Nutrition Research Reviews

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

Kitty Pham[1,2], Nigussie Assefa Kassaw[1,3], Anwar Mulugeta[1,2,4], Ang Zhou[1,5] and Elina Hyppönen[1,2]

[1]Australian Centre for Precision Health, Clinical & Health Sciences, University of South Australia, Adelaide, Australia; [2]South Australian Health and Medical Research Institute (SAHMRI), Adelaide, Australia; [3]School of Public Health, Addis Ababa University, Addis Ababa, Ethiopia; [4]Department of Pharmacology and Clinical Pharmacy, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia and [5]Medical Research Council Biostatistics Unit, School of Clinical Medicine, University of Cambridge, Cambridge, UK

Review Article

Cite this article: Pham K, Kassaw NA, Mulugeta A, Zhou A, and Hyppönen E (2025). Coffee and health outcomes: a systematic review of Mendelian randomisation studies. *Nutrition Research Reviews*, page 1 of 21. doi: 10.1017/S0954422425100206

Received: 18 November 2024
Revised: 1 September 2025
Accepted: 23 September 2025

Keywords:
Coffee; Caffeine; Literature review; Mendelian randomisation; MR; Systematic review

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

Corresponding authors: Kitty Pham; Email: kitty.pham@unisa.edu.au; Elina Hyppönen; Email: elina.hypponen@unisa.edu.au

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, Cumulative Index to Nursing and Allied Health Literature and two preprint repositories from inception to 30 September 2022, and included fifty-nine 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 Mendelian randomisation (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 oesophageal 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-cholesterol 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.

Systematic review registration: PROSPERO registration number CRD42021295323

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 (Fig. 1). Since genetic variants are randomly assigned at conception, MR overcomes the effect of unmeasured confounding and reverse causality. The variants can be selected on the basis of candidate genes known to affect the exposure or using results from genome wide association studies (GWAS)[13]. In recent years, the use of the MR method has increased in popularity, with many papers utilising the availability of large-scale cohort data and GWAS[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.

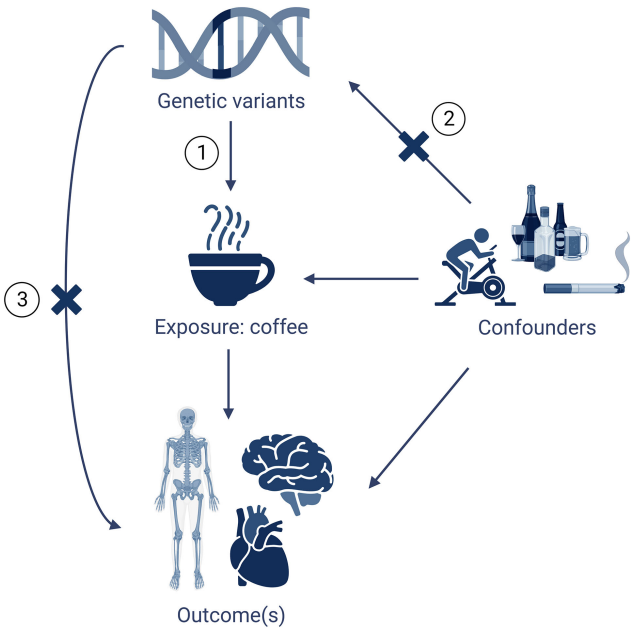

Fig. 1. Diagram explaining the three core assumptions of Mendelian randomisation studies. (1) Relevance assumption: the genetic variant(s) are associated with the exposure of interest. (2) Independence assumption: the genetic variant(s) are not associated with confounding factors associated with the exposure and outcome. (3) Exclusion restriction assumption: the genetic variant(s) are only associated with the outcome through the exposure of interest. Created with BioRender.com.

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 September 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 Population, Exposure/Intervention, Comparison, Outcomes and Study (PECOS) design framework, as described in Table 1. Two reviewers (K.P. and N.A.K.) independently screened the articles using Covidence[18] and any conflicts were resolved by a third reviewer (E.H.). The study selection process was documented using a PRISMA flow diagram template.

Data extraction

In the data extraction stage, two reviewers (K.P. and N.A.K.) 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 (for example, phenotypic analyses), only data relating to the MR analysis were extracted. The minimum 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 single nucleotide polymorphism (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 undertook a meta-analysis of 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 (for example, cups/d 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 Grading of Recommendations, Assessment, Development and Evaluations (GRADE) rating system[19]. Studies were ranked as high, moderate, low or very low certainty to describe how likely it was that the reported estimate was similar to the true effect. MR studies start as high certainty and can be rated down on the basis of risk of bias, imprecision, inconsistency, indirectness and publication bias. Certainty can be rated up for a 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

https://doi.org/10.1017/S0954422425100206 Published online by Cambridge University Press

Table 1. PECOS criteria for inclusion of studies

Parameter	Inclusion criteria	Exclusion criteria
Population	Adults, with no restriction on the basis of 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 (for example, abstracts, conference presentations, reviews and editorials) and any duplications across the databases.

adapted the domains to be relevant for MR studies and created a checklist to 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 ($r^2 > 0{\cdot}8$) (Supplementary Table 3)[21–23]. We firstly checked associations significant at genome wide significance level (p-value $<5 \times 10^{-8}$), then checked for any additional associations significant at $p < 1 \times 10^{-5}$.

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 on the basis of 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 owing to duplication (Fig. 2). We screened 299 articles in the title and abstract screening phase and excluded 201 that did not meet the inclusion criteria. A further thirty articles were excluded in the full-text screening phase. We extracted data from sixty-seven studies, which contained analyses of 241 outcome associations. After data extraction, we excluded forty-four outcome associations owing to overlapping outcome sample populations from fourteen studies. However, because some of these studies had other outcomes contributing to the review, the process resulted in the exclusion of only eight out of the fourteen studies. Details on excluded duplicate outcomes are described in Supplementary Table 4. Overall, we have presented results for fifty-nine 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%, fifty studies), while only nine 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%, thirty-nine 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 thirty-seven (62·7%) and fifteen (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 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 eleven (Table 2). In a majority of studies, all SNPs were associated with coffee consumption at a genome wide significance level ($p < 5 \times 10^{-8}$) and the clumping threshold was set to $r^2 < 0.001$ or $r^2 < 0.01$. Instrumental variable (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).

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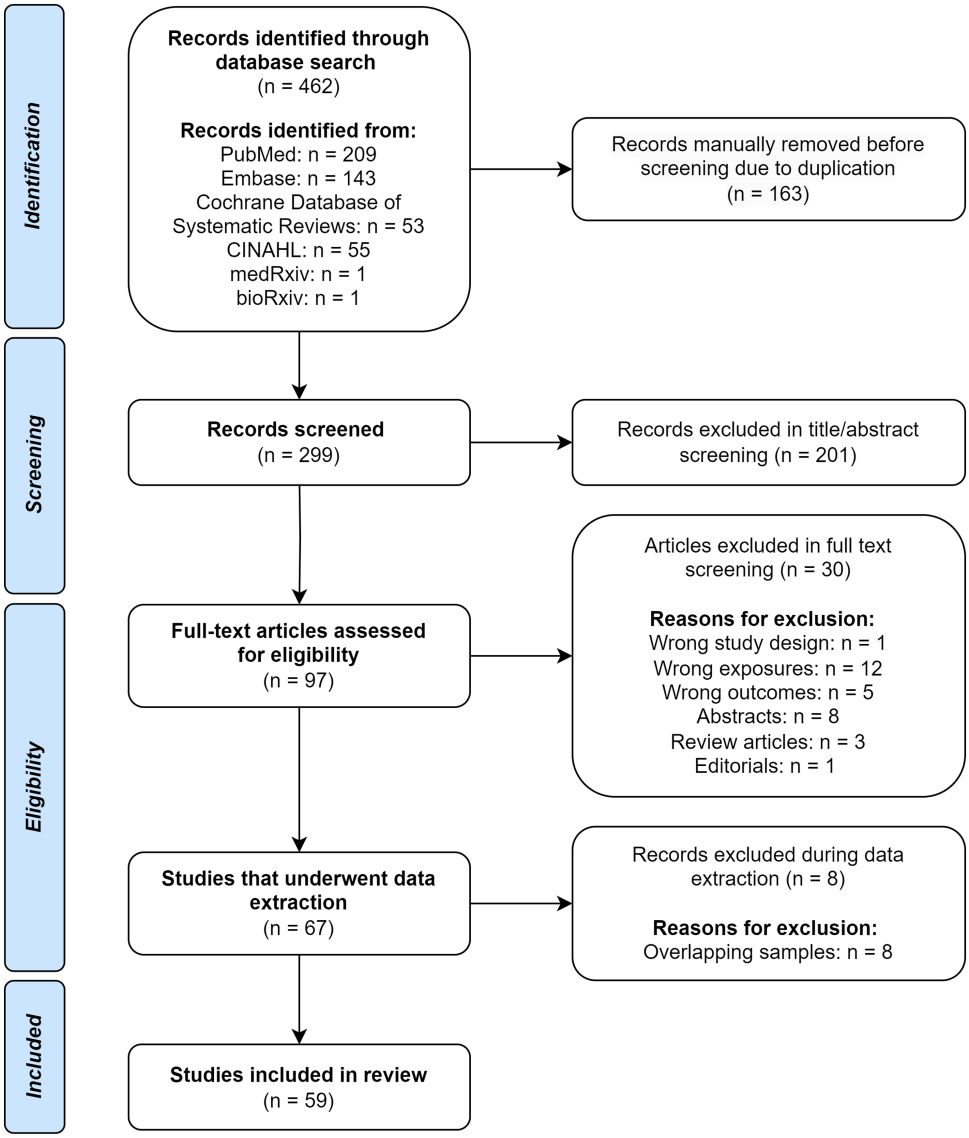

Fig. 2. PRISMA flow diagram summarising the identification, screening and eligibility assessment for studies included in this review.

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, fifty-one of fifty-nine 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 eight studies reported no formal pleiotropy assessment (Table 2).

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 that should be considered when assessing the MR associations (Supplementary Table 3). SNP rs1260326 (GKCR) was the most pleiotropic and was reported to be associated ($p < 5 \times 10^{-8}$) 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 and rs34060476), coronary artery disease (rs66723169), gout (rs1481012, rs7800944 and rs34060476), obesity and metabolic disease (rs1481012, rs4410790, rs7800944, rs6265, rs2470893, rs2472297, rs574367, rs10865548 and rs66723169) or addictive behaviours such as smoking and alcohol consumption (rs4410790, rs6265, rs2470893, rs34060476 and rs66723169), were all commonly flagged as potential pleiotropic associations. At $p < 1 \times 10^{-5}$, we identified further associations with diastolic blood pressure (rs2472297 and rs10865548), systolic blood pressure (rs10865548) and heart rate (rs597045 and 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%, thirty-four studies) ranked as high, nearly a third were ranked as moderate (30·5%, eighteen studies) and only a small proportion of studies were downgraded to a low or very low rating (11·9%, seven studies). We found that studies were most

https://doi.org/10.1017/S0954422425100206 Published online by Cambridge University Press

Table 2. Summary of the characteristics of fifty-nine Mendelian randomisation studies on coffee consumption included in this 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/d	European	4	CCGC	UKB and FinnGen	Yes
Zheng 2022	35369049	TSMR	Brain volume measures; fractional anisotropy; mean diffusivity	Cups/d	European	12	UKB	CHARGE, UKB, ADNI, MGH-GASROS and CROMIS-2 AF	Yes
Zhang 2022	35254179	TSMR	Amyotrophic lateral sclerosis	50% increase in cups/d	European	12	UKB	2 GWAS studies (PMID 29566793)	Yes
Zhang 2022	35334809	TSMR	Epilepsy	50% increase in cups/d	~86% European	12	UKB	ILAE and FinnGen	Yes
Yuan 2022	33418132	TSMR	Gallstone disease	50% increase in cups/d	European	9	UKB	UKB and FinnGen	Yes
Yuan 2022	34139333	TSMR	Diverticular disease	50% increase in cups/d	European	12	UKB	UKB and FinnGen	Yes
Yuan 2022	34690004	TSMR	Kidney stones	50% increase in cups/d	European	12	UKB	UKB and FinnGen	Yes
Yuan 2022	35013517	TSMR	Senile cataract	50% increase in cups/d	European	12	UKB	UKB and FinnGen	Yes
Yuan 2022	35029599	TSMR	Migraine	50% increase in cups/d	European	12	UKB	UKB and FinnGen	Yes
Yuan 2022	35119566	TSMR	Gastroesophageal reflux disease	50% increase in cups/d	European	11	UKB	UKB and Qskin	Yes
Yuan 2022	35488966	TSMR	Non-alcoholic fatty liver disease	50% increase in cups/d	European	12	UKB	eMERGE, UKB, Estonian Biobank, FinnGen and 11 clinics (PMID 32298765)	Yes
Shirai 2022	35348303	TSMR	Gout risk; serum uric acid	Days/week of drinking coffee | cups/d	Japanese | European	Up to 10 | 5	BioBank Japan | CCGC	Biobank Japan | GUGC	Yes
Pu 2022	36172525	TSMR	Rheumatoid arthritis	1SD increase in cups/d	European	27	UKB	18 studies (PMID 24390342)	Yes
Nordestgaard 2022	35405480	OSMR	Dementia outcomes	Cups/d	European	2	CGPS and CCHS		No
Narayan 2022	35166314	TSMR	Obesity outcomes; anthropometric measures	Cups/d	European	10	CCGC	GIANT	Yes
Lv 2022	36114324	TSMR	Low back pain	50% increase in cups/d	European	13	UKB	FinnGen	Yes
Li 2022	35537532	TSMR	Primary open-angle glaucoma	Cups/d	European	6	CCGC	18 studies (PMID 33627673)	Yes
Li 2022	36071939	TSMR	Renal cell carcinoma	50% increase in cups/d	European	12	UKB	FinnGen and IARC	Yes
Hoek 2022	35929454	TSMR	Peripheral artery disease	50% increase in cups/d	~72% European	14	UKB	MVP	Yes
Domenighetti 2022	34633332	TSMR	Parkinson's disease	ln(cups/d)	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/d (caffeinated coffee)	European	6	UKB		Yes
Chen 2022	35145549	TSMR	Migraine outcomes	50% increase in cups/d	European	9	UKB	IHGC	Yes
Carter 2022	36067583	TSMR	Cancer outcomes	50% increase in cups/d	European	12	UKB	UKB	Yes
Zhou 2021	33487505	TSMR	Serum lipid measures	Cups/d	European	4	CCGC	UKB	Yes

(*Continued*)

Table 2. (*Continued*)

Study	PMID	Method	Outcome (s) included in this review	Coffee unit	Ancestry	No. of SNPs	Exposure sample	Outcome sample	Pleiotropy assessed*
Zhang 2021	34459406	TSMR	Alzheimer's disease; intracerebral haemorrhage	50% increase in cups/d	European	14	UKB	IGAP, ISGC and FinnGen	Yes
Zhang 2021	34858340	TSMR	Osteoarthritis outcomes	1% increase in cups/d	European	11	UKB	UKB	Yes
Yuan 2021	34187701	TSMR	Pregnancy loss	50% increase in cups/d	European	12	UKB	UKB and FinnGen	Yes
Yuan 2021	34203356	TSMR	Cardiovascular disease outcomes	50% increase in cups/d	European	12	UKB	UKB and FinnGen	Yes
Yuan 2021	34666504	TSMR	Varicose veins	50% increase in cups/d	European	12	UKB	UKB and FinnGen	Yes
Wang 2021	34371827	TSMR	Prostate cancer	1% increase in cups/d	European	12	UKB	PRACTICAL and FinnGen	Yes
Wang 2021	34656958	TSMR	Huntington's disease (age of onset)	50% increase in cups/d	European	14	UKB	GeM-HD	Yes
van Oort 2021	33107078	TSMR	Longevity	50% increase in cups/d	European	14	UKB	20 studies (PMID 31413261)	Yes
Treur 2021	31733098	TSMR	Attention deficit hyperactivity disorder	Cups/d	European	4	CCGC	iPYSCH and PGC	Yes
Li 2021	medRxiv	TSMR	Serum lipid measures; body mass index	Cups/d	European	38	UKB	14 cohorts (PMID 27005778)	Yes
Kim 2021	33333105	TSMR	Intraocular pressure	Cups/d	European	8	CCGC	UKB	No
Karhunen 2021	34729997	TSMR	Aneurysmal subarachnoid haemorrhage; intracranial aneurysm	50% increase in cups/d	European	10	UKB	ISGC	Yes
Georgiou 2021	32628751	TSMR	Crohn's disease; ulcerative colitis	Cups/d	European	8	CCGC	UKIBDGC and UK10K	Yes
Ellingjord-Dale 2021	33465101	TSMR	Breast cancer outcomes	Cups/d	European	33	UKB	BCAC	Yes
Yuan 2020	32895727	TSMR	Type 2 diabetes mellitus	50% increase in cups/d	European	12	UKB	DIAGRAM	Yes
van Oort 2020	32682105	TSMR	Heart failure	50% increase in cups/d	European	14	UKB	HERMES	Yes
van Oort 2020	33131310	TSMR	Hypertension	50% increase in cups/d	European	14	UKB	UKB and FinnGen	Yes
Qian 2020	32034791	TSMR	Stroke outcomes	High *v.* infrequent/no consumption and cups/d	European	Up to 8	CCGC	MEGASTROKE and 6 studies (PMID 24656865)	Yes
Nordestgaard 2020	31486166	OSMR	Symptomatic gallstone disease	Cups/d	European	2	CGPS and CCHS		No
Nicolopoulos 2020	32284183	TSMR	Gout outcomes; obesity outcomes; menopausal disorders outcomes; osteoarthritis outcomes	Cups/d	European	8	CCGC	UKB	Yes
Lu 2020	32590313	TSMR	Multiple sclerosis	1% increase in cups/d	European	9	UKB	IMSGC	Yes
Kennedy 2020	31837886	TSMR	Kidney function outcomes	Cups/d	European	25	UKB	CKDGen	Yes
Yuan 2019	31482193	TSMR	Fracture risk, estimated mineral density measures	50% increase in cups/d	European	15	UKB	UKB and GEFOS	Yes
Yuan 2019	31558414	TSMR	Atrial fibrillation	50% increase in cups/d	91% European	9	UKB	AFGen	Yes
Ong 2019	31412118	OSMR	Cancer outcomes	Cups/d	European	35	UKB		Yes
Zhou 2018	29760501	OSMR	Global cognition; memory cognition	Cups/d	European	2	1958BC, ALSPAC-M, NFBC1966, YFS, HBCS, PIVUS, ULSAM, STR and TwinGene		Yes

Table 2. (*Continued*)

Ong 2018	29186515	TSMR	Ovarian cancer outcomes	Cups/d	European	4	CCGC	OCAC	No
Noyce 2018	bioRxiv	TSMR	Parkinson's disease	Cups/d	European	4	CCGC	IPDGC	Yes
Lee 2018	30076541	TSMR	Osteoarthritis	Categories (0–2, 3–4, 5–6, 7–9 and ≥10 cups/d); cups/d	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/d); cups/d	European	3	CCGC	6 studies (PMID 20453842) and GWAS (PMID 18204098)	Yes
Taylor 2017	27741566	OSMR	Mortality outcomes	Cups/d	European	2	PRACTICAL		No
Nordestgaard 2016	28031317	OSMR	Ischaemic stroke; ischaemic vascular disease; all-cause mortality	Cups/d	European	5	CGPS, CCHS, CIHDS and CARDIoGRAMplusC4		No
Kwok 2016	27845333	TSMR	Ischaemic heart disease; depression; body mass index; serum lipid traits; glycaemic traits	Cups/d	Mostly European	5	CCGC	CARDIoGRAMplusC4D, PGC, GLGC, GIANT, MAGIC, ADIPOGen and SSGAC	No
Nordestgaard 2015	26002927	OSMR	Metabolic syndrome; obesity; anthropometric measures; serum lipid measures; cardiovascular disease mortality	Cups/d	European	5	CGPS, CCHS and DIAGRAM		No

OSMR, one-sample Mendelian randomisation study; TSMR, two-sample Mendelian randomisation study.
*At least 1 method of formal pleiotropy assessment was performed (for example, MR-Egger intercept test, MR-PRESSO outlier test and leave-one-out analysis).

commonly downgraded in the risk of bias and imprecision domains, primarily owing 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 ischaemic attack or pulmonary embolism[25–35]. There was also insufficient evidence to support an association with stroke, ischaemic stroke (large vessel, small vessel and 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 three non-overlapping studies were also inconclusive (pooled odds ratio (OR) per 50% increase in coffee 1·09, 95% CI 0·71–1·48; pooled OR per 1 cup/d increase in coffee 1·60, 95% CI 1·07–2·13) (Fig. 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 ($p < 1 \times 10^{-5}$), 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 the 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/d increase in coffee 0£07, 95% CI 0·03–0·11) (Fig. 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 an increased risk of Alzheimer's disease (pooled OR per 1 cup/d increase in coffee 1·18, 95% CI 1·02–1·33) (Fig. 5). We also found probable evidence to support an association between coffee and a younger age of onset of Huntington's disease[42]. Studies on cognition, amyotrophic lateral sclerosis (ALS), Parkinson's disease,

https://doi.org/10.1017/S0954422425100206 Published online by Cambridge University Press

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	4593		–	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	3528		–	MR-E, WM, MVMR	Insufficient
van Oort 2020	Hypertension	UKB and FinnGen	70 228	482 997	–		Non-evaluable
Zhou 2022	Aortic aneurysm	UKB and FinnGen	5032	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	1660		–	MR-E, WM, MVMR	Insufficient
Yuan 2021	Transient ischaemic attack	UKB	4813		–	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	Ischaemic stroke	UKB	6566		–	MR-E, WM, MVMR	Insufficient
Qian 2020	Ischaemic stroke	MEGASTROKE	34 217	406 111	–	MR-E, WM, MR-P	Insufficient
Nordestgaard 2016	Ischaemic stroke	CARDIoGRAMplusC4	4589	112 509	–		Non-evaluable
Qian 2020	Large vessel ischaemic stroke	MEGASTROKE	4373	406 111	–	MR-E, WM, MR-P	Insufficient
Qian 2020	Small vessel ischaemic stroke	MEGASTROKE	5386	406 111	–	MR-E, WM, MR-P	Probable
Qian 2020	Cardioembolic ischaemic stroke	MEGASTROKE	7193	406 111	–	MR-E, WM, MR-P	Insufficient
Yuan 2021	Intracerebral haemorrhage	UKB	1504		–	MR-E, WM, MVMR	Insufficient
Zhang 2021	Intracerebral haemorrhage	ISGC and FinnGen	2556	126 436	↑		Non-evaluable
Qian 2020	Intracerebral haemorrhage	6 cohorts	1545	1481	–	MR-E, WM, MR-P	Probable
Karhunen 2021	Intracranial aneurysm	ISGC	6252	59 544	–	MR-E, WM, WMode	Insufficient
Karhunen 2021	Subarachnoid haemorrhage	ISGC	4196	59 544	–	MR-E, WM, WMode	Insufficient
Yuan 2021	Subarachnoid haemorrhage	UKB	1292		–	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	7733		–	MR-E, WM, MVMR	Insufficient
Yuan 2021	Varicose veins	UKB and FinnGen	22 691	506 382	↓	MR-E, WM, MVMR	Robust
Nordestgaard 2015	Systolic blood pressure	CGPS, CCHS and DIAGRAM	*n* total < 93 197		–		Non-evaluable
Nordestgaard 2015	Diastolic blood pressure	CGPS, CCHS and 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.

epilepsy, attention deficit hyperactivity disorder (ADHD) and cerebral microbleeds all reported null findings[43–49]. 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, I^2 87·5%) (Fig. 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].

https://doi.org/10.1017/S0954422425100206 Published online by Cambridge University Press

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.

There was one study reporting a robust association reported between coffee and lower grey matter volume (beta in standard deviation (SD) per 1 coffee cup/d increase −0·371, 95% CI −0·596 to −0·147)[44]. No associations were observed for other brain volume measures (total brain, white matter and hippocampus), white matter hyperintensity volume or MRI markers of small vessel disease (fractional anisotropy and 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[53–56] (Table 6). 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 oesophageal 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 an increased risk of multiple myeloma and a decreased risk of ovarian cancer, which were also not replicated in the FinnGen cohort. Meta-analysis of estimates from the UK Biobank and FinnGen suggest that coffee consumption is associated with an increased risk of oesophageal cancer (pooled OR per 50% increase in coffee 2·67, 95% CI 1·40–3·94). Given that the 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) (Fig. 6).

Metabolic traits

In the largest available study, coffee drinking had a suggestive association with an increased risk of type 2 diabetes mellitus[59] (Table 7). Coffee was also associated with markers of an 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. A meta-analysis could not be conducted for waist circumference as 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[62,63] (Table 8). Bae and Lee[63] suggested that there may be an association between coffee and an 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 an increased risk of osteoarthritis (OA) was identified in the UK Biobank cohort[61], while only suggestive evidence was identified within the Arthritis Research UK Osteoarthritis Genetics (arcOGEN) consortium[65]. The association remained when data was restricted 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

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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 and CCHS	2152		–		Non-evaluable
Zhang 2021	Alzheimer's disease	IGAP and FinnGen	20 068	210 993	↑		Non-evaluable
Nordestgaard 2022	All dementia	CGPS and CCHS	3784		↑		Non-evaluable
Nordestgaard 2022	Non-Alzhiemer's disease (vascular dementia proxy)	CGPS and CCHS	1584		–		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	9604		↓	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	7369	7018	–	MR-E, WM, WMode, MR-P	Insufficient
Noyce 2018	Parkinson's disease	IPDGC	13 708	95 282	–	MR-E	Insufficient
Zhang 2022	Epilepsy	ILAE and FinnGen	19 800	174 457	–		Non-evaluable
Treur 2021	Attention deficit hyperactivity disorder	iPSYCH and PGC	*n* total = 15 548		–	MR-E, WM, WMode	Insufficient
Kwok 2016	Depression	PGC	9240	9519	–		Non-evaluable
Zheng 2022	Any cerebral microbleed	5 cohorts	3556	22 306	–	MR-E, WM	Insufficient
Zheng 2022	Cerebral microbleed (strictly lobar)	5 cohorts	2179	22 306	–	MR-E, WM	Insufficient
Zheng 2022	Cerebral microbleed (mixed or strictly deep)	5 cohorts	1293	22 306	–	MR-E, WM	Insufficient
Yuan 2022	Migraine	UKB and FinnGen	7759	504 902	↓	MVMR	Probable
Chen 2022	Migraine	IHGC	59 674	316 078	–	MR-E, WM	Insufficient
Chen 2022	Migraine (with aura)	IHGC	6332	144 883	–	MR-E, WM	Insufficient
Chen 2022	Migraine (without aura)	IHGC	8348	139 622	–	MR-E, WM	Insufficient
Zheng 2022	Total brain volume	UKB	*n* total = 33 224		–	WM, WMode	Insufficient
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 and 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.

https://doi.org/10.1017/S0954422425100206 Published online by Cambridge University Press

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	1057		–	MR-E, WM	Insufficient
Carter 2022	Head and neck cancer	UKB	1983		–	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	4231		–	MR-E, WM	Insufficient
Carter 2022	Oesophageal cancer	UKB	1228		↑	MR-E, WM	Robust
Carter 2022	Oesophageal 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	6995		–	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	1866	195 745	↓	MR-E, WM, WMode	Probable
Carter 2022	Pancreatic cancer	UKB	1747		–	MR-E, WM	Insufficient
Carter 2022	Kidney cancer	UKB	1741		–	MR-E, WM	Insufficient
Li 2022	Renal cell carcinoma	FinnGen and IARC	6190	182 017	–		Non-evaluable
Carter 2022	Bladder cancer	UKB	3326		–	MR-E, WM	Insufficient
Carter 2022	Cervical cancer	UKB	1973		–	MR-E, WM	Insufficient
Carter 2022	Ovarian cancer	UKB	1839		↓	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	7488	23 379	–		Non-evaluable
Ong 2019	Endometrial cancer	UKB	1938		–		Non-evaluable
Carter 2022	Uterine cancer	UKB	2281		–	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	3576		–		Non-evaluable
Carter 2022	Non-Hodgkin's lymphoma	UKB	2878		–	MR-E, WM	Insufficient
Carter 2022	Leukaemia	UKB	1825		–	MR-E, WM	Insufficient

(*Continued*)

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Table 6. (*Continued*)

Author	Outcome	Outcome population	Cases	Controls		Sensitivity analyses	Robustness
Carter 2022	Multiple myeloma	UKB	930		↑	MR-E, WM	Probable
Carter 2022	Multiple myeloma	FinnGen	598		–	MR-E, WM	Insufficient
Carter 2022	Melanoma	UKB	5691		–	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.

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	9889	62 657	–	MR-E, WM	Insufficient
Narayan 2022	Obesity class III	GIANT	2896	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 and other hyperalimentation	UKB	12 228	248 101	↑	MR-E, WM, WMode, MR-P	Probable
Nordestgaard 2015	Obesity (highest *v.* lowest allele score)	CGPS, CCHS and DIAGRAM	746	4586	–		Non-evaluable
Nordestgaard 2015	Metabolic syndrome	CGPS, CCHS and DIAGRAM	1400	4544	–		Non-evaluable
Kwok 2016	Body mass index	GIANT	*n* total = 322 154		–		Non-evaluable
Nordestgaard 2015	Body mass index	CGPS, CCHS and DIAGRAM	*n* total < 93 197		–		Non-evaluable
Narayan 2022	Waist circumference	GIANT	*n* total = 231 353		–		Insufficient
Nordestgaard 2015	Waist circumference	CGPS, CCHS and 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 and DIAGRAM	*n* total < 93 197		↑		Non-evaluable
Nordestgaard 2015	Height	CGPS, CCHS and DIAGRAM	*n* total < 93 197		–		Non-evaluable
Nordestgaard 2015	Plasma glucose	CGPS, CCHS and 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.

https://doi.org/10.1017/S0954422425100206 Published online by Cambridge University Press

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	1311	1783	–	MR-E, WM	Insufficient
Pu 2022	Rheumatoid arthritis	6 cohorts	5539	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	8456	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	4462	17 885	↑	MR-E, WM, WMode, O	Probable
Lee 2018	Knee and hip osteoarthritis	arcOGEN	7410	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	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	2155	67 259	↓	MR-E, WM, WMode	Probable
Shirai 2022	Gout	Biobank Japan	3053	4554	↓	MR-E, WM, WMode	Probable
Nicolopoulos 2020	Gout	UKB	3423	248 101	–	MR-E, WM, WMode, MR-P	Insufficient
Nicolopoulos 2020	Gout and other arthropathies	UKB	3970	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; eBMD, estimated mineral density; 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.

the Global Urate Genetics Consortium (GUGC) and the Biobank Japan cohort reported a 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/d increase in coffee 0·71, 95% CI 0·53–0·88) (Fig. 7), MR-PRESSO distortion tests, conducted in the UK Biobank study, showed that the association was likely to be due to three potentially pleiotropic outlying variants (rs1260326, rs1481012 and rs7800944)[61]. No association was found between coffee and serum uric acid[68].

Diseases of the digestive system and renal system

Null findings were reported for diverticular disease, gastro-esophageal reflux disease, Crohn's disease, and ulcerative colitis (Table 9)[69–71]. 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 multivariable MR (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 a decreased risk of chronic kidney disease, higher estimated glomerular filtration rate, lower levels of albuminuria and a 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[34,55,78,79] (Table 10). 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].

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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 and 11 clinics	9917	787 961	↓		Non-evaluable
Yuan 2022	Diverticular disease	UKB and FinnGen	23 640	497 533	–		Non-evaluable
Yuan 2022	Gastroesophageal reflux disease	UKB, and QSkin	71 522	261 079	–		Non-evaluable
Georgiou 2021	Crohn's disease	UKIBDGC and UK10K	12 194	25 042	–	MR-E, WM, O	Insufficient
Georgiou 2021	Ulcerative colitis	UKIBDGC and UK10K	12 366	25 042	–	MR-E, WM, O	Insufficient
Yuan 2022	Gallstone disease	UKB and FinnGen	22 195	472 022	–		Probable
Nordestgaard 2020	Symptomatic gallstone disease	CGPS and CCHS	7294		↓		Probable
Yuan 2022	Kidney stones	UKB and 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 and Health Study; UKIBDGC, UK Inflammatory Bowel Disease Genetics Consortium; CKDGen, Chronic Kidney Disease Genetics.

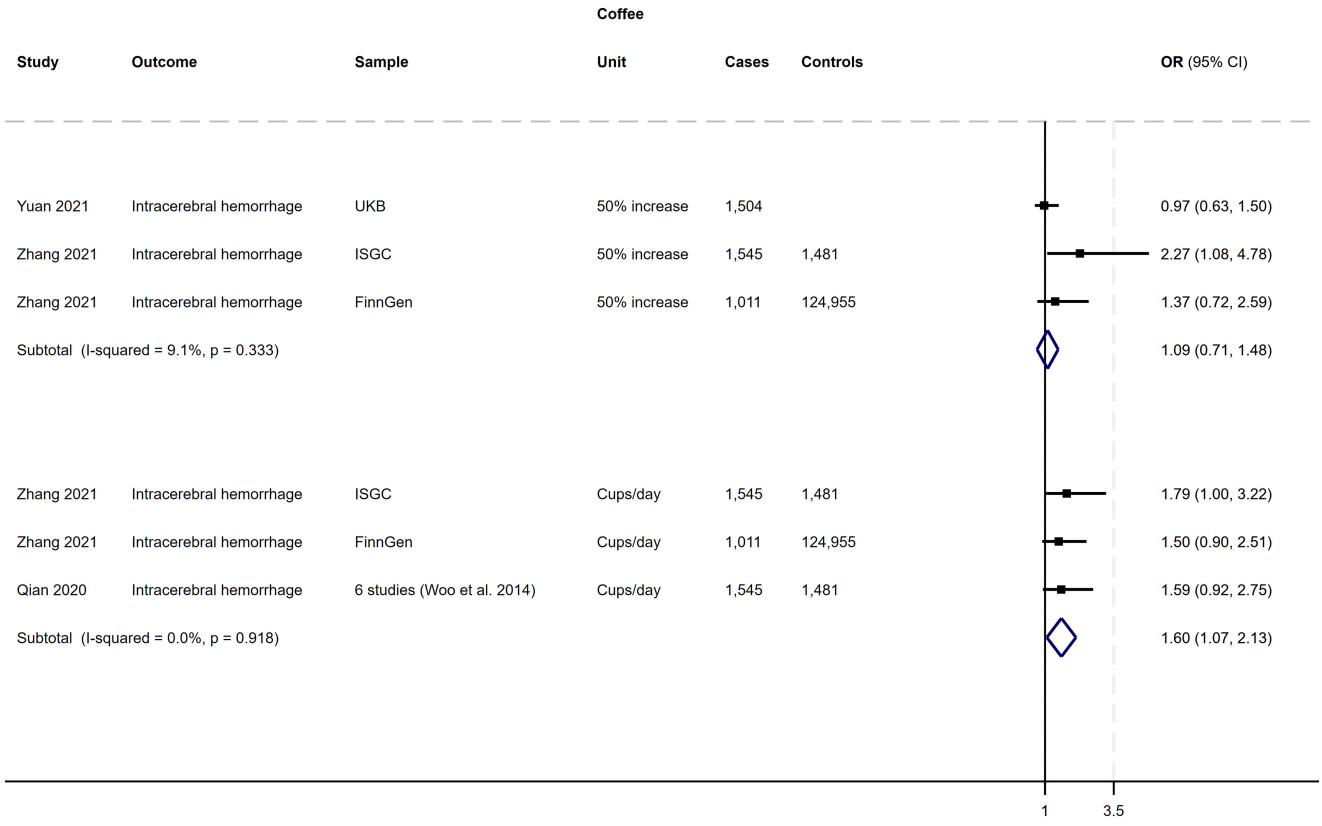

Fig. 3. Forest plot showing the meta-analysis of studies reporting on the effect of coffee consumption on intracerebral haemorrhage.[86]

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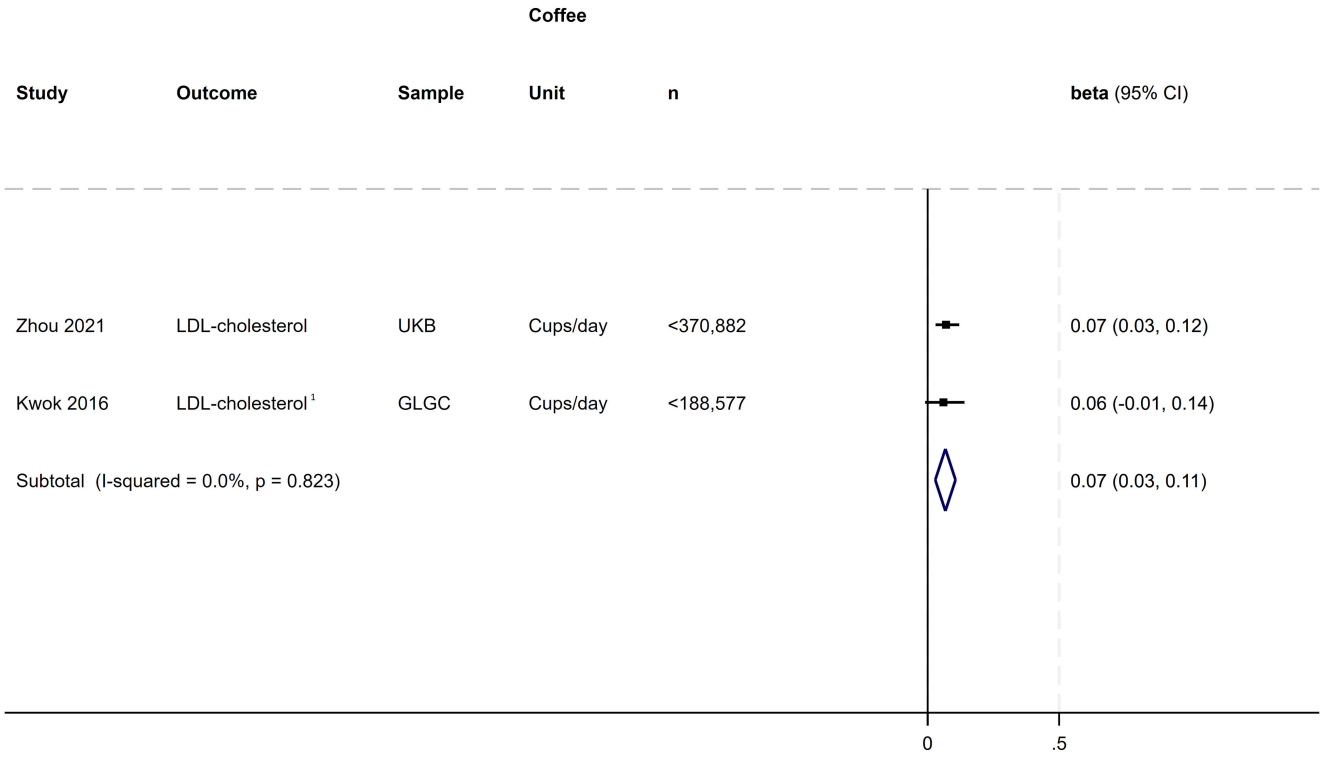

Fig. 4. Forest plot showing the meta-analysis of studies reporting on the effect of coffee consumption on LDL-cholesterol.
[1]Original estimate was described per SD change in LDL-cholesterol; converted to per 1 mM change in LDL-cholesterol based on 1 SD = 38·67 mg/dl = 1 mM.

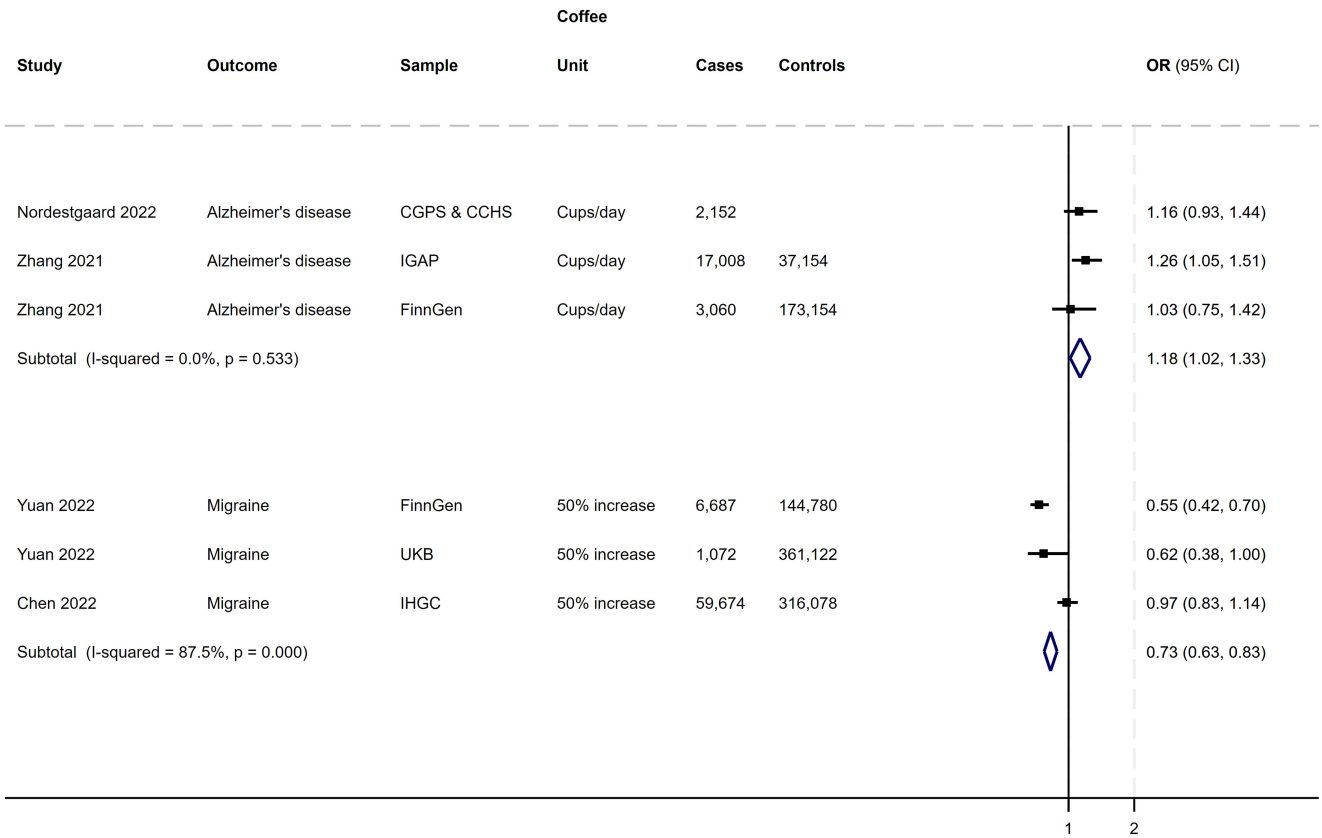

Fig. 5. Forest plot showing the meta-analysis of studies reporting on the effect of coffee consumption on Alzheimer's disease and migraines.

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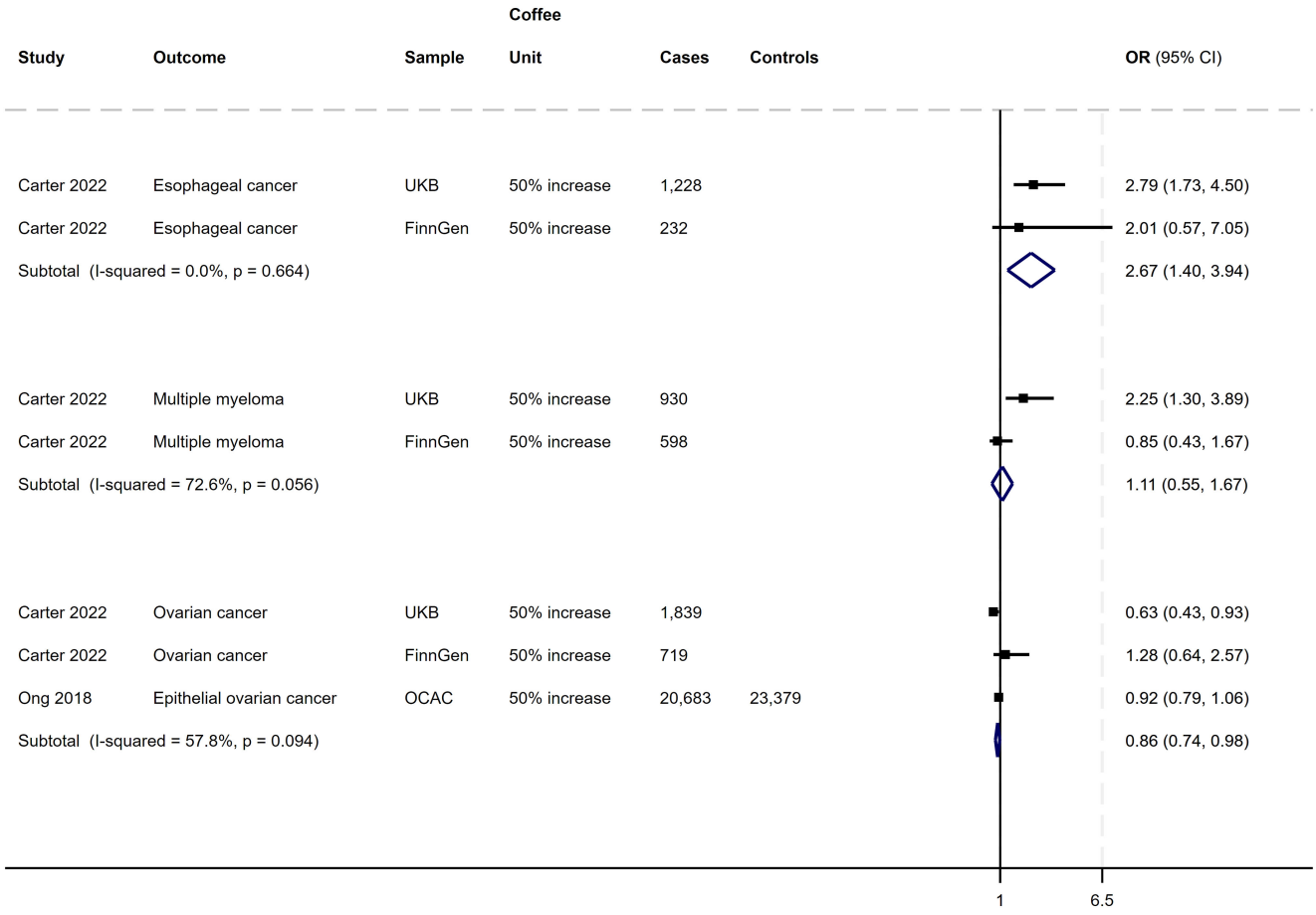

Fig. 6. Forest plot showing the meta-analysis of studies reporting on the effect of coffee consumption on oesophageal cancer, multiple myeloma and ovarian cancer.

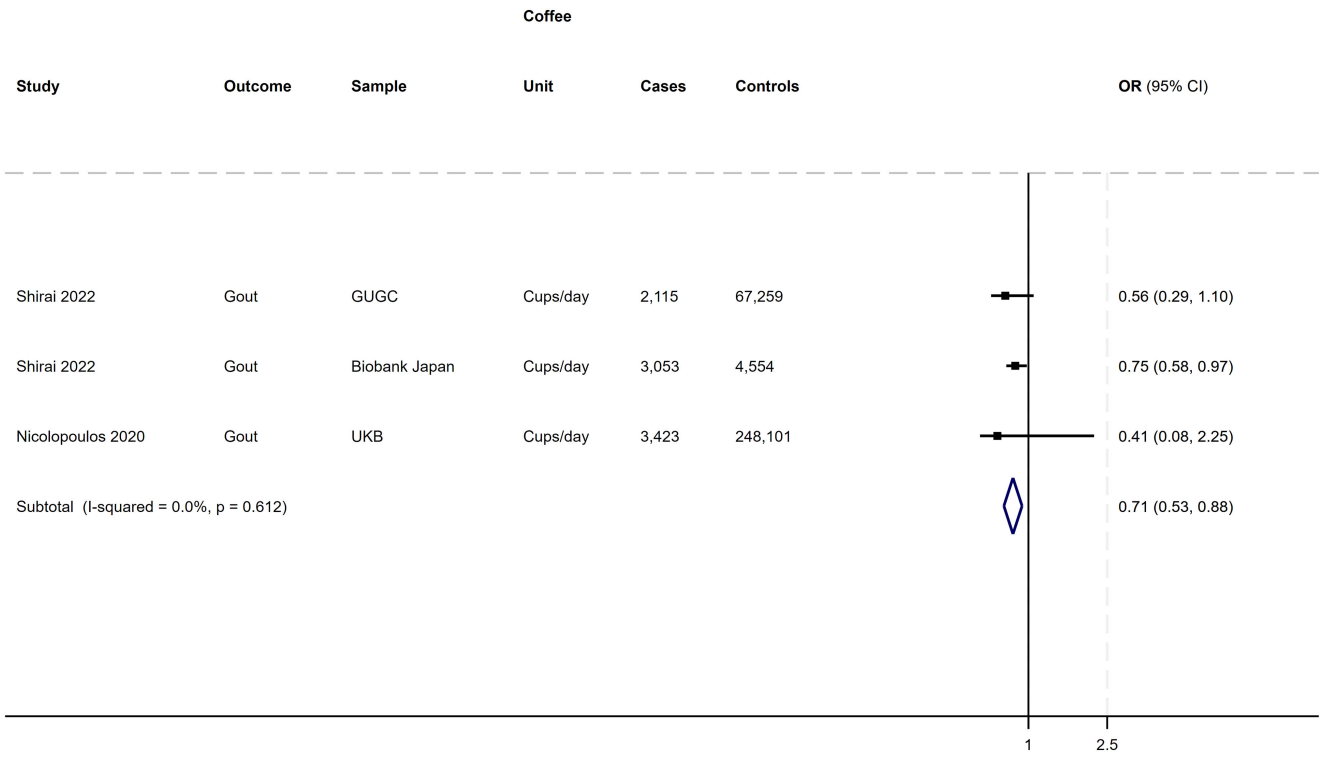

Fig. 7. Forest plot showing the meta-analysis of studies reporting on the effect of coffee consumption on gout.

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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	4081	11 474	–		Non-evaluable
Nordestgaard 2016	All-cause mortality	5 cohorts	12 656	112 509	–		Non-evaluable
Nordestgaard 2016	Cardiovascular disease mortality	5 cohorts	3671	104 766	–		Non-evaluable
Taylor 2017	Prostate cancer specific mortality	PRACTICAL	1754	12 256	–		Non-evaluable
Ong 2019	Overall cancer mortality	UKB	6998	270 342	–		Non-evaluable
Ong 2019	Cancer death in females	UKB	3836	143 465	–		Non-evaluable
Ong 2019	Cancer death in males	UKB	3165	143 465	–		Non-evaluable
Yuan 2021	Pregnancy loss	UKB	63 877	195 265			Non-evaluable
Nicolopoulos 2020	Menopausal and other postmenopausal disorders	UKB	8842	110 903	↓	MR-E, WM, WMode, MR-P	Probable
Nicolopoulos 2020	Postmenopausal bleeding	UKB	7494	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 and 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.

Discussion

Our review, including fifty-nine MR studies and 160 unique disease outcome associations, supports some possible benefits and harms with habitual coffee intake. Previous observational evidence (for umbrella reviews please see refs.[87,88]) 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[35,49,53,79,89], and for Alzheimer's disease/dementia, two studies[27,41] suggested potential increases in risk that warrant further research. This suggests that the phenotypic associations reported for coffee are likely to be 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 that summarised the MR evidence on coffee and caffeine consumption[90]. However, this review included only fifteen 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)[91].

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[10,92]. 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[93], the competitive antagonist binding of caffeine to the adenosine receptors may be a potential pathway underlying these associations[94,95]. 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

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disrupts adenosine homeostasis or alters the expression of adenosine receptors, which has been implicated in Alzheimer's disease[96]. 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 permeability[97]. Interestingly, a recently published MR study found an association between coffee and delayed age-of-onset of Parkinson's disease[98], 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 oesophageal cancer risk may reflect the association between hot beverage consumption and oesophageal cancer. A meta-analysis of studies on tea drinking found that participants who drank tea at higher temperatures had a higher risk of oesophageal squamous cell carcinomas[99]. It is possible that the consumption of hot beverages causes damage to the oesophageal cell mucosa, which may increase cell turnover rates and the risk of cancerous mutations[100]. This explanation is supported by a recent MR study, which found that the association between coffee and oesophageal cancer was attenuated in multivariable models additionally adjusting for hot beverage consumption[101].

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 an increased risk for multiple myeloma. More recent evidence provides further support for the association with multiple myeloma, including replication in an independent outcome cohort[102]. 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[103]. 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[104,105]. Similarly, recent literature suggests that coffee may associate with increased risks of endometrioid ovarian cancer, opposing previous studies that supported protective associations[106]. 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[107], MR studies in this review found no evidence of 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[108]. 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 *v.* 9–14 SNPs) have reported probable associations between coffee and increased risk of coronary artery calcification, myocardial infarction, atrial fibrillation and heart failure[109–111], 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[111]. Circumferential strain contributes to arterial wall thickening[112], which aligns with the theory that competitive adenosine receptor binding stimulates acute increases in blood pressure and arterial thickness, which may induce ventricular modelling and cardiac strain over time[113].

Many of the instruments used to reflect habitual coffee intake 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 and 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 tools established for MR studies, so our templates and tools had to be adapted from general tools for observational studies or previous publications. In addition, the GRADE system for assessing certainty of evidence is known to be a very 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[114]. 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[115]. All included studies implemented linear MR analyses, and uncertainties exist in the ability to use MR in evaluating nonlinear effects[116]. 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[117]. 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[118]. Similarly, a reporting standard for

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MR studies has only been recently established, so earlier studies lacked standardisation of methodology[91]. 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 from potential associations with a decreased risk of migraines, hepatocellular carcinoma, kidney disease, gallstone disease and ovarian cancer. We also did not observe any strong evidence of harm, although more research is needed to assess possible effects on oesophageal 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/d 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 should also aim to understand the underlying mechanisms of any causal associations and expand upon knowledge in non-European cohorts and cross-ethnic studies.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0954422425100206

Data availability statement. No new data were created or analysed in this study. All the work was developed using published data. Data sharing is not applicable to this article.

Acknowledgements. None.

Authorship. K.P. and N.A.K. conducted the literature search, study screening, data extraction and quality assessment. K.P. and A.Z. prepared the final data tables. K.P. conducted data analysis and wrote the paper. N.A.K. drafted the review protocol and the data extraction and quality assessment tool, with comments from K.P., A.M., A.Z. and E.H. K.P., A.M., A.Z. and E.H. interpreted results and revised the paper. All authors read and approved the final version of the manuscript for submission.

Financial support. This research is supported by an Australian Government Research Training Program (RTP) Scholarship (K.P. and N.A.K.), National Health and Medical Research Council Australia Leadership Investigator Award, GNT2025349 (E.H.), National Health and Medical Research Council Australia Project Grant, GNT1123603 (E.H.) and the Medical Research Future Fund, grant MRF2007431 (E.H.).

Declaration of Interests. The authors do not have any conflicts of interest to declare.

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