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REVIEW - SYSTEMATIC REVIEW - META-ANALYSIS

Caffeinated and decaffeinated coffee consumption and risk of all-cause mortality: a dose–response meta-analysis of cohort studies

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Abstract

Background: Previous meta-analysis showed an inverse association between coffee consumption and all-cause mortality. However, the relationship between caffeinated and decaffeinated coffee consumption and all-cause mortality is inconsistent. We aimed to identify and review the published evidence updating the association between coffee consumption and all-cause mortality and, furthermore, to investigate the association of caffeinated and decaffeinated coffee consumption and all-cause mortality.
Methods: We systematically searched PubMed and Web of Science for studies published up to 9 November 2017. Cohort studies in which authors reported relative risks (RRs) of all-cause mortality for at least three levels of coffee consumption were eligible. Random-effects models were used to estimate the pooled RR of all-cause mortality with coffee consumption. Restricted cubic splines were used to model the dose–response association.
Results: We included 21 cohort study articles (10 103 115 study participants and 240 303 deaths). We found a nonlinear association between coffee consumption and all-cause mortality ($P_{\text{nonlinearity}} < 0.001$). Compared with no or rare coffee consumption, with a consumption of 3 cups day^{-1}, the risk of all-cause mortality might reduce 13% (RR = 0.87; 95% confidence interval = 0.84–0.89).
Conclusions: The findings of the present study provide quantitative data suggesting that coffee consumption plays a role in reducing the risk of all-cause mortality. Similar inverse associations are found for caffeinated coffee and decaffeinated coffee.

Introduction

Coffee, which is one of the most widely consumed beverages in the world for centuries [(1)], contains many bioactive compounds. Subsequent to the finding of an inverse association between coffee consumption and mortality [(2)], extensive studies have been conducted to investigate the effects of coffee on health outcomes. Many epidemiological studies have indicated that coffee has strong acute effects, such as increased blood pressure [(3)], inhibited insulin activity [(4)] and worsened perceived sleep quality [(5)], which may be harmful to human health. However, the consumption of coffee has been found to be negatively correlated with cardiovascular disease [(6)], certain types of cancer [(7)], diabetes [(8)] and obesity [(9)] in some reviews or cohort studies.

Caffeine, comprising the main bioactive substance in coffee, has been found to reduce the risk of all-cause

mortality [10]. However, findings from a meta-analysis indicated that consumption of decaffeinated coffee has beneficial effects for type 2 diabetes [11] and reduced the risk of colorectal cancer [12]. There also has a cohort study to show that decaffeinated coffee intake was associated with a lower risk of mortality [13]. Three previous dose–response meta-analyses reported an inverse relationship between coffee consumption and all-cause mortality, without comparing different types of coffee [14–16].

Resolving whether coffee consumption is indeed associated with all-cause mortality and, furthermore, to determine whether this association varies by type of coffee, caffeinated or decaffeinated, which contain different bioactive compounds, is a key issue. Subsequent to the publication of previous meta-analyses on this issue, at least seven additional cohort articles on the association have been published. Therefore, we performed an updated dose–response meta-analysis on the association of coffee consumption and all-cause mortality risk using all of the available data. We also compared differences between caffeinated and decaffeinated coffee in the risk of all-cause mortality.

Materials and methods

Search strategy

We searched the databases PubMed and Web of Science for prospective cohort studies that evaluated the association between consumption of coffee and all-cause mortality by using a combination of medical subject heading terms and free texts (see Supporting information, Table S1). All English-language studies of humans published up to 9 November 2017 were eligible. This meta-analysis followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [17].

Study selection

Studies had to meet the following criteria: (i) the study design was prospective cohort study and followed a cohort of adults (≥18 years old at baseline); (ii) the exposure was coffee consumption (consumption was measured by cups day^{-1} in the original report or cups month^{-1} and cups week^{-1} were converted to cups day^{-1}), including total (all types), caffeinated and decaffeinated coffee; the outcome was all-cause mortality; (iii) relative risks (RRs), odds ratios (ORs) or hazard ratios (HRs) with 95% confidence intervals (CIs) were reported or could be derived; and (iv) the study investigated at least three exposure levels of coffee consumption at baseline, number of deaths, exposed participant/person-year numbers ascertained or sufficient data to calculate. If multiple articles were published from the same cohort, we included data from the study with the most informative reporting of coffee consumption levels or the largest sample size.

Data extraction and quality assessment

The data extracted by two investigators (QL and CG) comprised first author, publication year, sex, region, cohort name, sample size, follow-up years, mean or median age at baseline, method of coffee consumption assessment, types of coffee, levels of coffee consumption, deaths and exposed participant/person-year numbers per coffee consumption category, ORs/RRs/HRs for mortality with 95% CIs for each coffee consumption category, and covariates [age, sex, race, smoke status, alcohol drinking, body mass index (BMI), education status, physical activity, etc.] adjusted for in the multivariable analyses.

The study quality of the included articles was assessed by the Newcastle-Ottawa Scale [18]. Data were extracted by QL and the extraction was checked by CG. Any disagreements were referred to a third investigator (DH) and resolved by consensus.

Statistical analysis

If cohort studies reported HRs or ORs of coffee consumption with all-cause mortality, we used the method of Willi *et al.* [19] to assume HRs and ORs approximately equal to RRs. An article reporting data separately for males and females, smokers and nonsmokers, and caffeinated and decaffeinated coffee, or reporting multiple cohorts within the article, was treated as if it comprised independent studies. If the number of deaths was missing in each category, these data were inferred by the reported RRs/ORs/HRs and the number of total deaths. Groups were assumed to be of equal size if the exposed participant/person-year numbers were not reported for each category [20]. For each study, coffee consumption (cups day^{-1}) without a direct report was calculated as the median or midpoint duration of the reported category. If the highest or lowest category for coffee consumption was open-ended, the width of the interval was assumed to be the same as in the closest category [21].

If an article reported data separately for males and females, smokers and nonsmokers, and caffeinated and decaffeinated coffee or reported multiple cohorts, we used the fixed-effects model [22] to pool the results of independent studies, and then used the calculated RRs in our main analysis. Considering the within-study and between-study variation, summary RRs and 95% CIs for all-cause mortality for the highest versus the lowest level in coffee consumption were estimated using a random-effects model [22]. We used the method developed by Greenland *et al.* [23] to estimate study-specific dose-response

association, and the random-effects model [22] to pool the study-specific dose–response RR estimates. Study-specific RRs were calculated for every 1 cup day^{-1} increment in coffee consumption and then pooled. Moreover, we estimated study-specific slopes (nonlinear trends) and 95% CIs from the natural logs of the RRs and CIs across categories of coffee consumption to capture the detailed nature of the association by modelling coffee consumption with three knots at the 25th, 50th and 75th percentiles of the distribution and then testing whether the second spline coefficient was equal to zero to determine whether the association between coffee consumption and all-cause mortality was nonlinear [24]. A P value was calculated by testing the null hypothesis of the coefficient of the second spline equal to zero. STATA commands GLST for model fitting and LINCOME for estimating effect were used for the fitted model [11].

The Cochran Q and I^2 statistics [25] were used to test heterogeneity. The Q statistic was indicated at $P < 0.1$. For the I^2 statistic, low, moderate and high heterogeneity were defined by I^2 values of approximately 25%, 50% and 75%, respectively. To assess the stability of results and potential sources of heterogeneity, we performed a sensitivity analysis, excluding one study at a time, and subgroup analyses stratified by sex, region, smoking status, types of coffee consumed and covariates (age, alcohol drinking, BMI, education status and physical activity). To test the differences in RRs between subgroups, we used meta-regression models [26]. We used funnel plots and Begg's test to examine the presence of publication bias (small-study effects) [27]. All analyses involved using STATA, version 12.1 (Stata Corp., College Station, TX, USA).

Results

Characteristics of studies

We identified 21 cohort study articles (54 studies) [10,13,14,28–45] (10 103 115 study participants and 240 303 deaths) that provided information on the association between coffee consumption and all-cause mortality (Fig. 1). The descriptive characteristics of the cohort studies are provided in the Supporting information (Table S2). The duration of follow-up ranged from 3.8 to 28 years. All information on coffee consumption was collected using dietary questionnaires. Assessment of study quality produced a mean Newcastle-Ottawa Scale score of 8.7 (see Supporting information, Table S3).

Association of high versus low total coffee consumption and all-cause mortality

In this dose–response meta-analysis, 30 cohort studies were included. Compared with no or rare coffee consumption, the risk of all-cause mortality was reduced by 12% with the highest consumption (95% CI = 6–16%) (see Supporting information, Figure S1). Both of the funnel plots and Begg's test ($P = 0.187$) indicated that there was no publication bias for the present study (see Supporting information, Figure S2).

Dose–response analysis of the association between total coffee consumption and all-cause mortality

In total, 21 cohort study articles were included in the dose–response analysis. For every 1 cup day^{-1} increment in total coffee consumption, the pooled RR for all-cause mortality was 0.97 (95% CI = 0.96–0.98) (Fig. 2). The restricted cubic spline model suggested that the association between total coffee consumption and all-cause mortality was nonlinear ($P_{\text{nonlinearity}} < 0.001$). Furthermore, the association was approximately U-shaped, with the largest risk reduction observed for 3 cups day^{-1} (Fig. 3).

Comparison of association of caffeinated and decaffeinated coffee consumption with all-cause mortality

In total, five cohort study articles investigating caffeinated coffee and four cohort study articles investigating decaffeinated coffee were included in the dose–response analysis. For every 1 cup day^{-1} increment in coffee consumption, the risk of all-cause mortality did not differ between caffeinated and decaffeinated coffee (Table 1; see also Supporting information, Figure S3). Similar to total coffee, the evidence indicated a nonlinear association for both caffeinated coffee ($P_{\text{nonlinearity}} < 0.001$) and decaffeinated coffee ($P_{\text{nonlinearity}} < 0.001$) and the nonlinear association was approximately U-shaped (see Supporting information, Figure S4).

Subgroup analyses and sensitivity analyses and publication bias

We performed subgroup analyses by sex, region, smoking status and confounding factors (Table 1) to explore the sources of heterogeneity (Table 1). The results for smoking participants and without age adjustment showed no heterogeneity (Table 1). In Asian studies, the heterogeneity was low (Table 1).

Despite large heterogeneity, the inverse associations between coffee consumption and risk of all-cause mortality were not significantly different among many subgroups. However, the RR of the association was greater in studies with adjusted alcohol than in those without (Table 1). The risk of all-cause mortality did not substantial differ between males and females for every 1 cup day^{-1}

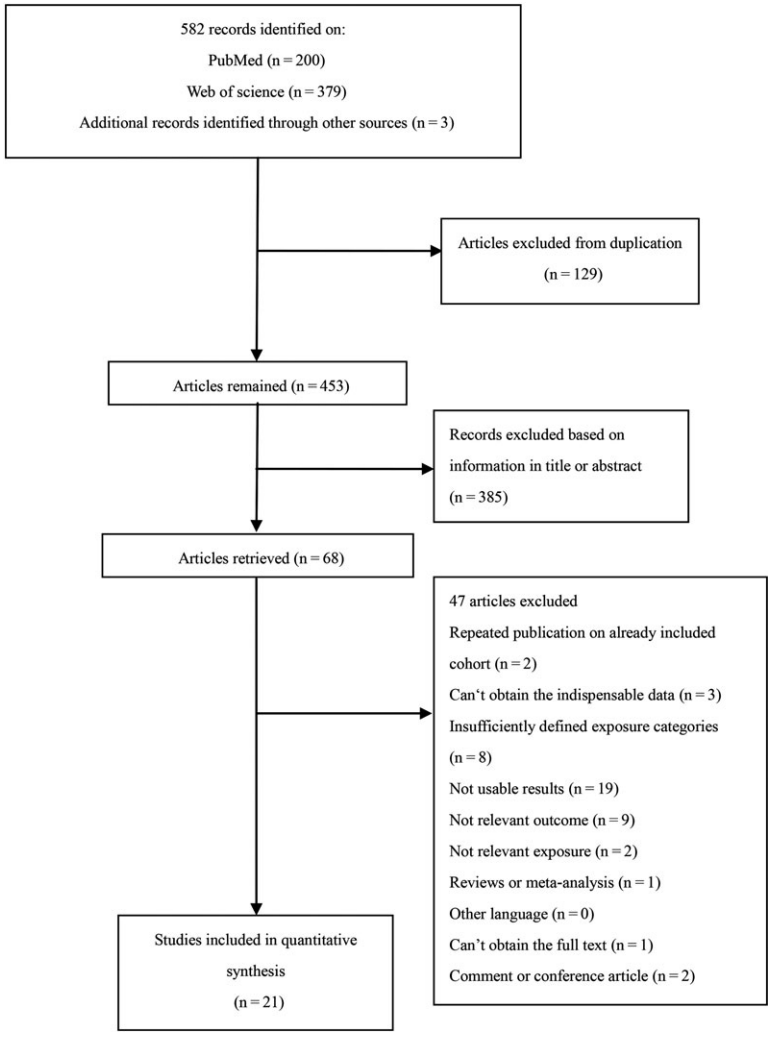

Figure 1 Flow chart of study selection.

increment in total coffee consumption (Table 1). The association between total coffee consumption and all-cause mortality was nonlinear for males and females (both $P_{\text{nonlinearity}} < 0.001$). It was approximately L-shaped for males. With increasing total coffee consumption, the risk of all-cause mortality continued to decrease. In particular, the decrease was rapid before 3 cups day^{-1} total coffee consumption and the subsequent change was gradual. However, the association was approximately U-shaped for females, with the largest risk reduction observed for 3 cups day^{-1} (see Supporting information, Figure S5). There was no difference for the coffee–mortality association among America, Europe and Asia (Table 1). The results by region indicated that the association between total coffee consumption and all-cause mortality was nonlinear ($P_{\text{nonlinearity}} = 0.013$ for Europe; $P_{\text{nonlinearity}} < 0.001$ for the USA; and $P_{\text{nonlinearity}} < 0.001$ for Asia). This association was reproducibly U-shaped in Europe and the USA and persistently decreased in Asia (see Supporting information, Figure S6).

On sensitivity analyses, by removing one study at a time, the size and direction of the pooled estimates were similar. We found no evidence of publication bias by Begg's test ($P = 0.184$) and by visual inspection of the funnel plots (see Supporting information, Figure S7).

Discussion

The present study comprises an updated meta-analysis of 21 prospective cohort articles evaluating a dose–response association between coffee consumption and risk of all-cause mortality. Similar to three published meta-analyses, we also demonstrated a nonlinear inverse association between coffee consumption and all-cause mortality. Compared with no or rare total coffee drinking, regularly drinking 3 cups day^{-1} may reduce the risk of all-cause

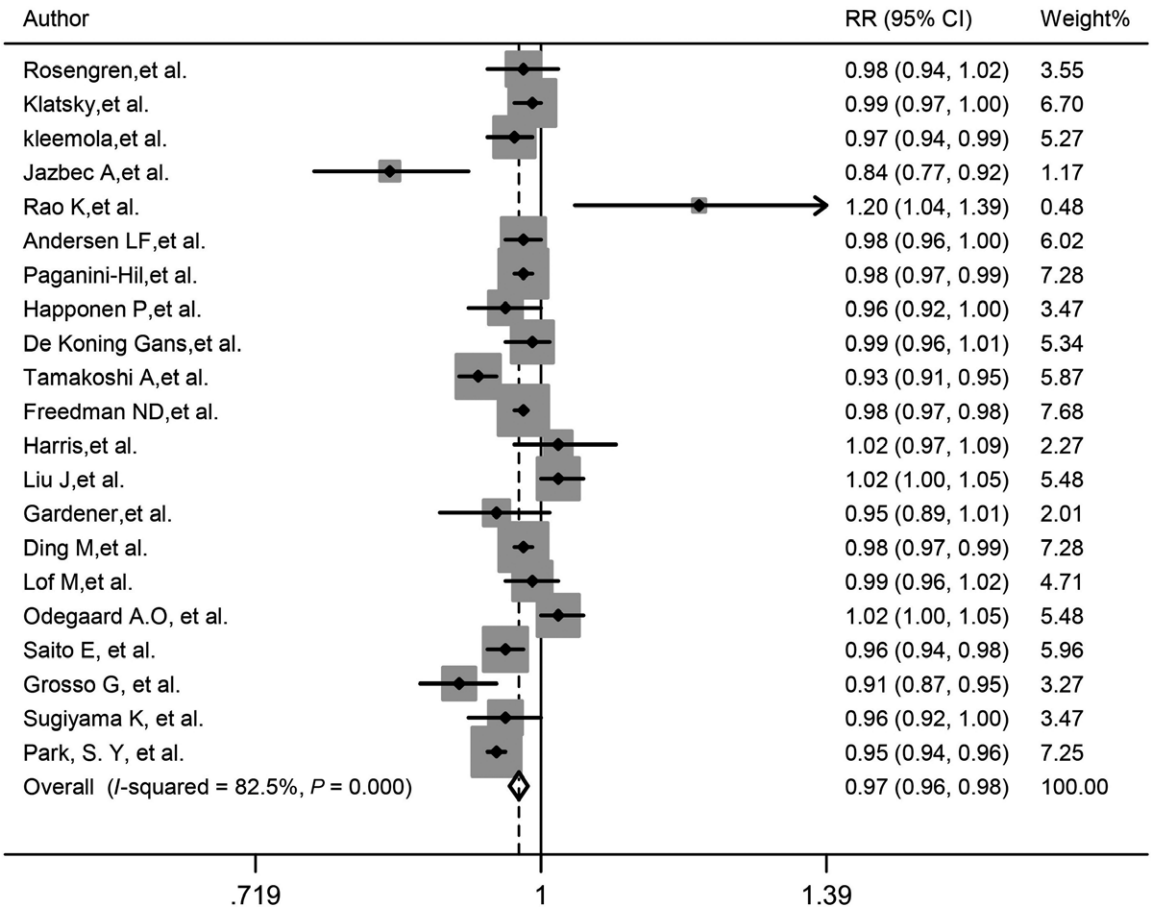

Figure 2 Forest plot of study-specific relative risk for all-cause mortality for every 1 cup day^{-1} increment in coffee consumption. CI, confidence interval; RR, relative risk.

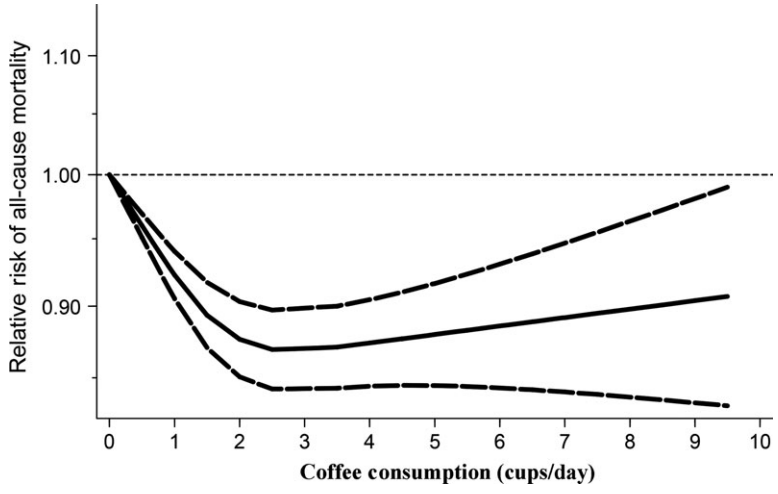

Figure 3 Nonlinear association of coffee consumption and all-cause mortality among all cohort studies.

mortality by 13%. Both caffeinated coffee and decaffeinated coffee consumption may be associated with a reduced risk of all-cause mortality.

For total coffee, the previous meta-analysis [15] indicated that the health-promoting effect of coffee was associated with female rather than male consumers. We also found

Table 1 Subgroup analysis and meta-regression of dose–response association of coffee consumption with all-cause mortality

Subgroups	Number of studies	Coffee consumption (per 1 cup day^{-1})		
		RR (95% CI)	I^2 (%)	*P*
All studies	30	0.97 (0.96–0.98)	82.50	<0.001*
Sex				0.651†
Male	10	0.97 (0.95–0.99)	81.60	<0.001*
Female	13	0.96 (0.94–0.98)	86.70	<0.001*
Region				0.408†
Europe	10	0.95 (0.92–0.98)	70.40	<0.001*
USA	15	0.98 (0.97–0.99)	76.50	<0.001*
Asia	8	0.94 (0.93–0.96)	16.90	0.297*
Smoking status				0.998†
Smoker	4	0.95 (0.92–0.98)	0.00	0.538*
Non-smoker	5	0.94 (0.90–0.98)	60.30	0.039*
Types of coffee				0.740†
Caffeinated	5	0.97 (0.95–0.99)	87.30	<0.001*
Decaffeinated	4	0.97 (0.96–0.98)	34.30	0.206*
Adjustment				
Age				0.479†
Yes	28	0.97 (0.96–0.98)	82.50	<0.001*
No	4	0.98 (0.97–1.00)	0.00	0.539*
Alcohol				0.041†
Yes	20	0.98 (0.97–0.99)	77.20	<0.001*
No	12	0.95 (0.92–0.97)	68.00	<0.001*
Body mass index				0.972†
Yes	21	0.97 (0.96–0.98)	77.20	<0.001*
No	11	0.97 (0.95–0.99)	85.60	<0.001*
Education				0.330†
Yes	16	0.96 (0.95–0.98)	77.90	<0.001*
No	16	0.97 (0.96–0.99)	83.10	<0.001*
Activity				0.768†
Yes	18	0.97 (0.96–0.98)	82.60	<0.001*
No	14	0.97 (0.95–0.99)	75.00	<0.001*

*The *P* for heterogeneity within each subgroup estimated by the I^2 statistic.

†The *P* for heterogeneity between each subgroup estimated by the meta-regression models.

CI, confidence interval; RR, relative risk.

similar results for low coffee consumption. The metabolic rate of caffeine, as the major biologically active component in coffee, was previously found to be significantly slower in females than males [46], which may explain why the result was different among sex in low coffee consumption, and with the coffee consumption increased, all-cause mortality was on a downward trend among men.

Additionally, we found that the subgroup of adjusted alcohol or non-adjusted may be a source of heterogeneity. Blood gamma-glutamyltransferase is an indicator of the degree of hepatocyte damage and its level was positively associated with all-cause mortality. Low consumption of coffee may lead to higher blood gamma-glutamyltransferase levels in heavy alcohol drinkers, particularly among males [47]. This may explain why the risk of all-cause mortality was different between groups of alcohol adjusted and non-adjusted for every 1 cup day^{-1} increment in total coffee consumption.

Although the explicit mechanisms of the association of coffee consumption and all-cause mortality remain unclear, several mechanisms have been proposed. Caffeine contained in the product coffee affects the cardiovascular system [48] and central nervous system [49]. Some studies [10,40] found moderate caffeine consumption to be associated with a reduced risk of all-cause mortality. Beyond that, we found decaffeinated coffee consumption to be beneficial for decreasing the risk of all-cause mortality. The novel finding was that we found no statistically significant difference between caffeinated and decaffeinated coffee (1 cup day^{-1} increment). Hence, bioactive components [50] other than caffeine may be responsible for this putative beneficial effect. Chlorogenic acid, the most abundant polyphenol in coffee, is easily absorbed and has a relatively high bioavailability [51–53]. Kahweol and cafestol have also been shown to possess chemopreventive potential by enhancing the endogenous defence systems against oxidative damage [54]. Similarly, trigonelline, a pyridine alkaloid, has neuroprotective [55] and hypoglycaemic [56] effects. In addition, coffee melanoidins have a good prebiotic potential [57]. Accordingly, the underlying mechanism remains to be established.

This meta-analysis has several strengths. (i) This updated dose–response meta-analysis included 21 prospective cohort articles (54 studies) and the relatively large total number of deaths provided high statistical power, which contributes to stable risk estimates. (ii) The Newcastle-Ottawa Scale score of 7–9 ensured the relatively high quality of the included studies. (iii) We included only cohort articles, which could minimise the recall bias, and obtained sufficient statistical power to detect the association. (iv) The inclusion of 54 studies enabled us to conduct several subgroup analyses to assess potential sources of heterogeneity. Specifically, we found direct associations between the intake of coffee in different subgroups and all-cause mortality. (v) We did not find evidence of publication bias, which could affect the results of a meta-analysis.

Some potential limitations also need to be acknowledged. (i) This meta-analysis could not establish causality because it included observational studies, and the unmeasured and insufficiently measured variables would result in inevitable residual confounding. Nevertheless, to investigate the robustness of our findings, we performed subgroup analyses. (ii) The studies presented obvious heterogeneity (I^2 = 82.50%; P < 0.001). We found that the subgroup of alcohol adjusted or not was a source of heterogeneity, which explained the 27.14% heterogeneity. (iii) Exposure might be unavoidably misclassified. However,

coffee drinking quantity was measured in cups. The cup size affects the coffee intake concentration but does not affect total consumption. (iv) The association could be related to reverse causation because individuals with chronic disease or poor health might decrease their coffee consumption. However, we only considered studies that analysed the general population and not specific disease populations. Therefore, the results of the present study are more applicable to healthy people without special diseases. (v) Even though the meta-analysis demonstrates an association of coffee consumption with all-cause mortality, randomised controlled trials are needed to explore whether the observed associations are causal. (vi) Because this was an aggregate data meta-analysis, the potential for ecological fallacy, specifically Simpson's paradox, exists.

Conclusions

In summary, the results of this dose–response meta-analysis indicated that coffee consumption was inversely associated with all-cause mortality. By regularly drinking 3 cups day^{-1}, the risk of all-cause mortality might reduce by 13%. There is no difference in the protective effect of caffeinated and decaffeinated coffee consumption on all-cause mortality. These findings could have a substantial impact on public health and even a small health-promoting effect. Thus, moderate coffee consumption could be integrated into a healthy diet and lifestyle.

Transparency declaration

The authors affirm that this manuscript is an honest, accurate and transparent reporting, which is compliant with MOOSE guidelines.

Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Association between coffee consumption and all-cause mortality (high/low).

Figure S2. Publication bias results of the association between coffee consumption and all-cause mortality.

Figure S3. Forest plot of study-specific relative risk for all-cause mortality for every 1 cup day^{-1} increment of caffeinated and decaffeinated coffee consumption.

Figure S4. Nonlinear association of coffee consumption with all-cause mortality in studies of (a) caffeinated coffee only and (b) decaffeinated coffee only.

Figure S5. Nonlinear association of coffee consumption with all-cause mortality: (a) studies of males only; (b) studies of females only.

Figure S6. Nonlinear association of coffee consumption with all-cause mortality for studies of (a) Americans only; (b) Europeans only; and (c) Asians only.

Figure S7. Publication bias results of the dose–response analysis of the association between coffee consumption and all-cause mortality.

Table S1. Systematic literature review search terms and strategy.

Table S2. Characteristics of studies included in the meta-analysis of coffee consumption and all-cause mortality.

Table S3. Quality assessment of the included cohort studies.