwok 2016	Childhood cognition	SSGAC	n total = 17,989		–		Non-evaluable
Wang 2021	Huntington's disease (age of onset)	GeM-HD	9,604		↓	MR-E, WM, O	Probable
Zhang 2022	Amyotrophic lateral sclerosis	2 GWAS studies	20,806	59,804	–	MR-E, WM, WMode, O	Insufficient
Domenighetti 2022	Parkinson's disease	Courage-PD	7,369	7,018	–	MR-E, WM, WMode, MR-P	Insufficient
Noyce 2018	Parkinson's disease	IPDGC	13,708	95,282	–	MR-E	Insufficient
Zhang 2022	Epilepsy	ILAE & FinnGen	19,800	174,457	–		Non-evaluable
Treur 2021	Attention deficit hyperactivity disorder	iPSYCH & PGC	n total = 15,548		–	MR-E, WM, WMode	Insufficient
Kwok 2016	Depression	PGC	9,240	9,519	–		Non-evaluable
Zheng 2022	Any cerebral microbleed	5 cohorts	3,556	22,306	–	MR-E, WM	Insufficient
Zheng 2022	Cerebral microbleed (strictly lobar)	5 cohorts	2,179	22,306	–	MR-E, WM	Insufficient
Zheng 2022	Cerebral microbleed (mixed or strictly deep)	5 cohorts	1,293	22,306	–	MR-E, WM	Insufficient
Yuan 2022	Migraine	UKB & FinnGen	7,759	504,902	↓	MVMR	Probable
Chen 2022	Migraine	IHGC	59,674	316,078	–	MR-E, WM	Insufficient
Chen 2022	Migraine (with aura)	IHGC	6,332	144,883	–	MR-E, WM	Insufficient
Chen 2022	Migraine (without aura)	IHGC	8,348	139,622	–	MR-E, WM	Insufficient
Zheng 2022	Total brain volume	UKB	n total = 33,224		–	WM, WMode	Insufficient

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Zheng 2022	Grey matter volume	UKB	n total 33,224	= ↑	WM, WMode	Robust
Zheng 2022	White matter volume	UKB	n total 33,224	= –	WM, WMode	Insufficient
Zheng 2022	Left hippocampus volume	UKB	n total 33,211	= –	WM, WMode	Insufficient
Zheng 2022	Right hippocampus volume	UKB	n total 33,211	= –	WM, WMode	Insufficient
Zheng 2022	White matter hyperintensity	UKB & CHARGE	n total 50,970	= –	WM, WMode	Insufficient
Zheng 2022	Fractional anisotropy	UKB	n total 17,663	= –	WM, WMode	Insufficient
Zheng 2022	Mean diffusivity	UKB	n total 17,467	= –	WM, WMode	Insufficient

↑ positive association (main analysis); ↓ negative association (main analysis); − null association (main analysis).

MR-E: MR-Egger; **WM:** weighted median; **WMode:** weighted mode; **MR-P:** MR-PRESSO; **MVMR:** multivariable MR, **O:** Other method.

CGPS: Copenhagen General Population Study; **CCHS:** Copenhagen City Heart Study; **IGAP:** International Genomics of Alzheimer's Project; **SSGAC:** Social Science Genetic Association Consortium; **GeM-HD:** Genetic Modifiers of Huntington's Disease; **Courage-PD:** Comprehensive Unbiased Risk Factor Assessment for Genetics and Environment in Parkinson's Disease; **IPDGC:** International Parkinson Disease Genomics Consortium; **ILAE:** International League Against Epilepsy; **iPSYCH:** Integrative Psychiatric Research; **PGC:** Psychiatric Genomics Consortium; **UKB:** UK Biobank: **IHGC:** International Headache Genetics Consortium; **CHARGE:** Cohorts for Heart and Aging Research in Genomic Epidemiology.

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Table 6: Summary of MR studies related to cancer and neoplasms.

Author	Outcome	Outcome population	Cases	Controls		Sensitivity analyses	Robustness
Carter 2022	Any cancer	UKB	59,647		–	MR-E, WM	Insufficient
Ong 2019	Cancer (females)	UKB	25,152	141,351	–	MR-E, WM, WMode	Insufficient
Ong 2019	Cancer (males)	UKB	21,324	131,834	–	MR-E, WM, WMode	Insufficient
Carter 2022	Brain cancer	UKB	1,057		–	MR-E, WM	Insufficient
Carter 2022	Head & neck cancer	UKB	1,983		–	MR-E, WM	Insufficient
Carter 2022	Breast cancer	UKB	15,695		–	MR-E, WM	Probable
Ellingjord-Dale 2021	Breast cancer	BCAC	122,977	105,974	–	MR-E, WM, WMode, MR-P	Suggestive
Ellingjord-Dale 2021	Breast cancer (ER negative)	BCAC	21,468	105,974	–	MR-E, WM, WMode, MR-P	Insufficient
Ellingjord-Dale 2021	Breast cancer (ER positive)	BCAC	69,501	105,974	–	MR-E, WM, WMode, MR-P	Probable
Carter 2022	Thyroid cancer	UKB	384		–	MR-E, WM	Insufficient
Carter 2022	Lung cancer	UKB	4,231		–	MR-E, WM	Insufficient
Carter 2022	Esophageal cancer	UKB	1,228		↑	MR-E, WM	Robust
Carter 2022	Esophageal cancer	FinnGen	232		–	MR-E, WM	Insufficient
Carter 2022	Digestive cancer	UKB	11,061		↑	MR-E, WM	Probable
Carter 2022	Non-digestive system cancer	UKB	48,586		–	MR-E, WM	Insufficient
Carter 2022	Colorectal cancer	UKB	6,995		–	MR-E, WM	Insufficient
Carter 2022	Stomach cancer	UKB	994		–	MR-E, WM	Insufficient
Carter 2022	Liver cancer	UKB	463		–	MR-E, WM	Insufficient
Carter 2022	Biliary tract cancer	UKB	604		–	MR-E, WM	Insufficient
Deng 2022	Hepatocellular carcinoma	Biobank Japan	1,866	195,745	↓	MR-E, WM, WMode	Probable
Carter 2022	Pancreatic cancer	UKB	1,747		–	MR-E, WM	Insufficient
Carter 2022	Kidney cancer	UKB	1,741		–	MR-E, WM	Insufficient
Li 2022	Renal cell carcinoma	FinnGen & IARC	6,190	182,017	–		Non-evaluable
Carter	Bladder cancer	UKB	3,326		–	MR-E, WM	Insufficient

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2022							
Carter 2022	Cervical cancer	UKB	1,973		_	MR-E, WM	Insufficient
Carter 2022	Ovarian cancer	UKB	1,839		↓	MR-E, WM	Probable
Carter 2022	Ovarian cancer	FinnGen	311		_	MR-E, WM	Insufficient
Ong 2018	Epithelial ovarian cancer	OCAC	20,683	23,379	_		Non-evaluable
Ong 2018	High-grade serous epithelial ovarian cancer	OCAC	7,488	23,379	_		Non-evaluable
Ong 2019	Endometrial cancer	UKB	1,938		_		Non-evaluable
Carter 2022	Uterine cancer	UKB	2,281		_	MR-E, WM	Insufficient
Carter 2022	Prostate cancer	UKB	10,506		_	MR-E, WM	Insufficient
Wang 2021	Prostate cancer	PRACTICAL	79,194	61,112	−	MR-E, WM, WMode, MR-P	Insufficient
Carter 2022	Testicular cancer	UKB	747		_	MR-E, WM	Insufficient
Ong 2019	Lymphoma	UKB	3,576		_		Non-evaluable
Carter 2022	Non-Hodgkin's lymphoma	UKB	2,878		_	MR-E, WM	Insufficient
Carter 2022	Leukaemia	UKB	1,825		_	MR-E, WM	Insufficient
Carter 2022	Multiple myeloma	UKB	930		↑	MR-E, WM	Probable
Carter 2022	Multiple myeloma	FinnGen	598		_	MR-E, WM	Insufficient
Carter 2022	Melanoma	UKB	5,691		_	MR-E, WM	Insufficient

↑ positive association (main analysis); ↓ negative association (main analysis); − null association (main analysis).

MR-E: MR-Egger; **WM:** weighted median; **WMode:** weighted mode; **MR-P:** MR-PRESSO; **MVMR:** multivariable MR, **O:** Other method.

UKB: UK Biobank; **BCAC:** Breast Cancer Association Consortium; **IARC:** International Academic and Research Consortium; **PRACTICAL:** Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome.

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Table 7: Summary of MR studies related to metabolic diseases.

Author	Outcome	Outcome population	Cases	Controls		Sensitivity analyses	Robustness
Yuan 2020	Type 2 diabetes mellitus	DIAGRAM	74,124	824,000	↑	MR-E. WM, MVMR	Suggestive
Kwok 2016	Glycated haemoglobin (HbA1c)	MAGIC	n total = 46,368		–		Non-evaluable
Kwok 2016	Fasting glucose	MAGIC	n total = 133,010		–		Non-evaluable
Kwok 2016	Fasting insulin	MAGIC	n total = 108,557		–		Non-evaluable
Kwok 2016	HOMA beta-cell function	MAGIC	n total = 36,466		–		Non-evaluable
Kwok 2016	HOMA insulin resistance	MAGIC	n total = 37,037		–		Non-evaluable
Kwok 2016	Adiponectin	MAGIC	n total = 35,355		–		Non-evaluable
Narayan 2022	Obesity class I	GIANT	32,858	65,697	↑	MR-E, WM	Suggestive
Narayan 2022	Obesity class II	GIANT	9,889	62,657	–	MR-E, WM	Insufficient
Narayan 2022	Obesity class III	GIANT	2,896	47,468	–	MR-E, WM	Insufficient
Nicolopoulos 2020	Obesity	UKB	12,096	248,101	↑	MR-E, WM, WMode, MR-P	Probable
Nicolopoulos 2020	Overweight, obesity + other hyperalimentation	UKB	12,228	248,101	↑	MR-E, WM, WMode, MR-P	Probable
Nordestgaard 2015	Obesity (highest vs lowest allele score)	CGPS, CCHS & DIAGRAM	746	4,586	–		Non-evaluable
Nordestgaard 2015	Metabolic syndrome	CGPS, CCHS & DIAGRAM	1,400	4,544	–		Non-evaluable
Kwok 2016	Body mass index	GIANT	n total = 322,154		–		Non-evaluable
Nordestgaard 2015	Body mass index	CGPS, CCHS & DIAGRAM	n total < 93,197		–		Non-evaluable
Narayan 2022	Waist circumference	GIANT	n total = 231,353		–		Insufficient
Nordestgaard 2015	Waist circumference	CGPS, CCHS & DIAGRAM	n total < 93,197		↑		Non-evaluable
Narayan 2022	Hip circumference	GIANT	n total = 213,038		–	MR-E, WM	Insufficient
Narayan 2022	Waist to hip ratio	GIANT	n total = 210,082		↑	MR-E, WM	Probable
Nordestgaard 2015	Weight	CGPS, CCHS & DIAGRAM	n total < 93,197		↑		Non-evaluable
Nordestgaard 2015	Height	CGPS, CCHS & DIAGRAM	n total < 93,197		–		Non-evaluable
Nordestgaard 2015	Plasma glucose	CGPS, CCHS & DIAGRAM	n total < 93,197		–		Non-evaluable

↑ positive association (main analysis); ↓ negative association (main analysis); − null association (main analysis).
MR-E: MR-Egger; **WM:** weighted median; **WMode:** weighted mode; **MR-P:** MR-PRESSO; **MVMR:** multivariable MR, **O:** Other method.
MAGIC: Meta-Analyses of Glucose and Insulin-related traits Consortium; **UKB:** UK Biobank; **CGPS:** Copenhagen General Population Study; **CCHS:** Copenhagen City Heart Study; **DIAGRAM:** DIAbetes Genetics Replication And Meta-analysis; **GIANT:** Genetic Investigation of ANthropometric Traits.

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Table 8: Summary of MR studies related to autoimmune and inflammatory diseases.

Author	Outcome	Outcome population	Cases	Controls		Sensitivity analyses	Robustness
Lu 2020	Multiple sclerosis	IMSGC	14,802	26,703	−	MR-E, WM	Insufficient
Bae 2018	Systemic lupus erythematosus	5 cohorts	1,311	1,783	_	MR-E, WM	Insufficient
Pu 2022	Rheumatoid arthritis	6 cohorts	5,539	20,169	↑	MR-E, WM, WMode, O	Probable
Bae 2018	Rheumatoid arthritis	18 cohorts	14,361	43,923	−	MR-E, WM	Insufficient
Nicolopoulos 2020	Osteoarthritis	UKB	48,042	272,516	↑	MR-E, WM, WMode, MR-P	Probable
Nicolopoulos 2020	Osteoarthritis localised	UKB	29,602	272,516	↑	MR-E, WM, WMode, MR-P	Probable
Nicolopoulos 2020	Osteoarthritis unspecified	UKB	27,010	272,516	↑	MR-E, WM, WMode, MR-P	Probable
Nicolopoulos 2020	Osteoarthritis localised (primary)	UKB	8,456	272,516	↑	MR-E, WM, WMode, MR-P	Probable
Zhang 2021	Self-reported osteoarthritis	UKB	12,658	50,898	↑	MR-E, WM, WMode, O	Probable
Zhang 2021	Hip osteoarthritis	UKB	12,625	50,898	_	MR-E, WM, WMode, O	Insufficient
Zhang 2021	Knee osteoarthritis	UKB	4,462	17,885	↑	MR-E, WM, WMode, O	Probable
Lee 2018	Knee & hip osteoarthritis	arcOGEN	7,410	11,009	↑	MR-E, WM	Suggestive
Nicolopoulos 2020	Arthropathy unspecified	UKB	36,353	280,100	↑	MR-E, WM, WMode, MR-P	Probable
Nicolopoulos 2020	Other arthropathies	UKB	36,496	280,100	↑	MR-E, WM, WMode, MR-P	Probable
Nicolopoulos 2020	Monoarthritis unspecified	UKB	15,313	280,100	↑	MR-E, WM, WMode, MR-P	Probable
Yuan 2019	Fracture risk	UKB	53,184	373,611	−	MR-E, WM	Insufficient
Yuan 2019	Estimated mineral density (eBMD)	UKB	n total = 426,824		_	MR-E, WM	Insufficient
Yuan 2019	eBMD of femoral neck	GEFOS	n total = 32,965		_	MR-E, WM	Insufficient
Yuan 2019	eBMD of forearm	GEFOS	n total = 32,965		−	MR-E, WM	Suggestive
Yuan 2019	eBMD of lumbar spine	GEFOS	n total = 32,965		_	MR-E, WM	Insufficient
Shirai 2022	Gout	GUGC	2,155	67,259	↓	MR-E, WM, WMode	Probable
Shirai 2022	Gout	Biobank Japan	3,053	4,554	↓	MR-E, WM, WMode	Probable
Nicolopoulos 2020	Gout	UKB	3,423	248,101	_	MR-E, WM, WMode, MR-P	Insufficient
Nicolopoulos 2020	Gout & other arthropathies	UKB	3,970	248,101	_	MR-E, WM, WMode, MR-P	Insufficient
Shirai 2022	Serum uric acid	GUGC	n total = 110,347		_	MR-E, WM, WMode	Insufficient
Shirai 2022	Serum uric acid	Biobank Japan	n total = 121,745		−	MR-E, WM, WMode	Insufficient

↑ positive association (main analysis); ↓ negative association (main analysis); − null association (main analysis).
MR-E: MR-Egger; **WM:** weighted median; **WMode:** weighted mode; **MR-P:** MR-PRESSO; **MVMR:** multivariable MR, **O:** Other method.
IMSGC: International Multiple Sclerosis Genetics Consortium; **UKB:** UK Biobank; **arcOGEN:** Arthritis Research UK Osteoarthritis Genetics; **GEFOS:** GEnetic Factors for OSteoporosis; **GUGC:** Global Urate Genetics Consortium.

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Table 9: Summary of MR studies related to the digestive system and renal system.

Author	Outcome	Outcome population	Cases	Controls		Sensitivity analyses	Robustness
Yuan 2022	Non-alcoholic fatty liver disease	5 cohorts & 11 clinics	9,917	787,961	↓		Non-evaluable
Yuan 2022	Diverticular disease	UKB & FinnGen	23,640	497,533	–		Non-evaluable
Yuan 2022	Gastroesophageal reflux disease	UKB, & QSkin	71,522	261,079	–		Non-evaluable
Georgiou 2021	Crohn's disease	UKIBDGC & UK10K	12,194	25,042	–	MR-E, WM, O	Insufficient
Georgiou 2021	Ulcerative colitis	UKIBDGC & UK10K	12,366	25,042	–	MR-E, WM, O	Insufficient
Yuan 2022	Gallstone disease	UKB & FinnGen	22,195	472,022	–		Probable
Nordestgaard 2020	Symptomatic gallstone disease	CGPS & CCHS	7,294		↓		Probable
Yuan 2022	Kidney stones	UKB & FinnGen	10,392	561,265	↓		Non-evaluable
Kennedy 2020	Estimated Glomerular filtration rate (eGFR)	CKDGen	total n = 133,814		↑	MR-E, WM, WMode	Probable
Kennedy 2020	Chronic kidney disease	CKDGen	12,385	104,780	↓		Probable
Kennedy 2020	Albuminuria	CKDGen	total n = 54,116		↓		Probable

↑ positive association (main analysis); ↓ negative association (main analysis); − null association (main analysis).

MR-E: MR-Egger; **WM:** weighted median; **WMode:** weighted mode; **MR-P:** MR-PRESSO; **MVMR:** multivariable MR, **O:** Other method.

UKB: UK Biobank; **QSkin:** QSkin Sun & Health Study; **UKIBDGC:** UK Inflammatory Bowel Disease Genetics Consortium; **CKDGen:** Chronic Kidney Disease Genetics.

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Table 10: Summary of MR studies related to mortality and other outcomes.

Author	Outcome	Outcome population	Cases	Controls		Sensitivity analyses	Robustness
van Oort 2021	Longevity	20 cohorts	11,262	25,483	–	MR-E, WM, MR-P, O	Insufficient
Taylor 2017	All-cause mortality	PRACTICAL	4,081	11,474	–		Non-evaluable
Nordestgaard 2016	All-cause mortality	5 cohorts	12,656	112,509	–		Non-evaluable
Nordestgaard 2016	Cardiovascular disease mortality	5 cohorts	3,671	104,766	–		Non-evaluable
Taylor 2017	Prostate cancer specific mortality	PRACTICAL	1,754	12,256	–		Non-evaluable
Ong 2019	Overall cancer mortality	UKB	6,998	270,342	–		Non-evaluable
Ong 2019	Cancer death in females	UKB	3,836	143,465	–		Non-evaluable
Ong 2019	Cancer death in males	UKB	3,165	143,465	–		Non-evaluable
Yuan 2021	Pregnancy loss	UKB	63,877	195,265			Non-evaluable
Nicolopoulos 2020	Menopausal + other postmenopausal disorders	UKB	8,842	110,903	↓	MR-E, WM, WMode, MR-P	Probable
Nicolopoulos 2020	Postmenopausal bleeding	UKB	7,494	110,903	↓	MR-E, WM, WMode, MR-P	Probable
Lv 2022	Low back pain	FinnGen	13,178	164,682	–	MR-E, WM, WMode, MR-P	Insufficient
Li 2022	Primary Open-Angle Glaucoma (POAG)	18 cohorts	16,677	199,580	↑	MR-E, WM, WMode, MR-P	Probable
Kim 2021	Intraocular pressure (IOP)	UKB	total n = 92,699		–	MR-E, WM, WMode	Insufficient
Yuan 2022	Senile cataract	UKB & FinnGen	26,489	509,767	↑		Non-evaluable
Cresswell 2022	Current tinnitus	UKB	22,293	88,474	↓		Non-evaluable

↑ positive association (main analysis); ↓ negative association (main analysis); − null association (main analysis).

MR-E: MR-Egger; **WM:** weighted median; **WMode:** weighted mode; **MR-P:** MR-PRESSO; **MVMR:** multivariable MR, **O:** Other method.

PRACTICAL: Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome; **UKB:** UK Biobank.

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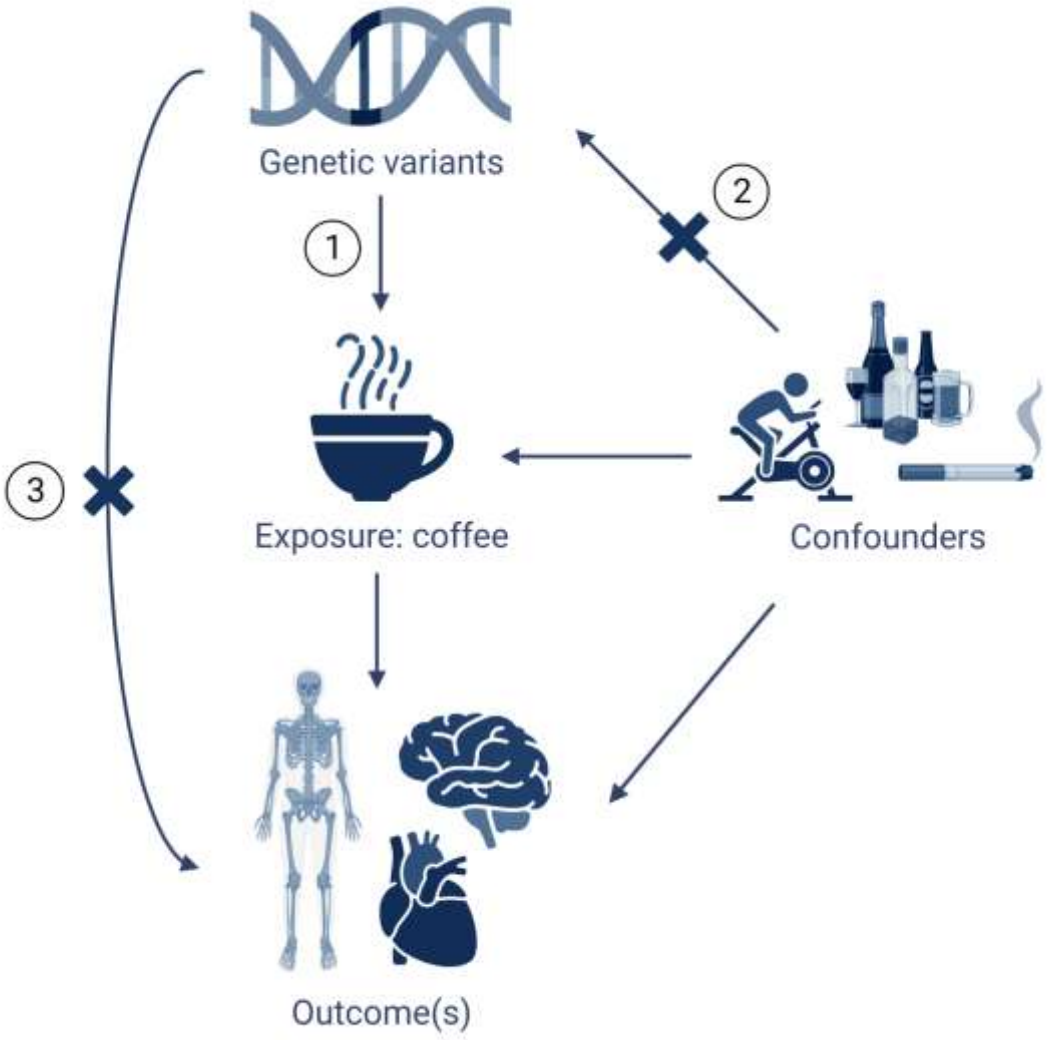

Figure 1: Diagram explaining the 3 core assumptions of Mendelian randomisation studies.

① **Relevance assumption:** the genetic variant(s) are associated with the exposure of interest.

② **Independence assumption:** the genetic variant(s) are not associated with confounding factors associated with the exposure and outcome.

③ **Exclusion restriction assumption:** the genetic variant(s) are only associated with the outcome through the exposure of interest.

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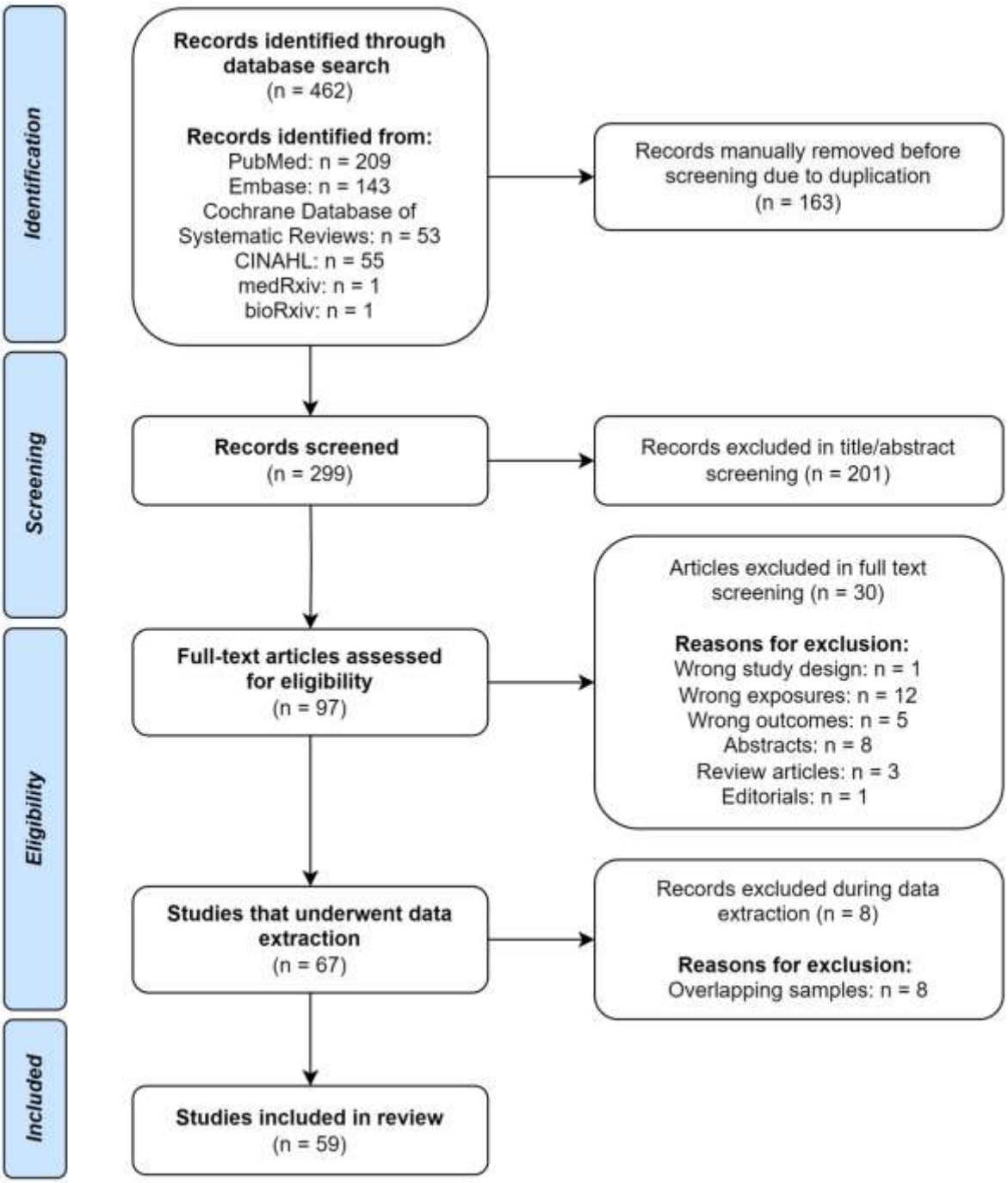

Figure 2: PRISMA flow diagram summarising the identification, screening and eligibility assessment for studies included in this review.

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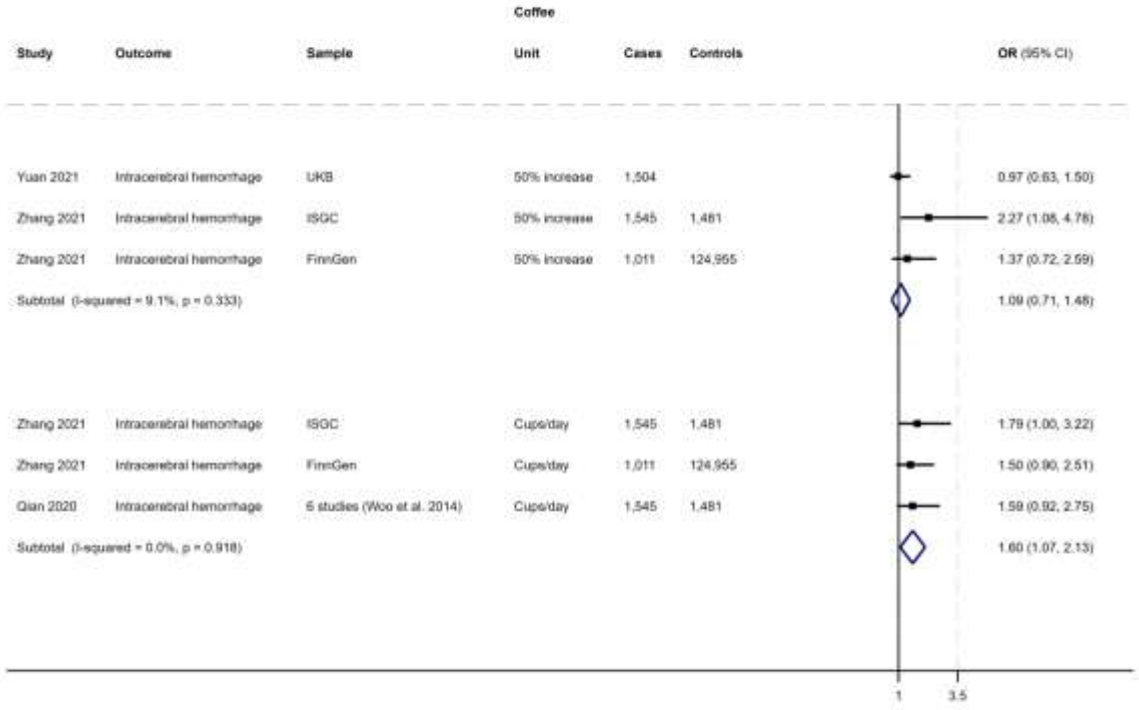

Figure 3: Forest plot showing the meta-analysis of studies reporting on the effect of coffee consumption on intracerebral haemorrhage.

[1]Woo D, Falcone GJ, Devan WJ, Brown WM, Biffi A, Howard TD, Anderson CD, ... International Stroke Genetics Consortium. Meta-analysis of genome-wide association studies identifies 1q22 as a susceptibility locus for intracerebral hemorrhage. Am J Hum Genet. 2014 Apr 3;94(4):511-21. doi: 10.1016/j.ajhg.2014.02.012. Epub 2014 Mar 20. PMID: 24656865; PMCID: PMC3980413.

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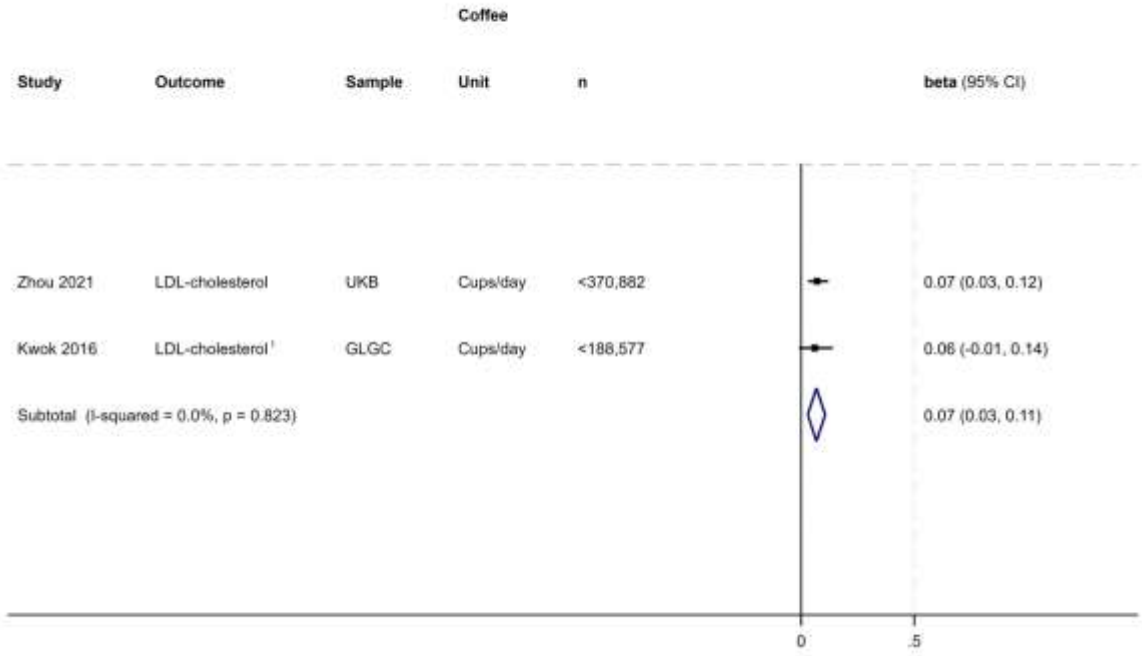

Figure 4: Forest plot showing the meta-analysis of studies reporting on the effect of coffee consumption on LDL-cholesterol.

[1]Original estimate was described per SD change in LDL-C; converted to per 1 mmol/L change in LDL-C based on 1SD = 38.67 mg/dL = 1 mmol/L.

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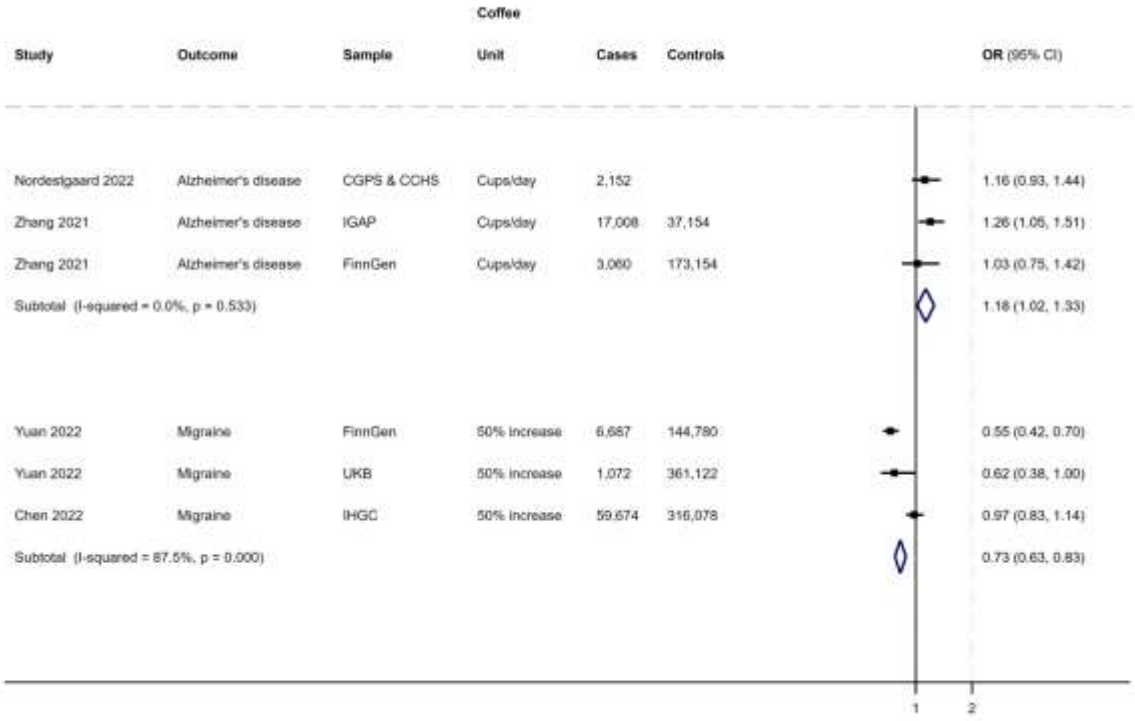

Figure 5: Forest plot showing the meta-analysis of studies reporting on the effect of coffee consumption on Alzheimer's disease and migraines.

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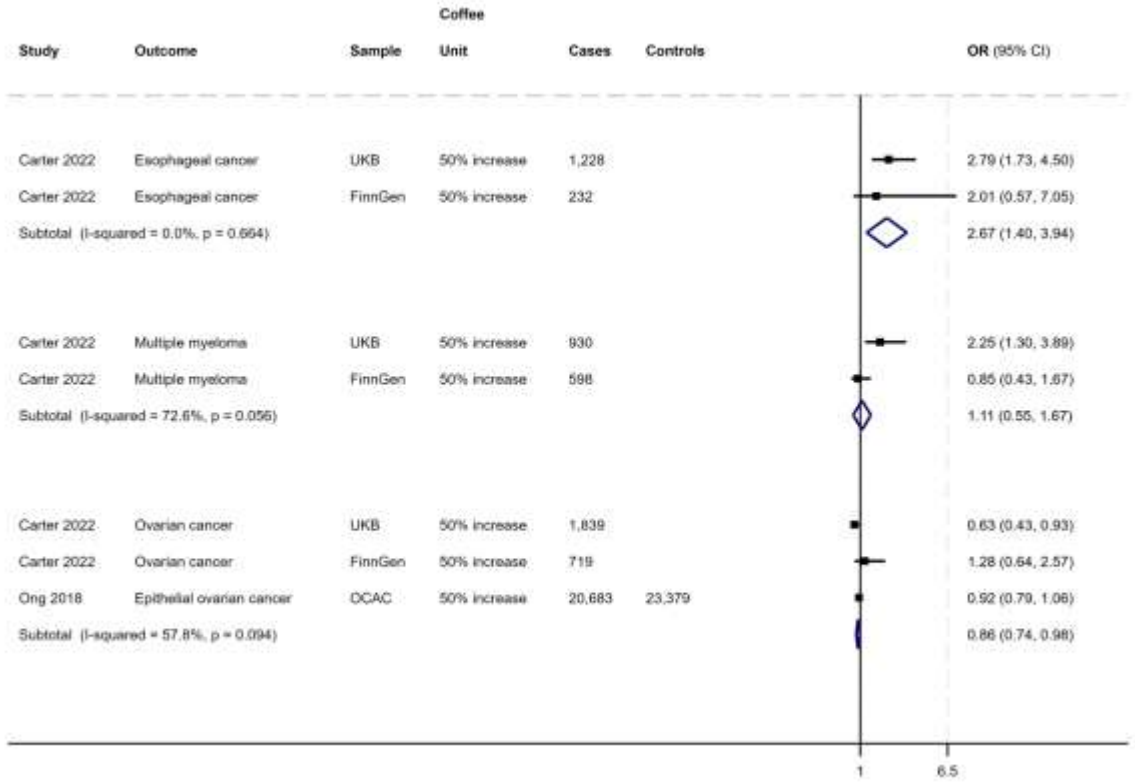

Figure 6: Forest plot showing the meta-analysis of studies reporting on the effect of coffee consumption on esophageal cancer, multiple myeloma, and ovarian cancer.

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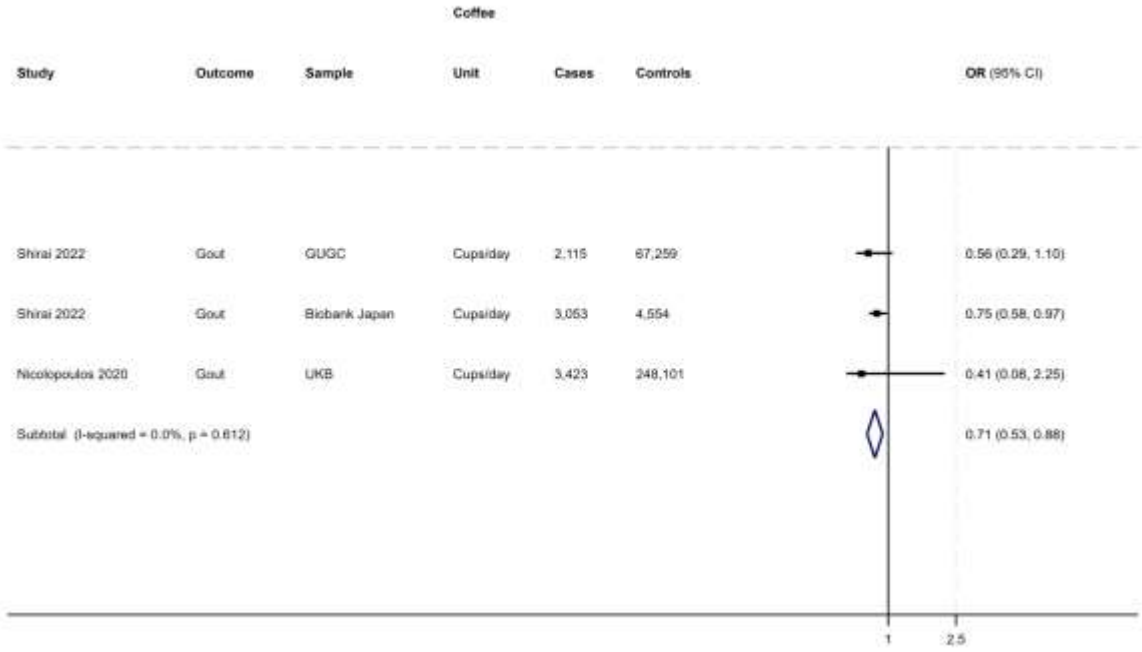

Figure 7: Forest plot showing the meta-analysis of studies reporting on the effect of coffee consumption on gout.

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