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ORIGINAL ARTICLE

The correlation between the intake of coffee and the prevalence of asthma: a dose response meta-analysis and Mendelian randomization study

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Popular scientific summary

- Moderate coffee consumption (around 2-3 cups per day) may be associated with a lower risk of asthma.
- This study provides further evidence for a potential link between coffee and asthma risk.
- It's crucial to consult with a healthcare professional before making any significant dietary changes.

Abstract

***Objectives*:** Asthma contributes to a significant global disease burden. Coffee has been linked to a reduced risk of asthma in several epidemiological studies. However, conflicting findings create confusion regarding the role of coffee in asthma management. We executed a consolidated analysis in conjunction with a Mendelian randomization (MR) study with the aim of scrutinizing the potential correlation between coffee intake and the susceptibility to asthma development. Furthermore, we analyzed the dose-response relationship between coffee intake and the onset of asthma.
***Methods*:** In this meta-analysis, we searched online to identify studies involving coffee consumption on the risk of asthma. The primary outcome was the risk of asthma development. We used RevMan and R language to calculate the pooled results and create plots. A meta-package dosresmeta was used for dose-response analysis. In the MR analyses, we obtained data from public databases. MR studies were conducted using genome-wide association data for coffee intake. Independent genetic instrumental variants strongly associated with each exposure (P < 5*10^-8) were considered as instruments. The inverse variance-weighted method was used in the primary analysis. Sensitivity analyses were also conducted.
***Results*:** We ultimately incorporated four publications into our meta-analysis. Our study encompassed 671,417 participants and elucidated a negative correlation between the intake of ground coffee and the incidence of asthma (pooled odds ratios [OR] = 0.86, 95% confidence interval [CI] = 0.82–0.91, I^2 = 66.2%). A potential nonlinear relationship between coffee and asthma was discovered. A J-shaped dose-response association was found between ground coffee consumption and the risk of asthma development, with the lowest risk of asthma occurring at approximately 2–3 cups per day. In the MR study, the findings suggest a decrease in asthma risk associated with ground coffee consumption (OR = 0.982, 95% CI 0.972–0.992; P = 0.000). Sensitivity analyses revealed that the causality estimations were robust.
***Conclusion*:** A comprehensive analysis of epidemiological studies and an MR analysis indicate a correlation between coffee intake and a decreased risk of asthma. Furthermore, dose-response analysis of observational studies reveals that consuming an optimal amount of 2–3 cups of coffee every day is associated with the lowest risk of asthma, as opposed to abstaining from coffee or consuming more than four cups daily.

Keywords: *coffee*; *asthma*; *meta-analysis*; *systematic review*; *dose-response*; *causal relationship*; *Mendelian randomization study*

To access the supplementary material, please visit the article landing page

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Chronic respiratory diseases, such as asthma, contribute to a significant global disease burden. The majority of these conditions have an inflammatory component that remains uncontrolled (1). Coffee, one of the most widely welcomed drinks worldwide (2), has been linked to a decreased risk of asthma in several epidemiological publications (3, 4). Additionally, preclinical studies have demonstrated anti-inflammatory effects associated with caffeine consumption (5). However, there are reports suggesting that coffee consumption may lead to decreased lung function (6). These conflicting findings create confusion regarding the role of coffee in asthma management. Mendelian Randomization (MR) has emerged in recent years as a novel methodological approach for investigating causal relationships (7). MR leverages genetic data as instrumental variables to evaluate the causal associations between modifiable risk factors and health outcomes. The primary advantage of MR lies in its capacity to furnish causal evidence while mitigating common confounders endemic to observational studies, including reverse causation and confounding variables. Consequently, we conducted a pooled analysis and MR study to investigate the relationship between coffee intake and the risk of developing asthma. Furthermore, we analyzed the dose-response relationship between coffee consumption and the onset of asthma. The results from this analysis will aid in drawing a more comprehensive conclusion. Therefore, the primary objective of this analysis is to determine the causal effect of coffee consumption on the development of asthma.

Methods

Meta-analysis

Registration of the protocol

PROSPERO platform was used for protocol registration (the International Prospective Register of Systematic Reviews, https://www.crd.york.ac.uk/PROSPERO/). The protocol ID is CRD42023428362. This meta-analysis was reported following the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (8).

Literature search

We performed a comprehensive search online for articles published up until May 2023, utilizing databases such as PubMed (www.ncbi.nlm.nih.gov/pubmed) and the Cochrane Central Register of Controlled Trials (CENTRAL) (onlinelibrary.wiley.com/Cochrane library/). Our search strategy included the terms '(coffee[Title/Abstract]) AND (asthma [Title/Abstract])'. Additionally, we conducted manual searches of the reference lists of pertinent reviews to ensure a thorough examination of the available literature.

Criteria of inclusion and exclusion

Eligible studies were identified following the listed criteria:
1. Observational studies with at least two dosage groups.
2. Outcome associated with the development of asthma.
3. Studies should provide risk of relative risks (RRs), odds ratios (ORs), hazard ratios (HRs) and confidence intervals (CIs) as outcomes. Exclusion criteria included: 1) Not clinical research. 2) Letters, case reports, or reviews. Two authors assessed the abstracts and titles to assess the eligibility of every single eligible study. If there were discrepancies between different reviewers, a third party author would be consulted for a consensus.

Data extraction

We gathered information from each qualifying research, which included the name of author, publication time, location, study methodology, sample sizes, age, gender, outcomes, and covariates. We evaluated the quality of individual entries based on the Newcastle-Ottawa Scale (NOS) (9, 10) for prospective cohorts. The characteristics of the eligible publications and their populations can be found in Table 1.

Statistical analysis

The Review Manager (V5.4; Cochrane Collaboration, Oxford, UK) was utilized in assessing the risk of bias for the included publications, data analyses, and creating plots. The Chi^2 and I^2 were employed to assess heterogeneity. If the *P-value* was greater than 0.1 or I^2 was less than 40%, a fixed-effect model analysis was conducted. In cases of high heterogeneity, a random-effect meta-analysis would be applied. In the present analyses, the coffee consumption group was compared to the control. Odds ratios were utilized for the analysis of dichotomous variables. The open-source edition of R software (Version 4.2.3, Vienna, Austria) was employed for dose-response analysis and plotting. A meta-package called 'dosresmeta' was used (11). Both linear and non-linear estimations were performed simultaneously. If the *P-value* for linear estimation was greater than 0.05, demonstrating no significant linear relationship, we continued with non-linear estimation to evaluate the dose-response relationship between coffee consumption and the development of asthma.

MR study

Study design

We performed an MR analysis using publicly accessible data from the open genome-wide association study (GWAS) program to investigate the causal links between coffee intake and asthma risk. In this study, we made the following crucial assumptions: Instrumental variables were strongly correlated with coffee consumption and not associated with any confounders of coffee intake and asthma development. The instrumental variables

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Table 1. Characteristics of the eligible trials and their participants

Author (year)	Region	Design	Sample size		Age		Gender		Outcomes	Adjustment
			E	C	E	C	M	F		
Lin 2022 (3)	UK	PC	331,487	93,503	55.52±8.21	NA	19,5568	22,9157	Incidence of asthma	Age, gender, race, smoking status, BMI, education level, Townsend deprivation index.
Wee 2020 (4)	Korea	CC	3,146*	158,902#	55.9±8.7*	53.2±8.4#	55,559*	106,489#	Incidence of asthma	Age, sex, BMI category, smoking status, alcohol consumption, and nutritional intake coffee, green tea, and soda consumption
Schwartz 1992 (18)	US	CS	9,577	2,518	NA	NA	NA	NA	Incidence of asthma	Age, gender, smoking and race.
Pagano 1988 (17)	Italy	CS	56,233	16,051	NA	NA	34,787	37,497	Incidence of asthma	Age, gender, smoking, geographical area, education and alcohol consumption

RC, Retrospective cohort; PC, Prospective Cohort; CC, Case Control; CS, Cross Sectional.
*Express the case group, # Express the control group in case control study.

influenced the outcome solely through exposure (12). All data utilized in this study were acquired from public sources, thus avoiding any ethical conflicts. Our findings are reported following the guidelines of Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization (STROBE-MR) (13).

GWAS summary data for coffee intake and genetic instruments selection

Data pertaining to the correlation between single nucleotide polymorphisms (SNPs) and coffee consumption were procured from the accessible GWAS website (14) (https://gwas. mrcieu.ac.uk/) (Table 2). In line with the guidelines of the TwoSampleMR package (15, 16), we established the following criteria for selecting appropriate genetic instruments: SNPs related to exposure must meet a significance threshold ($P < 5*10$^-8). To prevent linkage disequilibrium (LD), we carried out a setup with $R^2 < 0.001$ and a 10,000 kb clumping window. We excluded SNPs that demonstrated a significant association with heart failure ($P < 5*10$^-8). We adopted SNPs with F value greater than ten, indicating that the genetic variants had strongly estimated effects. Important information such as the effect allele, other allele, β, se, and *P-value*, was recorded for subsequent procedure.

GWAS summary data for asthma

Genetic factors contributing to the development of asthma were identified through summary-level GWAS results from the UK Biobank, which are also publicly retrievable in the open GWAS database (Table 2).

MR analysis

In this research, we adopted five unique methods to examine the causality of coffee consumption on asthma risk. These methods comprised MR-Egger regression, random-effects inverse variance weighted (IVW), simple mode, weighted median, and weighted mode strategies. The IVW method was used as the primary analysis method to assess the connections between coffee intake and asthma development, as it is the most frequent selection in MR studies and provides the most accurate results when selected SNPs are deemed valid instruments. The remaining four methods were used as supplementary techniques in the MR analysis.

Sensitivity analyses

The conducted sensitivity analyses encompassed examinations for genetic pleiotropy, assessments of heterogeneity, funnel plot evaluation, and the application of a leave-one-out analytical approach. The Cochran's Q statistic was used for estimating the heterogeneity of the IVW method. The *P-value* was utilized to test the heterogeneity, with a *P-value* of less than 0.05 showing heterogeneity. We used the intercept from MR-Egger regression method to assess horizontal pleiotropy. A leave-one-out analysis was conducted by removing every single SNP and testing the remaining SNPs

Table 2. Characteristics of the data used in the MR study

Trait	ID on open GWAS project	Data source	Year	Population	Gender	n case	n control
Exposures							
Coffee Consumption	ukb-d-1508_3	UK Biobank	2018	European	Males and Females	64,962	218,487
Outcomes							
Asthma	ukb-b-20208	UK Biobank	2018	European	Males and Females	1,877	461,133

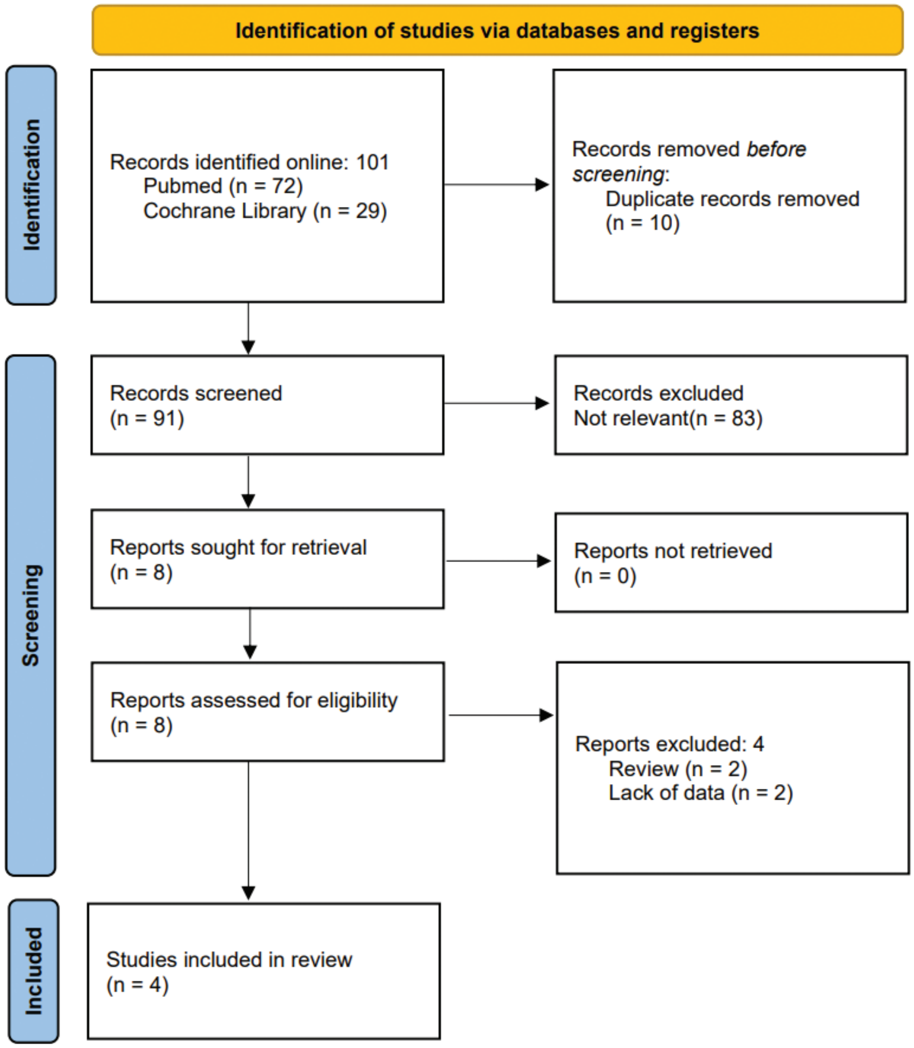

Fig. 1. Study flow diagram for meta-analysis of coffee intake and incident of asthma.

to discover outliers. Lastly, we employed a funnel plot for an asymmetry of visual inspection, which may indicate violations of the MR assumption due to pleiotropy.

Statistical analysis and plot

Causality estimates were presented as ORs and 95% CIs. A P-value of less than 0.05 was considered statistically significant. Plots were generated using the TwoSampleMR package (https://mrcieu.github.io/TwoSampleMR/) and ForestPloter package (https:// github.com/adayim/forestploter)in R language.

Results

Meta-analysis

Study description

Utilizing the aforementioned search methodology, we identified a total of 101 records, with duplicates removed. Following a thorough examination of the abstracts and titles, we obtained the full texts for eight records, ultimately incorporating four of them into our analysis. Figure 1 displays the specifics of the excluded records. Overall, our study encompassed 671,417 participants.

Risk of bias

In the selected publications, the risk of bias was assessed based on the NOS (Table 3). The observational studies demonstrated a median level of risk of bias. Notably, two recent articles exhibited higher quality and provided comprehensive data for analysis. However, the other two articles were published quite some time ago, resulting in less complete data being available.

Meta-analysis

The present analysis indicated an inverse association between the consumption of ground coffee and the

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Table 3. Risk of bias of the included observational studies

	Selection				Comparability	Outcome		
	1)Representativeness of the Exposed Cohort	2)Selection of the Non-Exposed Cohort	3)Ascertainment of Exposure	4)Demonstration That Outcome of Interest Was Not Present at Start of Study	1)Comparability of Cohorts on the Basis of the Design or Analysis	1)Assessment of Outcome	2)Was Follow-Up Long Enough for Outcomes to Occur	3)Adequacy of Follow Up of Cohorts
Lin 2022	I	I	I	I	I	I	I	I
Wee 2020	I	I	I	I	I	I	I	I
Schwartz 1992	I	I	I	I		I		
Pagano 1988	I	I	I	I		I		

occurrence of asthma (3, 4, 17, 18) (OR = 0.86, 95% CI: 0.82–0.91, I^2 = 66.2%, Fig. 2).

Dose-response analysis

We discovered a non-linear relationship between coffee consumption and asthma. We conducted both linear and nonlinear estimations, with the linear estimation resulting in Chi^2 = 1.8811 (df = 1) and a *P*-value of 0.17, indicating no significant linear relationship. Concurrently, the Wald test for nonlinearity yielded a *P*-value of < 0.01. Thus, the null hypothesis was rejected, and a potential nonlinear relationship between coffee consumption and asthma development was proposed. A J-shaped dose-response association was observed between ground coffee intake and

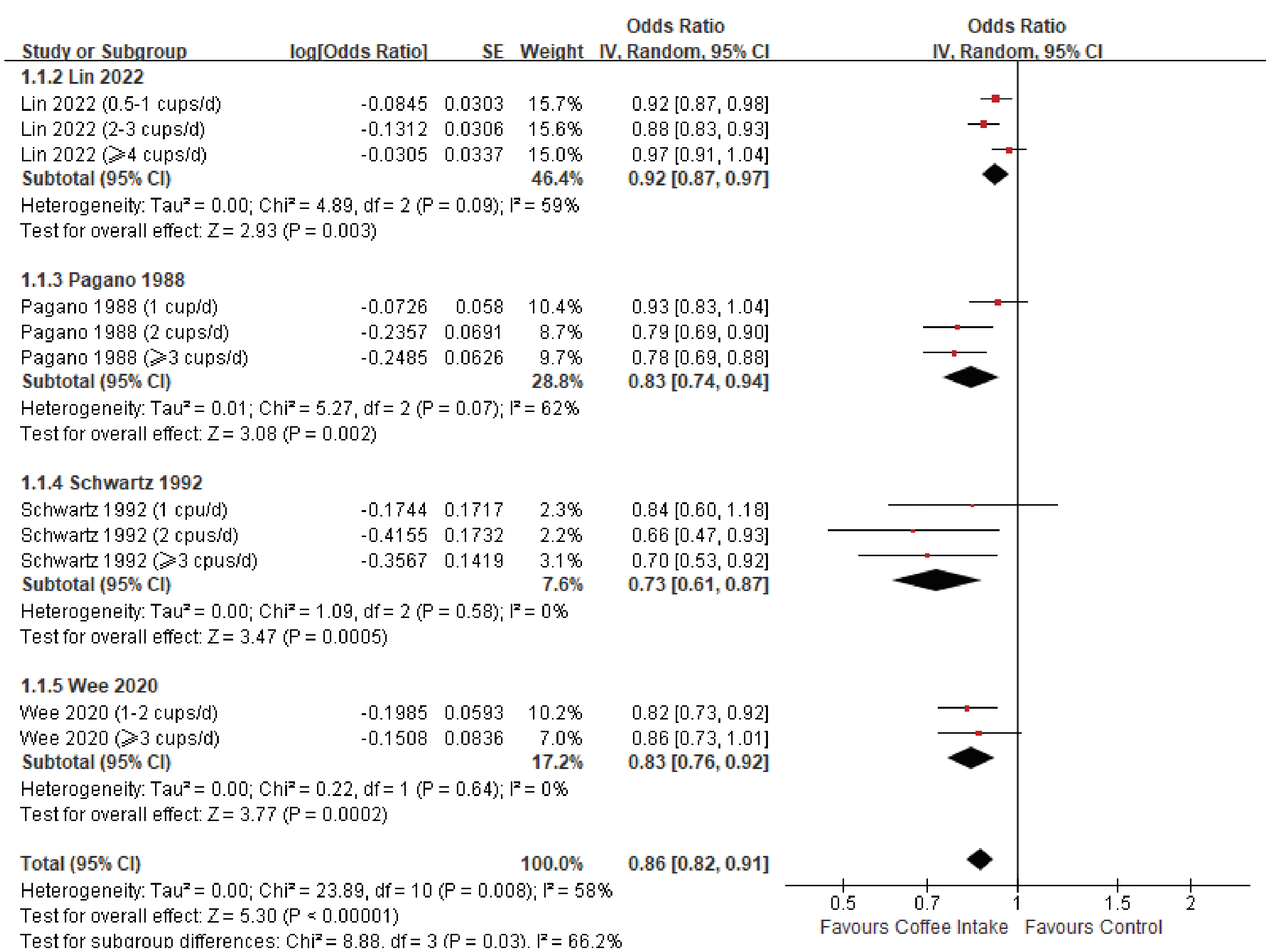

Fig. 2. Forest plot of meta-analysis for the association of coffee intake and incident of asthma.

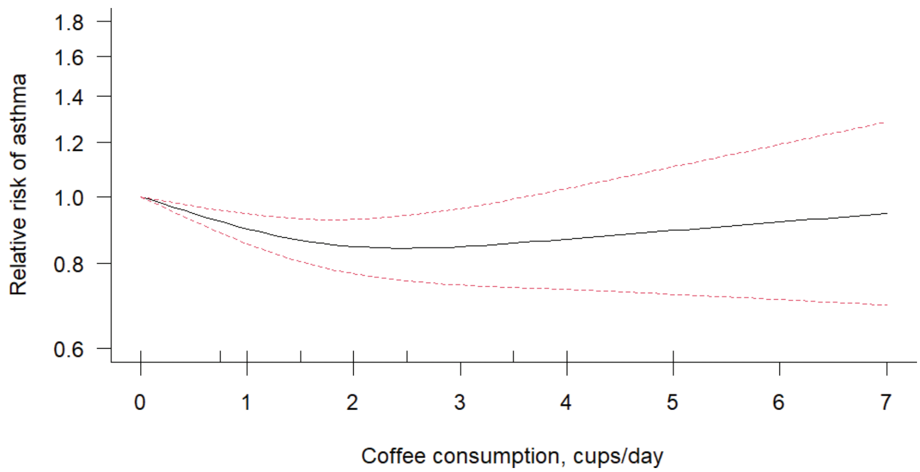

Fig. 3. Dose-response meta-analysis of coffee consumption on risk of asthma.

the development of asthma (Fig. 3), with the lowest risk of asthma occurring at approximately 2–3 cups per day.

MR study

Characteristics of the instruments

After the completion of the instrument selection process, we identified a total of 22 SNPs for predicting ground coffee consumption, and 14 index SNPs were used for predicting asthma. The F statistic pertaining to the genetic instrumental variables utilized in this research surpassed a threshold of 10. This observation signifies the absence of any weak instrumental variables employed within the confines of this study.

MR analysis

The MR analysis provides estimations utilizing various methodologies to determine the causal effects of the consumption of ground coffee on the risk of asthma, as illustrated in Fig. 4. The findings suggest a notable decrease in asthma risk associated with coffee intake (OR = 0.982, 95% CI 0.972–0.992; P = 0.000). Scatter plots representing the MR analyses can be observed in Fig. 5. The causality of coffee consumption on asthma risk per allele is depicted in Fig. 6.

Heterogeneity and sensitivity tests

To evaluate the dependability of our results, we conducted analyses, which encompassed leave-one-out analysis, the MR-Egger intercept test, Cochran's Q test, and a funnel plot. The outcomes of the Cochran's Q and MR-Egger intercept test can be viewed in Table 4. There was no indication of pleiotropy between the instruments and outcomes. P-values of the MR-Egger intercept tests were above 0.05. Moreover, no heterogeneity was identified in the Cochran's Q test. The leave-one-out analysis revealed that the causality of coffee intake and the development of asthma were not impacted by any independent SNP, as illustrated in Supplementary material Supplementary Fig. S1. The funnel plots for the analysis displayed an even distribution of data points surrounding the funnel, indicating the lack of significant asymmetry (Supplementary Fig. S2).

Discussion

In this meta-analysis, using the previously mentioned search methodology, we identified a total of 101 records after removing duplicates. After conducting a thorough examination of the abstracts and titles, we obtained the complete PDFs for eight records, ultimately including four of them in our analysis. Our study encompassed

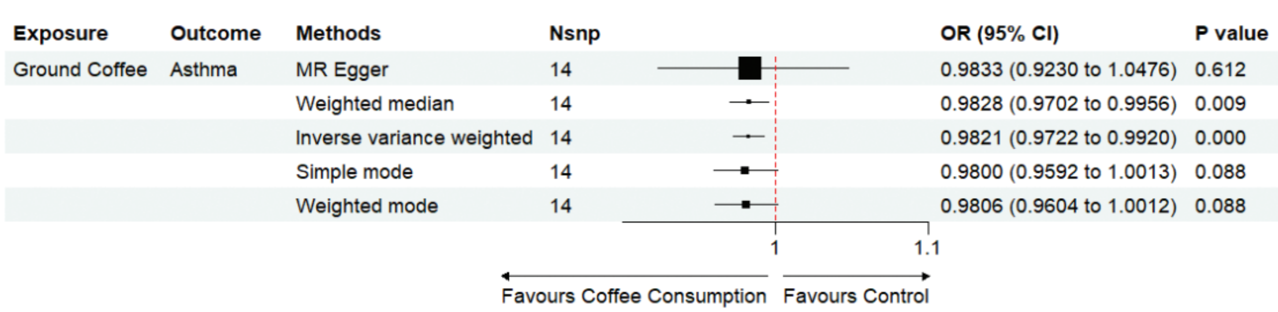

Fig. 4. MR analysis indicated the causal effects of coffee consumption on the risk of asthma.

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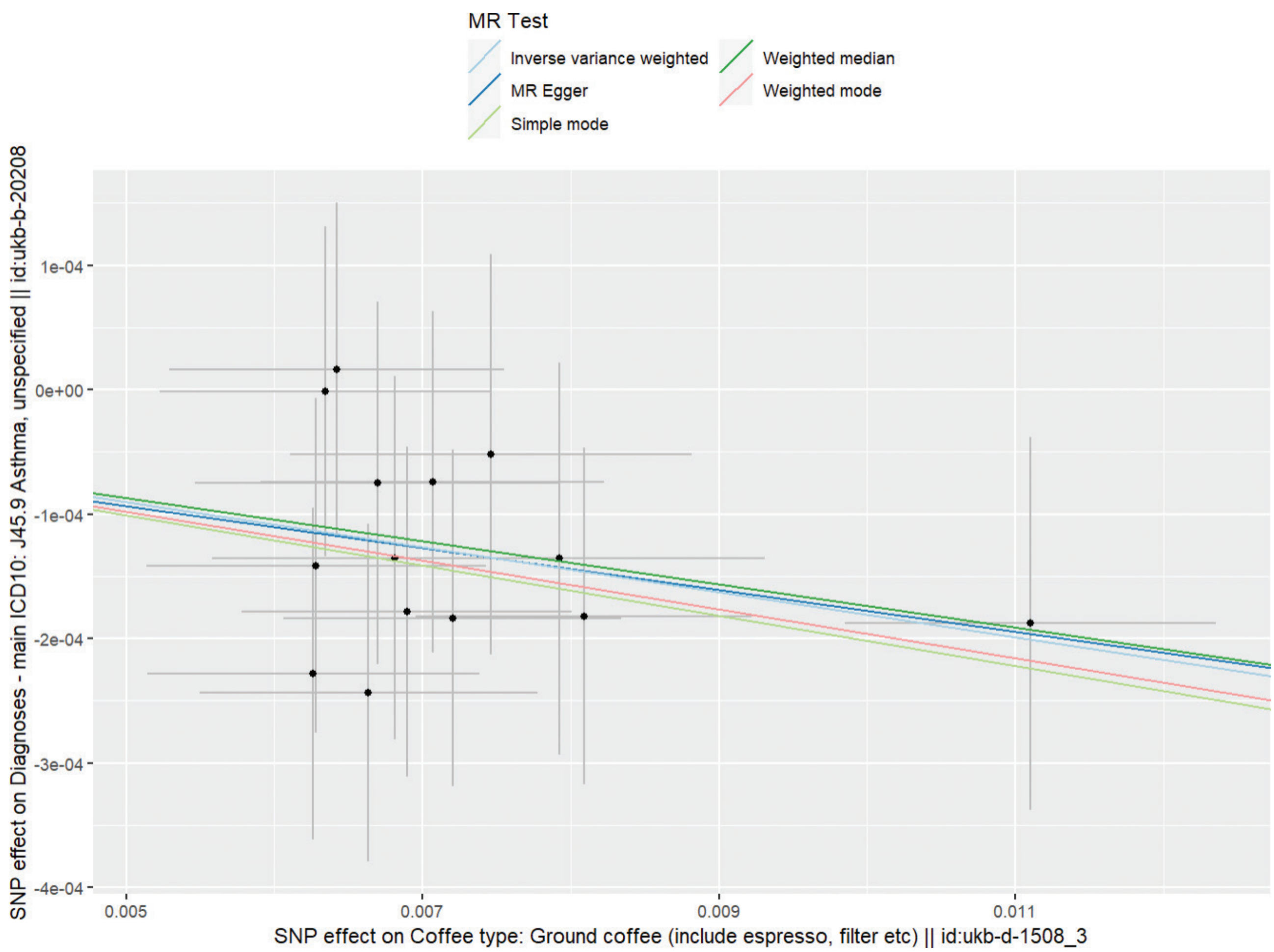
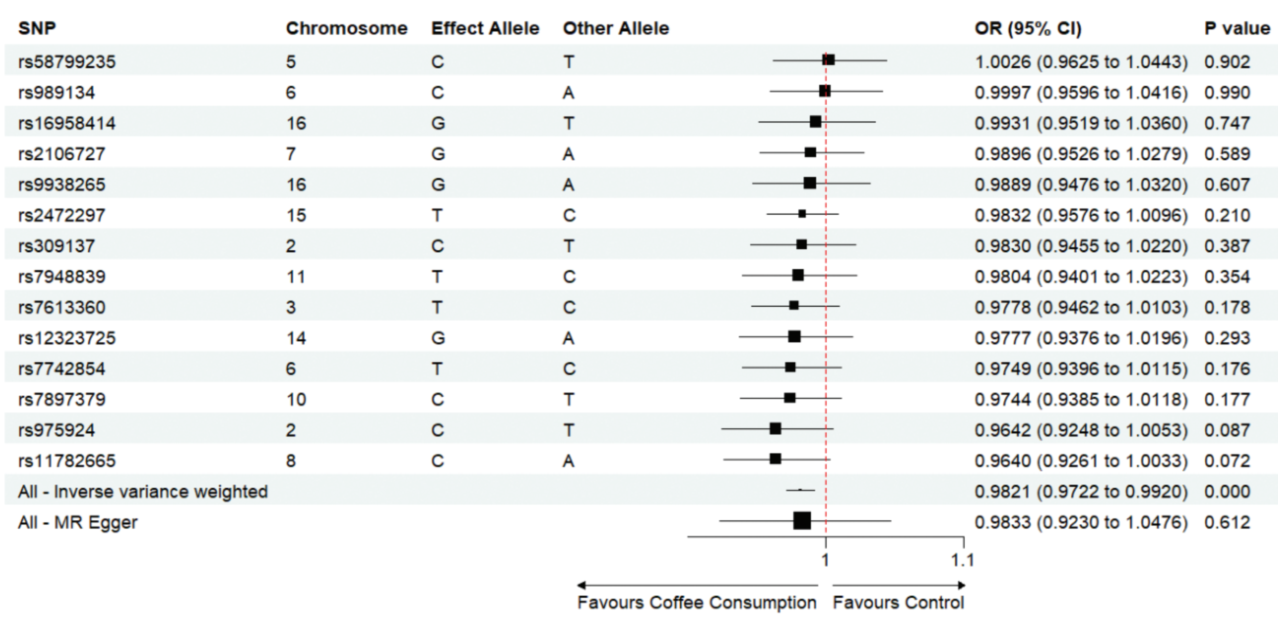


Fig. 5. Scatter plot for MR analysis of coffee consumption on risk of asthma.



SNP	Chromosome	Effect Allele	Other Allele	OR (95% CI)	P value
rs58799235	5	C	T	1.0026 (0.9625 to 1.0443)	0.902
rs989134	6	C	A	0.9997 (0.9596 to 1.0416)	0.990
rs16958414	16	G	T	0.9931 (0.9519 to 1.0360)	0.747
rs2106727	7	G	A	0.9896 (0.9526 to 1.0279)	0.589
rs9938265	16	G	A	0.9889 (0.9476 to 1.0320)	0.607
rs2472297	15	T	C	0.9832 (0.9576 to 1.0096)	0.210
rs309137	2	C	T	0.9830 (0.9455 to 1.0220)	0.387
rs7948839	11	T	C	0.9804 (0.9401 to 1.0223)	0.354
rs7613360	3	T	C	0.9778 (0.9462 to 1.0103)	0.178
rs12323725	14	G	A	0.9777 (0.9376 to 1.0196)	0.293
rs7742854	6	T	C	0.9749 (0.9396 to 1.0115)	0.176
rs7897379	10	C	T	0.9744 (0.9385 to 1.0118)	0.177
rs975924	2	C	T	0.9642 (0.9248 to 1.0053)	0.087
rs11782665	8	C	A	0.9640 (0.9261 to 1.0033)	0.072
All - Inverse variance weighted				0.9821 (0.9722 to 0.9920)	0.000
All - MR Egger				0.9833 (0.9230 to 1.0476)	0.612

Fig. 6. Causal effects of coffee consumption on the risk of asthma per allele.

Table 4. Heterogeneity and pleiotropy test of MR analysis of coffee intake on asthma incidence.

Exposure	Outcome	Method	Heterogeneity Test			Pleiotropy Test		
			Q	Q_df	P value	Egger Intercept	se	P value
Coffee Consumption	Asthma	IVW	4.25	13	0.99	-0.000009	0.00023	0.97

671,417 participants. The quality of the included literature varied, with some being of high quality while others had relatively incomplete information. This analysis demonstrated an inverse trend between the consumption of ground coffee and asthma development (OR = 0.86, 95% CI 0.82–0.91, I^2 = 66.2%). In the dose-response analysis, we discovered a nonlinear relationship between coffee consumption and asthma. A J-shaped dose-response trend was found between ground coffee and the risk of asthma development, with the lowest risk of asthma occurring at approximately 2–3 cups per day.

The MR analysis employs a diverse range of methods to ascertain the causality between coffee consumption and asthma risk. The results indicate a notable reduction in asthma risk in conjunction with coffee consumption (OR = 0.982, 95% CI 0.972–0.992; *P* = 0.000). Furthermore, no horizontal pleiotropy was discovered between the instruments and outcomes. Additionally, the Cochran's Q test analysis did not reveal any heterogeneity.

The available literature on the effects of coffee and caffeine in asthma management is limited. Nevertheless, several factors may contribute to coffee's potential in reducing asthma risk.

Firstly, caffeine acts as a bronchodilator (19), reducing respiratory muscle fatigue (1).Although the exact mechanism behind caffeine's bronchodilator effect is not fully understood, it is believed to be associated with its ability to inhibit the enzyme phosphodiesterase. This enzyme is responsible for breaking down cyclic adenosine monophosphate (cAMP), a molecule crucial in regulating airway muscles. Caffeine also provides a certain level of lung protection, possibly due to its ability to reduce pulmonary inflammation (5).This effect might be attributed to caffeine's ability to block phosphodiesterase's action, an enzyme involved in airway constriction. Caffeine, as well as its analogs, specifically designed to enhance selectivity and potency to selected biological targets, has played a critical role in functioning as phosphodiesterases, adenosine receptors, and calcium channels. All of these pathways played a role in bronchial dilation (20). Research has shown that Coffea extracts can inhibit neutrophil migration and decrease pro-inflammatory cytokines concentration of IL-6 and TNF-α (21). Nebulized caffeine consistently enhanced outcomes in an animal model of airway hyperresponsiveness. Experimental findings demonstrated a statistically significant reduction in maximal airway resistance in mice administered with aerosolized caffeine (22). An additional study observed that coffee consumption effectively suppressed the T helper 2-mediated specific antibody response. This suppression significantly mitigated airway hyperresponsiveness and systemic allergic reactions induced by ovalbumin food allergens (23). Moreover, coffee exposure may be associated with alterations in the gut microbiome (24). Despite these findings, it is crucial to emphasize that caffeine is not regarded as a primary treatment for asthma.

The constraints and potential weaknesses inherent in the present study ought to be delineated: Firstly, in terms of the meta-analysis for epidemiology, the quality and quantity of the original studies included in our research are not extremely ideal. Consequently, we were unable to conduct subgroup analysis, sensitivity analysis, and evaluation of publication bias. In the future, prospective cohort studies may provide stronger evidence. Secondly, our findings from the MR analyses were based on data from GWASs conducted exclusively on European people, which lacks ancestral and cultural diversity. As a result, it remains unclear whether these results can be used in other ethnics. Thirdly, based on previous experience, for coffee-related MR studies, two-sample MR studies may not be sufficient to fully reflect the U-shaped or J-shaped dose-response trends. More comprehensive data might be needed to complete linear or non-linear MR studies, which could potentially yield more reliable results. Lastly, asthma presents as a heterogeneous condition with distinct subtypes. The pathogenesis and progression of each subtype may vary, and we have not yet explored the potential association between coffee consumption and the various asthma subtypes.

Conclusion

A comprehensive meta-analysis of epidemiological studies and an MR analysis indicate a correlation between coffee intake and a decreased risk of asthma. Furthermore, dose-response analysis of observational studies reveals that consuming an optimal amount of 2–3 cups/d of coffee is associated with the lowest development risk of asthma, as opposed to abstaining from coffee or consuming more than four cups daily.

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Conflict of interest and funding

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