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META-ANALYSIS

Coffee consumption and all-cause and cause-specific mortality: a meta-analysis by potential modifiers

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Abstract

Coffee consumption has been associated with decreased mortality in previous studies. As aging, obesity, and lifestyle factors affect the risk of mortality, the association between coffee and mortality needs to be examined in various subpopulations by characteristics of subjects. To quantitatively assess this association, we conducted an updated meta-analysis including stratified analyses by potential modifiers. We searched in the PubMed and Web of Science databases through March 8, 2019, and conducted meta-analysis including linear and non-linear dose–response analyses. We identified 40 studies including 3,852,651 subjects and 450,256 all-cause and cause-specific deaths. Non-linear inverse associations between coffee consumption and mortality from all-causes, cardiovascular disease (CVD), and cancers were found. The lowest relative risk (RR) was at intakes of 3.5 cups/day for all-cause mortality (RR = 0.85, 95% CI 0.82–0.89), 2.5 cups/day for CVD mortality (RR = 0.83, 95% CI 0.80–0.87), and 2 cups/day for cancer mortality (RR = 0.96, 95% CI 0.94–0.99), while additional intakes were not associated with further lower mortality. An inverse association between coffee consumption and all-cause mortality was maintained irrespective of age, overweight status, alcohol drinking, smoking status, and caffeine content of coffee. By region, Europe and Asia showed stronger inverse associations than US. A non-linear inverse association was found for mortality from respiratory disease and diabetes, while linear inverse association was found for mortality from non-CVD, non-cancer causes. Moderate coffee consumption (e.g. 2–4 cups/day) was associated with reduced all-cause and cause-specific mortality, compared to no coffee consumption. The inverse association between coffee and all-cause mortality was consistent by potential modifiers except region.

Keywords Coffee · Mortality · Meta-analysis · Age · BMI · Alcohol consumption

Introduction

Coffee is a complex mixture of over a thousand bioactive compounds including caffeine, chlorogenic acids, and diterpenes [1]. As coffee is one of the most commonly consumed beverages around the world, its potential effects on human health could be large on a population scale. Coffee was considered as potentially harmful to human health because of caffeine which may raise blood pressure [2], and the possible carcinogenicity of coffee had been suggested regarding certain cancers such as urinary bladder cancer [3, 4]. However, recent summary results from cumulative evidence show that moderate coffee consumption is associated with decreased risk of type 2 diabetes, cardiovascular disease (CVD), mortality, and several types of cancers, including liver and endometrial cancers, and possibly colorectal, breast, and prostate cancers [5, 6]. These findings suggest that coffee may be included as part of healthy diet.

Many observational studies have investigated the association between coffee consumption and mortality from all-causes, CVD, and cancers in the general population [7–45]. Some of the studies have also reported the estimates stratified by various factors including age, BMI, alcohol drinking or smoking status [8, 9, 12, 13, 22, 25, 27, 31, 33–35, 37, 43–45]. Several clinical studies suggested that the effect of

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coffee consumption could be different by age [46, 47] or obesity status [48, 49]. Elderly were more sensitive to the pressor effects of caffeine [47] and obese people had smaller thermogenesis induced by coffee than lean people [48]. Also coffee consumption has been found positively associated with lifestyle factors such as smoking and alcohol drinking [10, 43]. Considering that aging, obesity, alcohol drinking and smoking are closely linked to the incidence of chronic disease, it is of interest to examine possible variations in the association between coffee intake and mortality by these factors. Several meta-analyses to determine the relation of coffee intake and risk of mortality [50, 51] indicated that high coffee consumption was associated with lower risk of premature mortality, but to our knowledge, no meta-analysis has stratified by age, BMI, or alcohol drinking. There was only one meta-analysis that provided the results by smoking status and found an inverse association between coffee consumption and mortality in non-smokers [50]. Furthermore, no meta-analysis has reported pooled RR of mortality from respiratory disease, diabetes, and non-CVD, non-cancer causes.

Therefore, this meta-analysis examined the association between coffee consumption and all-cause mortality, including results stratified by age, BMI, alcohol consumption, smoking status, sex, and geographical region, and separately by caffeine content of the coffee. In addition, we conducted a meta-analysis of coffee consumption in relation to mortality from CVD, cancer, respiratory disease, diabetes, and all non-CVD, non-cancer causes.

Methods

Literature search and study selection

A systematic literature search on PubMed and ISI Web of Science databases for studies of coffee and mortality published through March 8, 2019 was conducted. The search terms were as follows: "(coffee OR caffeine OR hot beverages)" combined with "(mortality OR death OR survival OR fatal)". Manual search was also performed to identify additional relevant studies by reviewing the reference list of review and retrieved articles. The searches were limited to articles published as full-length and in English. Inclusion criteria were as follows: (1) had a prospective design; (2) the exposure of interest was coffee consumption; (3) the outcome of interest was mortality from all-causes, CVD, or cancer; (4) reported relative risks (RR) and confidence intervals (CI) or sufficient data to calculate them. Studies that evaluated risk of mortality in people with disease were excluded. When more than one study reported the results from the same cohort, we selected the study which included longer follow-up times and larger sample sizes.

Data extraction

Two independent authors (Y. K. and Y. J.) extracted data according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines [52]. The following information was collected from each study: year of publication; first author's surname; country and study cohort name; baseline age and sex of participants; number of deaths; number of participants or person-years; follow-up period; each category of coffee consumption; RR and 95% CI for all categories of coffee consumption; adjustment factors. Any discrepancies between the authors in this process were addressed by discussion.

Quality assessment

Quality of the original studies which were included in meta-analysis was evaluated using the Newcastle–Ottawa Scale [53]. The quality assessment scale awards 0–13 points based on three perspectives, as follows: selection of study population; comparability; outcome assessment. We considered studies with a total score of ≥ 9 points to represent high quality.

Statistical analysis

The random-effects models by Dersimonian and Laird [54], which incorporated variations both within and between studies, were used to calculate pooled RR of all-causes, CVD, and cancer mortality for the highest versus lowest coffee consumption and for 1 cup a day increment. When studies had not used the lowest category as a reference, we recalculated the RRs and their 95% CI relative to the lowest category. For any study which provided results separately by sex, we combined the RRs and then included the pooled RR in the meta-analysis.

Linear dose–response relationships were evaluated using the method developed by Greenland and Longnecker [55–57] to estimate the study specific slope lines. Studies that provided RRs for only 2 exposure categories [17, 34, 39] or did not report the number of deaths and subjects for each coffee consumption category [18, 24, 25, 28] could not be included in dose–response analysis. We used the median value of coffee consumption for each exposure category. If the upper category was open-ended, we assumed the same interval as the adjacent category. A potential non-linear dose–response relationship was also assessed between coffee consumption and mortality using restricted cubic splines with 4 knots at fixed percentiles (5, 35, 65, and 95%) of the aggregated exposure. We computed the *P* value for non-linearity by testing the null hypothesis in which the coefficient of the second spline is equal to zero [58].

To investigate whether the association between coffee consumption and all-cause mortality differed by age (< 60/≥ 60 years), sex, BMI (< 25/≥ 25 kg/m^2), alcohol consumption (low/high), smoking status (non-smoker/smoker), geographical region (US/Europe/Asia) or caffeine content of coffee (decaffeinated/caffeinated), we conducted stratified analysis when separated data were available.

Heterogeneity among the studies was evaluated using the Q statistic, and inconsistency was quantified through the I^2 statistic. To investigate the robustness of the pooled RR, sensitivity analysis excluding one study at a time was conducted. Publication bias was assessed with Begg's [59] and Egger's tests [60]. A two-tailed $P < 0.05$ was assumed to be statistically significant. The Stata/SE software (version 14.2; Stata Corp LP, College Station, Texas) was used for all the statistical analyses.

Results

Study characteristics

A total of forty prospective cohort studies from 39 articles (1 article [8] provided results from 3 cohorts and 2 articles [41, 44] reported results for mortality from different causes from the same cohort) involving 3,852,651 subjects and 323,120 deaths from all-causes, 229,884 deaths from cancer, and 81,188 deaths from CVD (2 studies [24, 28] did not report the number of deaths) were included in this meta-analysis [7–45]. Details of the study selection are shown in Fig. 1. Table 1 shows the main characteristics of studies included in the meta-analysis. The follow-up periods ranged from 6 to 28 years. Studies were conducted in Europe (n = 17) [10, 12–15, 17, 18, 21, 26, 30, 34, 38–40, 42, 43, 45], US (n = 15) [7–9, 11, 19, 20, 22, 24, 25, 27, 28, 32, 33]. Japan (n = 6) [16, 29, 31, 35–37, 41, 44], Singapore (n = 1) [31], and Australia (n = 1) [23]. Several studies provide separated results by age (n = 11) [8, 9, 25, 27, 33, 35, 37, 44, 45], BMI (n = 7) [8, 9, 13, 27, 43], alcohol consumption (n = 4) [9, 12, 13, 27], smoking status (n = 15) [8, 9, 12, 13, 22, 27, 31, 33–35, 43–45], and type of coffee (n = 12) [7–9, 11, 13, 27, 32, 33, 42, 43]. The results of quality assessment showed that all studies had high qualities indicating nine or higher scores.

All-cause and cause-specific mortality

A total of thirty six prospective cohort studies from 34 articles including 323,120 deaths and 2,837,526 subjects examined the association between coffee consumption and all-cause mortality [7–9, 11–14, 16–23, 25–28, 30–40, 42–45]. The pooled RR for highest versus lowest consumption was 0.88 (95% CI 0.84–0.92) with significant heterogeneity ($P < 0.001$, $I^2 = 76.6\%$) (Table 2, Supplementary Figure 1). The heterogeneity was slightly reduced when two outlying studies [19, 25] were excluded ($P < 0.001$, $I^2 = 67.0\%$). A significant non-linear association between coffee intake and all-cause mortality was found (P for non-linearity < 0.0001) (Fig. 2). The largest reduction in RR was observed with the consumption of 3.5 cups/day (RR = 0.85, 95% CI 0.82–0.89), compared with no coffee consumption.

A total of thirty one prospective cohort studies from 29 articles with 81,188 deaths and 2,631,398 subjects were included in the analysis of coffee consumption and CVD mortality [7–9, 11–15, 17, 18, 21–23, 25–27, 29–31, 33–36, 38, 40, 42–45]. The pooled RR for highest versus lowest consumption was 0.87 (95% CI 0.82–0.94) with moderate heterogeneity ($P = 0.001$, $I^2 = 49.5\%$) (Table 2, Supplementary Figure 2). The heterogeneity was decreased after excluding two outlying studies [22, 29] ($P = 0.04$, $I^2 = 33.9\%$). We found some evidence of nonlinearity for the association between coffee intake and CVD mortality (P for non-linearity < 0.0001) (Fig. 3). The largest reduction in RR for CVD mortality was observed in consumption of 2.5 cups/day (RR = 0.83, 95% CI 0.80–0.87), compared with no coffee consumption.

A total of twenty six prospective cohort studies from 24 articles including 229,884 deaths and 3,419,278 subjects investigated the association between coffee consumption and cancer mortality [7–14, 16, 17, 24, 26, 27, 31, 33–38, 41–43, 45]. The pooled RR for highest versus lowest consumption was 0.99 (95% CI 0.94–1.04) with moderate heterogeneity ($P < 0.001$, $I^2 = 57.9\%$) (Table 2, Supplementary Figure 3). The observed heterogeneity was decreased after excluding two outlying studies [8, 26] ($P = 0.004$, $I^2 = 51.0\%$). In the dose–response analysis, a significant linear relationship was not observed (Table 2), and some evidence of a non-linear association between coffee intake and cancer mortality was found (P for non-linearity < 0.0001) (Fig. 4). Compared with no coffee consumption, the pooled RR of cancer mortality for 2–2.5 cups/day of coffee was 0.96 (95% CI 0.94–0.99), and no further cancer mortality reduction was observed with further coffee consumption, with no significant positive association observed at high levels of coffee consumption.

A total of nine studies including 14,694 deaths and 2,101,160 subjects reported the association between coffee consumption and respiratory disease mortality [8, 9, 13, 27, 31, 33, 35, 38, 43]. The pooled RR for highest versus lowest consumption was 0.90 (95% CI 0.75–1.07) (Table 2). There was some evidence of non-linearity in the analyses of mortality from respiratory disease (P for non-linearity < 0.0001) (Fig. 5). Despite significant non-linearity, RRs were reduced sequentially from 1 through to 6.5 cups/day by 28%. A total of four studies including 4010 deaths and 886,933 subjects provided the estimates for the association between coffee consumption and diabetes mortality [8, 9, 27, 33]. The pooled RR for highest versus lowest consumption

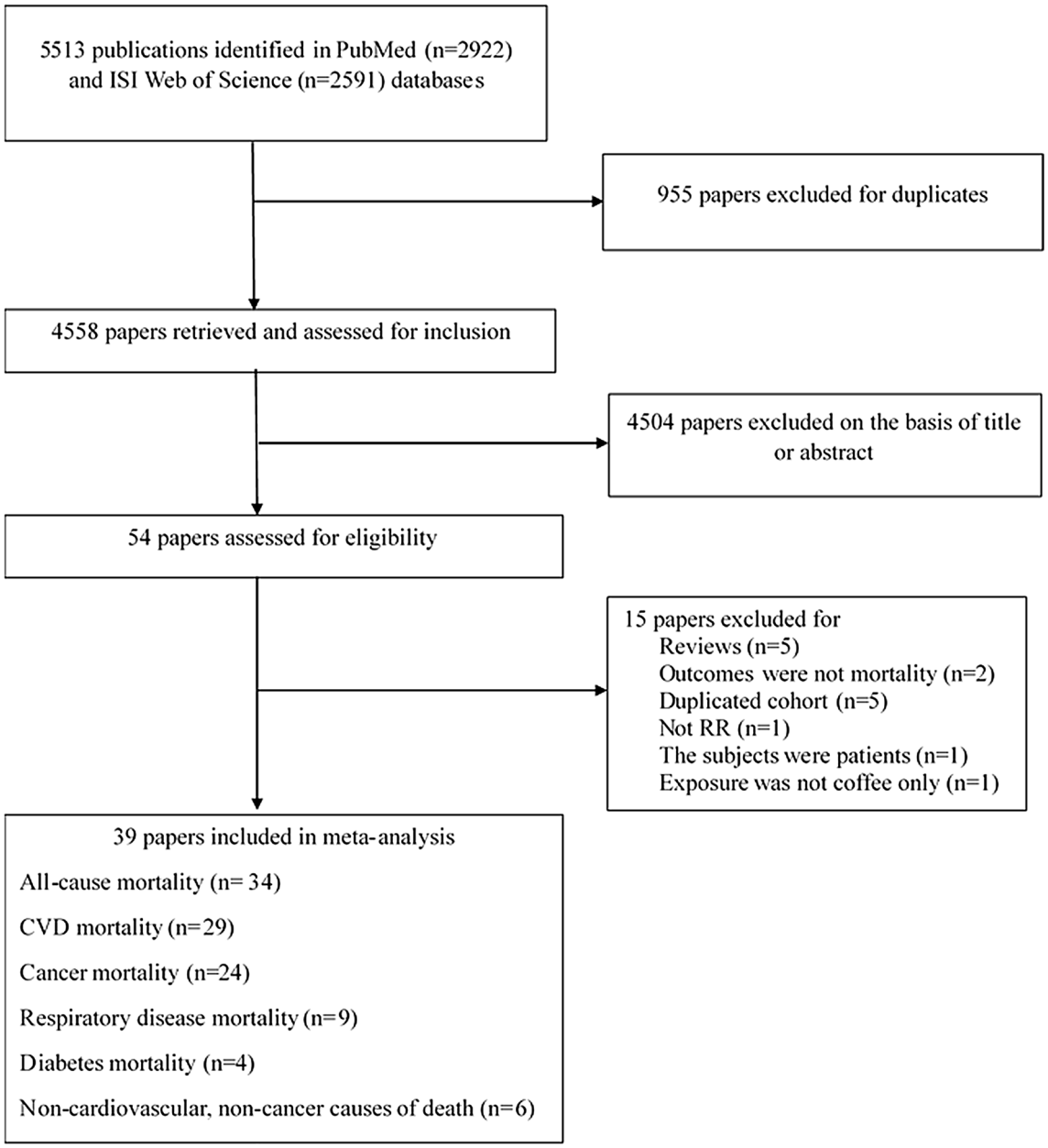


Fig. 1 Flow chart of study selection

was 0.76 (95% CI 0.65–0.90) (Table 2). A non-linear inverse association between coffee consumption and diabetes mortality (*P* for non-linearity = 0.006) was observed, showing most of the reduction in risk for consumption of 2.5 cups/day (RR = 0.70, 95% CI 0.60–0.81) (Fig. 6). A total of six studies including 3330 deaths and 141,783 subjects reported the association between coffee consumption and mortality from non-CVD and non-cancer causes [7, 14, 26, 34, 36, 45]. The pooled RR for highest versus lowest consumption was 0.65 (95% CI 0.51–0.83) (Table 2). The pooled RR for 1 cup/day increment of coffee consumption was 0.93 (95% CI 0.91–0.96), and there was little evidence of non-linearity (*P* for non-linearity = 0.054) (Fig. 7).

Stratified analyses of all-cause mortality for coffee consumption

When we conducted a stratified analysis by alcohol consumption, the inverse association was suggestively stronger among heavy drinkers (RR = 0.80, 95% CI 0.71–0.91) compared with low alcohol drinkers (RR = 0.87, 95% CI 0.79–0.95) (*P* for low vs. high alcohol consumption = 0.46) (Table 3). By smoking status, the results from non-smokers

Table 1 Characteristics of the prospective cohort studies included in the meta-analysis

References	Country	Cohort name	Follow-up year	Age at baseline	Study size		Cause of death	Adjustment for covariates	NOS score
					Participants	No. of death			
Kahn [19]	US	Seventh-Day Adventists	1960–1980 (21 year)	≥ 30 year	20,969	5654	All causes	Age, gender, smoking history, history of heart disease, stroke, hypertension, diabetes, or cancer,, age at initial exposure to the Adventist Church	10
Jacobsen et al. [17]	Norway		1967–1978 (11.5 year)	≥ 35 year	13,664 M	2583 M	All causes CVD Cancer	Age, cigarette smoking, residence	10
Vandenbrouck et al. [39]	Netherland		1953–1982 (25 year)	40–65 year	1583 M 1508 F	842 M 473 F	All causes	Age, gender, BMI, cigarettes, pipe or cigar, alcohol, living parents, serum cholesterol, systolic blood pressure	10
LeGrady et al. [22]	US	The Chicago Western Electric Company Study	1959–1978 (19 year)	40–56 year	1910 M	452 M	All causes CVD	Age, diastolic blood pressure, serum cholesterol, smoking status.	13
Rosengren et al. [34]	Sweden	Multifactor Primary Prevention Trial	1974–1983 (7.1 year)	51–59 year	6765 M	478 M	All causes CVD Cancer Non-CVD, non-cancer causes	Age, BMI, smoking, registration for alcohol abuse, systolic blood pressure, diabetes, family history of myocardial infarction, mental stress, physical activity, occupational class.	10
Lindsted et al. [24]	US	Adventist Mortality Study	1960–1985 (26 year)	≥ 30 year	9484 M	N/A	Cancer	BMI, smoking, physical activity, education, race, marital status, stroke, heart disease, cancer history, hypertension, exercise, sleep, dietary pattern (refined group, meat, dairy products, fruit and vegetables, cereal and bread, low food frequency)	9
Klatsky et al. [20]	US	Northern California Kaiser Permanente Medical Care Program	1978–1988	NA	128,934	4501	All causes	Age, gender, BMI, smoking, alcohol, race, education, marital status	10

Table 1 (continued)

References	Country	Cohort name	Follow-up year	Age at baseline	Study size		Cause of death	Adjustment for covariates	NOS score
					Participants	No. of death			
Hart et al. [15]	Scotland		1970–1994 (21 year)	35–64 year	5766 M	625 M	CVD	Age, Smoking, BMI, diastolic blood pressure, cholesterol, social class, age leaving full time education, angina, electrocardiogram ischaemia	11
Woodward et al. [40]	Scotland	The Scottish Heart Health Study	1984–1993 (7.7 year)	40–59 year	5645 M 5800 F	372 M 201 F	All causes CVD	Age, gender, BMI, smoking, housing tenure, activity at work and leisure, Bortner score, cotinine, systolic blood pressure, fibrinogen, total cholesterol, HDL-cholesterol, triglycerides, alcohol, vitamin C, tea consumption	10
Kleemola et al. [21]	Finland		1972–1986 (10 year)	30–59 year	10,075 M 10,387 F	1201 M 444 F	All causes CVD	Age, gender, smoking, serum cholesterol level, blood pressure, and history of myocardial infarction	12
Iwai et al. [16]	Japan	Tottori prefecture	1989–1999 (9.9 year)	40–79 year	1404 M 1451 F	246 M 115 F	All causes Cancer	Age, gender, smoking and alcohol (men only), history of selected diseases, physical	12
Jazbec et al. [18]	Croatia		1972–1999	35–59 year	1561 M 1776 F	568 M 382 F	All causes CVD	Age, gender, smoking, diastolic blood pressure, stomach ulcer, feeling of well-being, region	12
Andersen et al. [7]	US	Iowa Woman's Health Study	1986–2001 (15 year)	55–69 year	27,312 F	4265 F	All causes CVD Cancer Non-CVD, non-cancer causes	Age, smoking, intake of alcohol, BMI, waist-hip ratio, education, physical activity, use of estrogens, use of multivitamin supplements, energy intake, and intakes of whole and refined grain, red meat, fish, seafood, total fruit and vegetables	12

Table 1 (continued)

References	Country	Cohort name	Follow-up year	Age at baseline	Study size		Cause of death	Adjustment for covariates	NOS score
					Participants	No. of death			
Paganini-Hill et al. [32]	US	Leisure World Cohort Study	1981–2004	≥ 44 year	4980 M 8644 F	11,386	All causes	Age, sex, smoking, exercise, BMI, alcohol intake, and histories of hypertension, angina, heart attack, stroke, diabetes rheumatoid arthritis and cancer	12
Happonen et al. [14]	Finland		1991–2005 (14.5 year)	70–94 year	311 M 506 F	623	All causes CVD Cancer Non-CVD, non-cancer causes	Age, gender, BMI, smoking, calendar period, marital status, educational level, previous occupational group, history of myocardial infarction, presence of diabetes mellitus, cognitive impairment, physical disability	12
Sugiyama et al. [36]	Japan	Miyagi Cohort Study	1990–2001 (10.3 year)	40–64 year	18,287 M 19,455 F	1647 M 807 F	All causes CVD Cancer Non-CVD, non-cancer causes	Age, gender, BMI, smoking, alcohol, past history of hypertension and diabetes, education, walking time, green tea, oolong tea, black tea, rice, miso soup, meat, dairy products, fish, vegetables, fruits, energy	12
Tamakoshi et al. [37]	Japan	Japan Collaborative Cohort Study	1988–2006 (16 year)	40–79 year	46,465 M 64,327 F	11,178 M 8354 F	All causes Cancer	Age, gender, BMI, smoking, alcohol, walking hours, sleep duration, green-leafy vegetables, green tea, education, stress, marital status, past history of cancer, myocardial infarction or stroke	12

Table 1 (continued)

References	Country	Cohort name	Follow-up year	Age at baseline	Study size		Cause of death	Adjustment for covariates	NOS score
					Participants	No. of death			
Mineharu et al. [29]	Japan	Japan Collaborative Cohort Study for Evaluation of Cancer Risk	1988–2003 (13.1 year)	40–79 year	76,979	1681 M 1436 F	CVD	Age, BMI, smoking status, alcohol intakes, history of hypertension, history of diabetes, education, waking hours, hours of sports participation, perceived mental stress, multivitamin use, vitamin E supplement use, consumption of total fruits, total vegetable, total beans, total meat, total fish and total daily energy intake	10
Freedman et al. [9]	US	National Institutes of Health (NIH)–AARP Diet and Health Study	1995–2008 (13.6 year)	50–71 year	229,119 M 173,141 F	33,731 M 18,784 F	All causes CVD Cancer Respiratory disease Diabetes	Age, gender, BMI, smoking, alcohol, race, education, health status, diabetes, marital status, physical activity, total energy intake, fruits, vegetables, red meat, white meat, saturate fat, and use of vitamin supplements, postmenopausal hormone use	12
Gardener et al. [11]	US	Northern Manhattan Study	1993–2012 (11 year)	68.3 year	2461	863	All causes CVD Cancer	Age, gender, BMI, race, education, pack-years of smoking, alcohol consumption, energy, protein, carbohydrates, total fat, saturated fat, history of vascular risk factors, other non-water beverage consumption, coffee additives (milk, cream, nondairy creamer), tea	10

Table 1 (continued)

References	Country	Cohort name	Follow-up year	Age at baseline	Study size		Cause of death	Adjustment for covariates	NOS score
					Participants	No. of death			
Liu et al. [25]	US	Aerobics Center Longitudinal	1971–2003 (17 year)	20–87 year	43,727	2512	All causes CVD	Age, baseline examination year, decaffeinated coffee use, regular tea use, decaffeinated or herbal tea use, physical inactivity, BMI, smoking, alcohol consumption, diabetes, hypertension, hypercholesterolemia, and family history of CVD, fitness	10
Ding et al. [8]	US	Nurses' Health Study	1984-(28 year)	30–55 year	74,890 F	31,956	All causes CVD Cancer Respiratory disease Diabetes	Age, smoking, baseline disease status, BMI, physical activity, overall dietary pattern, total energy intake, sugar-sweetened beverage consumption, alcohol consumption, menopausal status, postmenopausal hormone use	9
	US	Nurses' Health Study II	1991-(21 year)	25–42 year	93,054 F			Age, smoking, baseline disease status, BMI, physical activity, overall dietary pattern, total energy intake, sugar-sweetened beverage consumption, alcohol consumption, menopausal status, postmenopausal hormone use	9
	US	Health Professional Follow-up Study	1986-(26 year)	40–75 year	40,557 M			Age, smoking, baseline disease status, BMI, physical activity, overall dietary pattern, total energy intake, sugar-sweetened beverage consumption, alcohol consumption,	9
Löf et al. [26]	Sweden	Swedish Women's Lifestyle and Health Cohort	1991–2010 (18 year)	30–49 year	49,259 F	1576 F	All causes CVD Cancer Non-CVD, non-cancer causes	BMI, education, smoking, alcohol, parity and age at first birth	10

Table 1 (continued)

References	Country	Cohort name	Follow-up year	Age at baseline	Study size		Cause of death	Adjustment for covariates	NOS score
					Participants	No. of death			
Loftfield et al. [27]	US	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial	1993–2001 (20 year)	55–74 year	90,317	8718	All causes CVD Cancer Respiratory disease Diabetes	Age, sex, smoking, race/ethnicity, educational level, marital status, employment status, presence or absence of diabetes, BMI, any supplemental vitamin use in the previous 12 months, regular ibuprofen or aspirin use in the previous 12 months, receipt of menopausal hormone therapy, alcohol consumption, total daily energy intake, and quintile of daily intake of red and processed meat, white meat, saturated fat, fruits, and vegetables	10
Odegaard et al. [31]	Singapore	Singapore Chinese Health Study	1993–2001 (16.3 year)	45–74 year	52,584	10,029	All causes CVD Cancer Respiratory disease	Age, sex, dialect, education, year of interview, moderate and vigorous activity, sleep, BMI, hypertension (except for cancer), non-beverage vegetable-fruit-soy–rich dietary pattern score, and energy intake, coffee, black tea, alcohol, soft drinks, juice, and green tea	13
Saito et al. [35]	Japan	Japan Public Health Center–based prospective Study	1990–2011 (18.7 year)	40–69 year	90,914	12,874	All causes CVD Cancer Respiratory disease	Age, sex, public health center area, smoking status, alcohol consumption, BMI, history of hypertension, history of diabetes, leisure-time sports or physical exercise, intakes of green tea, Chinese tea, black tea, soda and juice, energy, fruit, vegetables, fish, meat, dairy products, rice, and miso soup, job status	12

Table 1 (continued)

References	Country	Cohort name	Follow-up year	Age at baseline	Study size		Cause of death	Adjustment for covariates	NOS score
					Participants	No. of death			
Loomba et al. [28]	US	NHANES	1988–2006	≥ 45 year	8608	NA	All causes CVD	Sex, race, total cholesterol, low-density lipoprotein levels, and high density lipoprotein levels	9
Nordestgaard et al. [30]	Denmark	Copenhagen General Population Study	1977–2014 (6 year)	42–72 year	95,366	5422	All causes CVD	Age, sex, income, systolic blood pressure, plasma triglycerides, LDL cholesterol, HDL cholesterol, BMI, diabetes, smoking status, cumulated smoking in pack-years, time since smoking cessation in former smokers, alcohol intake, physical inactivity, use of antihypertensive medication, use of lipid-lowering medication and hormone replacement therapy in post-menopausal women	11
Park et al. [33]	US	Multiethnic Cohort	1993–2012 (16.2 year)	45–75 year	185,855	58,397	All causes CVD Cancer Respiratory disease Diabetes	Age at cohort entry, sex, ethnicity, the effects of smoking: smoking status; average number of cigarettes; squared average number of cigarettes; number of years smoking (time-dependent); number of years since quitting (time-dependent); and interactions between ethnicity and smoking status, average number of cigarettes, squared average number of cigarettes, and number of years smoking, BMI, education, physical activity, alcohol consumption, total energy intake, energy from fat, and preexisting illness	10

Table 1 (continued)

References	Country	Cohort name	Follow-up year	Age at baseline	Study size		Cause of death	Adjustment for covariates	NOS score
					Participants	No. of death			
Gunter et al. [13]	Europe	European Prospective Investigation into Cancer and Nutrition	16.4 year	≥ 35 year	130,662 M 321,081 F	18,302 M 23,391 F	All causes CVD Cancer Respiratory disease	Age, energy intake, center, BMI, physical activity, smoking status and intensity, smoking duration, education, menopausal status, ever-use of contraceptive pill or menopausal hormone therapy, alcohol consumption, red and processed meat, fruits and vegetables	12
Grosso et al. [12]	Eastern Europe	HAPIEE study	2002–2011 (6.1 year)	45–69 year	13,350 M 15,119 F	1435 M 686 F	All causes CVD Cancer	Age, sex, smoking status, BMI, educational level, physical activity, alcohol intake (> 12 g/d), hypertension, diabetes, hypercholesterolaemia, history of CVD or cancer, family history of CVD, family history of cancer, total energy intake, vitamin supplement use, SFA, PUFA and n-3 PUFA intake, menopausal status (in women)	10
Lim et al. [23]	Australia	Calcium Intake Fracture Outcome Study	2003–2013 (10 year)	≥ 70 year	1055 F	362 F	All causes CVD	Age, blood pressure, prevalent CVD, diabetes and estimated glomerular filtration rate	11
Sado et al. [41]	Japan	Three-Prefecture Cohort Study	15 year	40–79 year	39,685 M 43,124 F	3021 M 1635 F	Cancer	Age, sex, region, history of hypertension and diabetes mellitus, BMI, smoking status, alcohol drinking, type of job, consumption of rice, bread, meat, fish, egg, milk, green and yellow vegetables, non-green and non-yellow vegetables, fruit, miso soup, pickled vegetable, black tea, and green tea.	10

Table 1 (continued)

References	Country	Cohort name	Follow-up year	Age at baseline	Study size		Cause of death	Adjustment for covariates	NOS score
					Participants	No. of death			
Gapstur et al. [10]	US	Cancer Prevention Study-II	1982–2012	28–94 year	922,896	118,738	Cancer	Age, sex, smoking variables, race, marital status, education, alcohol consumption, BMI, physical activity, family history of cancer, red and processed meat/vegetable intake, current tea drinking	10
van den Brandt et al. [38]	Netherlands	Netherlands Cohort Study	1986–1996	55–69 year	120,852	8665	All causes CVD Cancer Respiratory disease	Age, cigarette smoking status, number of cigarettes smoked per day, and years of smoking, history of physician-diagnosed hypertension and diabetes, body height, BMI, non-occupational physical activity, highest level of education, intake of alcohol, nuts, vegetables and fruit, tea, energy, use of nutritional supplements, postmenopausal hormone replacement therapy (in women)	12
Loftfield et al. [43]	United Kingdom	UK Biobank Cohort study	7 year	38–73 year	498,134	14,225	All causes CVD Cancer Respiratory disease	Age, sex, smoking, race/ethnicity, alcohol drinking, general health status, education level, BMI, physical activity, tea intake	10
Torres-Collado et al. [42]	Spain	EUREYE-Spain study and the Valencia Nutrition Survey	12 year	≥ 65 year	903	403	All causes CVD Cancer	Age, sex, study, educational level, BMI, waist circumference, sleeping time, smoking habit, self-reported diabetes, high cholesterol, hypertension, relative Mediterranean Diet, main physical activity, leisure time	12

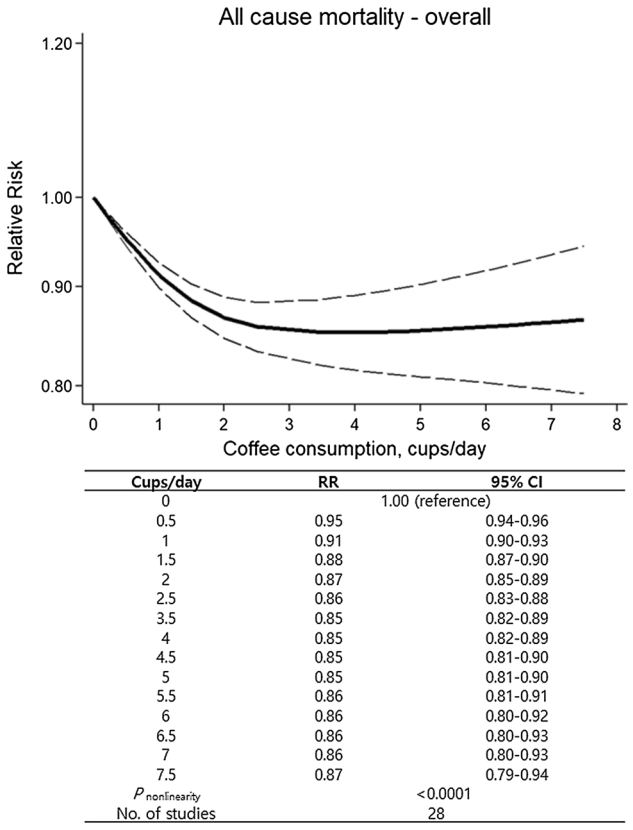
Table 1 (continued)

References	Country	Cohort name	Follow-up year	Age at baseline	Study size		Cause of death	Adjustment for covariates	NOS score
					Participants	No. of death			
Navarro et al. [45]	Spain	Seguimiento Universidad de Navarra—University of Navarra Follow-Up	10 year	38 ± 10 year	19,888	337	All causes CVD Cancer Non-CVD, non-cancer causes	Age, sex, alcohol consumption, years of attained university education, marital status, smoking, BMI, total energy intake, adherence to the Mediterranean diet, between-meal snacking and following special diets, leisure-time physical activity, television watching (hours), baseline hypertension, diabetes, and high blood cholesterol, previous history of cancer, cardiovascular disease, and depression	12
Sado et al. [44]	Japan	Three-Prefecture Cohort Study	15 year	40–79 year	39,685 M 43,124 F	7955 M 5725 F	All causes CVD	Age group, prefecture, area, history of hypertension, history of diabetes mellitus, stroke, heart disease, BMI, smoking status, alcohol drinking, type of job, type of insurance, consumption of rice, bread, meat, fish, egg, milk, green and yellow vegetable, non-green and non-yellow vegetable, fruit, miso soup, pickled vegetable, black tea, and green tea	10

BMI body mass index, *CVD* cardiovascular disease, *F* female, *HAPIEE* Health, Alcohol and Psychosocial factors In Eastern Europe, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *M* male, *NHANNES* National Health and Nutrition Examination Survey, *PUFA* poly unsaturated fatty acid, *SFA* saturated fatty acid

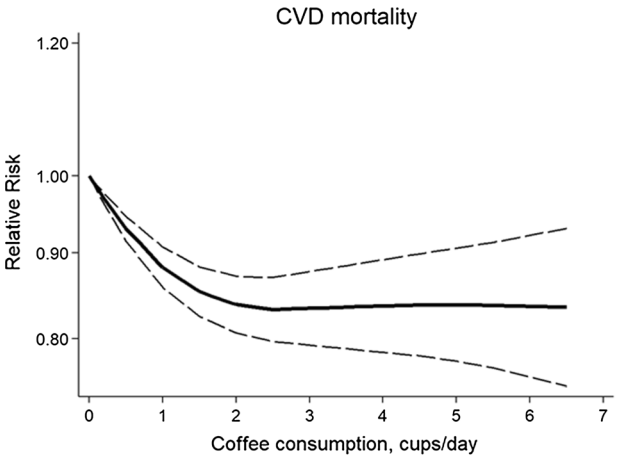
Table 2 Summary of pooled relative risks (RR) of all cause-and cause-specific mortality for coffee consumption

	No. of studies	RR	95% CI	Heterogeneity	
				I^2	*P* value
All-cause mortality					
High versus low	35	0.88	0.84–0.92	76.6	< 0.001
Per 1 cup/day	30	0.97	0.96–0.98	83.3	< 0.001
CVD mortality					
High versus low	29	0.87	0.82–0.94	49.5	0.001
Per 1 cup/day	24	0.96	0.95–0.97	59.8	< 0.001
Cancer mortality					
High versus low	23	0.99	0.94–1.04	57.9	< 0.001
Per 1 cup/day	20	0.99	0.99–1.00	70.5	< 0.001
Respiratory disease mortality					
High versus low	9	0.90	0.75–1.07	75.6	< 0.001
Per 1 cup/day	8	0.95	0.92–0.98	75.9	0.001
Diabetes mortality					
High versus low	4	0.76	0.65–0.90	0.0	0.59
Per 1 cup/day	3	0.91	0.88–0.95	27.4	0.25
Non-CVD, non-cancer causes mortality					
High versus low	5	0.65	0.51–0.83	52.1	0.08
Per 1 cup/day	5	0.93	0.91–0.96	5.9	0.38



Cups/day	RR	95% CI
0	1.00 (reference)	
0.5	0.95	0.94-0.96
1	0.91	0.90-0.93
1.5	0.88	0.87-0.90
2	0.87	0.85-0.89
2.5	0.86	0.83-0.88
3.5	0.85	0.82-0.89
4	0.85	0.82-0.89
4.5	0.85	0.81-0.90
5	0.85	0.81-0.90
5.5	0.86	0.81-0.91
6	0.86	0.80-0.92
6.5	0.86	0.80-0.93
7	0.86	0.80-0.93
7.5	0.87	0.79-0.94
$P_{nonlinearity}$	<0.0001	
No. of studies	28	

Fig. 2 Pooled dose-response association between coffee consumption and all-cause mortality. Solid lines represent relative risk (RR), dashed lines represent 95% confidence intervals

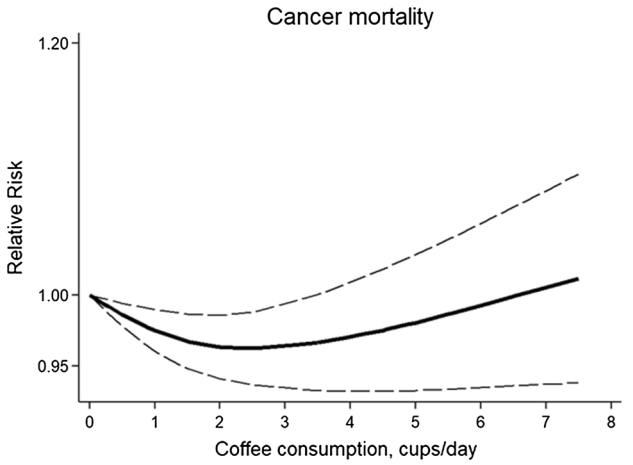


Cups/day	RR	95% CI
0	1.00 (reference)	
0.5	0.93	0.91-0.95
1	0.88	0.86-0.91
1.5	0.85	0.82-0.88
2	0.84	0.81-0.87
2.5	0.83	0.80-0.87
3.5	0.84	0.79-0.88
4.5	0.84	0.78-0.90
5	0.84	0.78-0.91
5.5	0.84	0.77-0.91
6.5	0.84	0.75-0.93
$P_{nonlinearity}$	<0.0001	
No. of studies	21	

Fig. 3 Pooled dose-response association between coffee consumption and CVD mortality. Solid lines represent relative risk (RR), dashed lines represent 95% confidence intervals

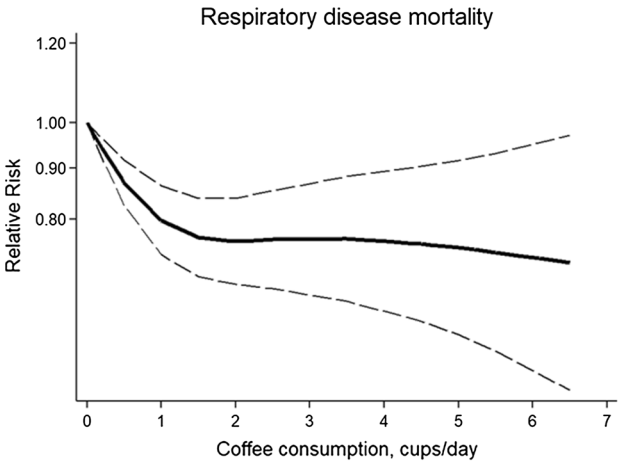
(RR = 0.85, 95% CI 0.80–0.90) showed a suggestively stronger inverse association than those from smokers (RR = 0.88, 95% CI 0.81–0.96) (*P* for non-smokers vs. smokers = 0.42). There was some evidence of difference in RRs by geographic region. A significant inverse association was observed among studies in Europe (RR = 0.81, 95% CI 0.74–0.88) and Asia (RR = 0.83, 95% CI 0.76–0.91), while a non-significant inverse association was shown among studies in the US (RR = 0.96, 95% CI 0.89–1.03). No significant differences were found by baseline age, overweight status, sex, and caffeine content of coffee (*P* for difference > 0.6 in all comparisons).

The stratified dose–response meta-analysis by age showed similar results for younger people (< 60 years) (RR = 0.96, 95% CI 0.94–0.98) and older people (≥ 60 years) (RR = 0.96, 95% CI 0.95–0.97) for 1 cup/day increment of coffee consumption (Table 3). However, we found evidence of a non-linear association in both younger people (*P* for non-linearity < 0.001) and older people (*P* for non-linearity = 0.003) (Fig. 8). The pooled RR showed the greatest reduction at consumption of 6.5 cups/day in younger people (RR = 0.78, 95% CI 0.75–0.82) and 4.5 cups/day in older people (RR = 0.85, 95% CI 0.80–0.91), compared with no coffee consumption. The inverse association was slightly stronger in younger people (RR = 0.80, 95% CI 0.77–0.82) than older



Cups/day	RR	95% CI
0	1.00 (reference)	
0.5	0.99	0.98-0.99
1	0.97	0.96-0.99
1.5	0.97	0.95-0.99
2	0.96	0.94-0.99
2.5	0.96	0.94-0.99
3.5	0.97	0.93-1.00
4.5	0.98	0.93-1.02
5	0.98	0.93-1.03
5.5	0.99	0.93-1.04
6.5	1.00	0.94-1.07
7.5	1.01	0.94-1.09
$P_{nonlinearity}$	<0.0001	
No. of studies	17	

Fig. 4 Pooled dose-response association between coffee consumption and cancer mortality. Solid lines represent relative risk (RR), dashed lines represent 95% confidence intervals



Cups/day	RR	95% CI
0	1.00 (reference)	
0.5	0.87	0.83-0.92
1	0.80	0.74-0.86
1.5	0.77	0.70-0.84
2	0.76	0.69-0.84
2.5	0.76	0.68-0.85
3.5	0.76	0.66-0.88
4.5	0.76	0.63-0.90
5	0.75	0.61-0.92
5.5	0.74	0.59-0.93
6.5	0.72	0.54-0.97
$P_{nonlinearity}$	<0.0001	
No. of studies	7	

Fig. 5 Pooled dose-response association between coffee consumption and respiratory disease mortality. Solid lines represent relative risk (RR), dashed lines represent 95% confidence intervals

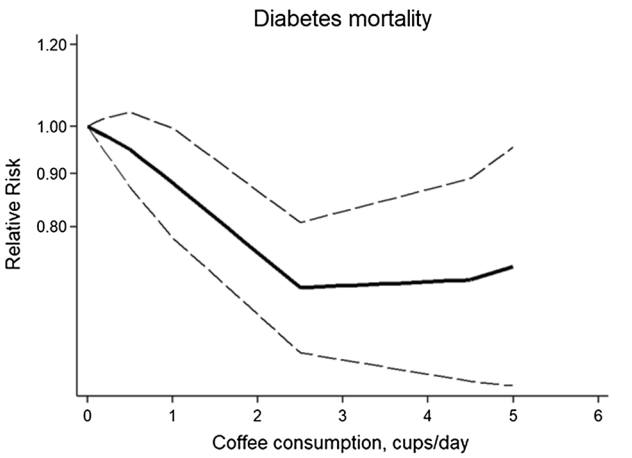
people (RR = 0.86, 95% CI 0.82–0.91) at consumption of 3.5 cups/day. By smoking status, the inverse association was slightly stronger in non-smokers than smokers (P for non-smokers vs. smokers = 0.33) (Table 3).

Publication bias

There was no evidence of publication bias with Begg's test for mortality from all-causes ($P = 0.31$), CVD ($P = 0.39$), and cancer ($P = 0.32$), and Egger's test for mortality from all-causes ($P = 0.25$), CVD ($P = 0.75$), and cancer ($P = 0.14$). In addition, we found no indication of publication bias for mortality from other deaths (Begg's $P > 0.4$ and Egger's $P > 0.2$ for the all analyses).

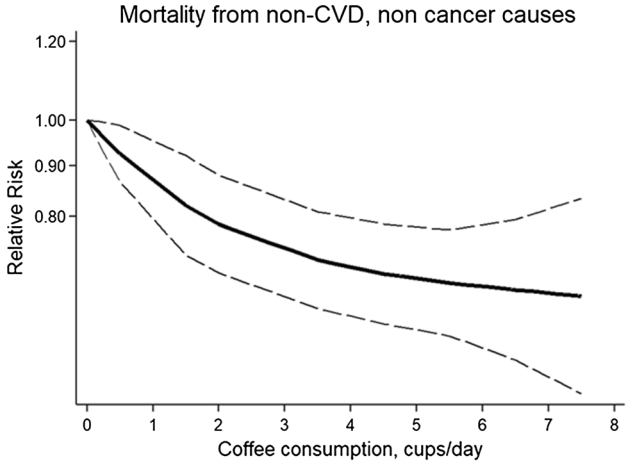
Discussion

Findings from our meta-analysis of 40 prospective cohort studies indicate lower mortality from all-causes (12% lower risk) and CVD (13% lower risk) in the comparison of highest versus lowest coffee consumption categories, which was similar by categories of age, sex, overweight status, alcohol drinking, smoking status, and by caffeine content of coffee.



Cups/day	RR	95% CI
0	1.00 (reference)	
0.5	0.95	0.87-1.03
1	0.88	0.78-1.00
2.5	0.70	0.60-0.81
4.5	0.71	0.57-0.89
5	0.73	0.56-0.95
$P_{nonlinearity}$	0.006	
No. of studies	3	

Fig. 6 Pooled dose-response association between coffee consumption and diabetes mortality. Solid lines represent relative risk (RR), dashed lines represent 95% confidence intervals



Cups/day	RR	95% CI
0	1.00 (reference)	
0.5	0.93	0.87-0.99
1.5	0.82	0.73-0.92
2	0.79	0.70-0.88
3.5	0.72	0.65-0.81
4.5	0.70	0.62-0.79
5.5	0.69	0.61-0.78
6.5	0.67	0.57-0.79
7.5	0.66	0.53-0.83
$P_{nonlinearity}$	0.054	
No. of studies	4	

Fig. 7 Pooled dose-response association between coffee consumption and mortality from non-CVD, noncancer causes. Solid lines represent relative risk (RR), dashed lines represent 95% confidence intervals

Table 3 Summary of pooled relative risks (RR) of all-cause mortality for coffee consumption

	No. of studies	RR	95% CI	P for difference
High versus low analysis				
Baseline age				
< 60 years	17	0.85	0.77–0.95	0.89
≥ 60 years	10	0.87	0.79–0.96	
BMI				
< 25 kg/m^2	7	0.90	0.82–0.99	0.66
≥ 25 kg/m^2	7	0.88	0.83–0.93	
Alcohol consumption				
Low	4	0.87	0.79–0.95	0.46
High	4	0.80	0.71–0.91	
Smoking status				
Non-smoker	14	0.85	0.80–0.90	0.42
Smoker	14	0.88	0.81–0.96	
Sex				
Male	18	0.87	0.81–0.94	0.86
Female	18	0.88	0.83–0.93	
Geographic region				
US	14	0.96	0.89–1.03	
Europe	15	0.81	0.74–0.88	0.01[a]
Asia	6	0.83	0.76–0.91	0.05[b]
By caffeine content of coffee				
Decaffeinated	11	0.89	0.85–0.93	0.75
Caffeinated	8	0.90	0.82–0.99	
Dose–response analysis (per 1 cup/day)				
Baseline age				
< 60 years	10	0.96	0.94–0.98	0.92
≥ 60 years	7	0.96	0.95–0.97	
Smoking status				
Non-smoker	8	0.95	0.93–0.97	0.33
Smoker	8	0.97	0.96–0.99	

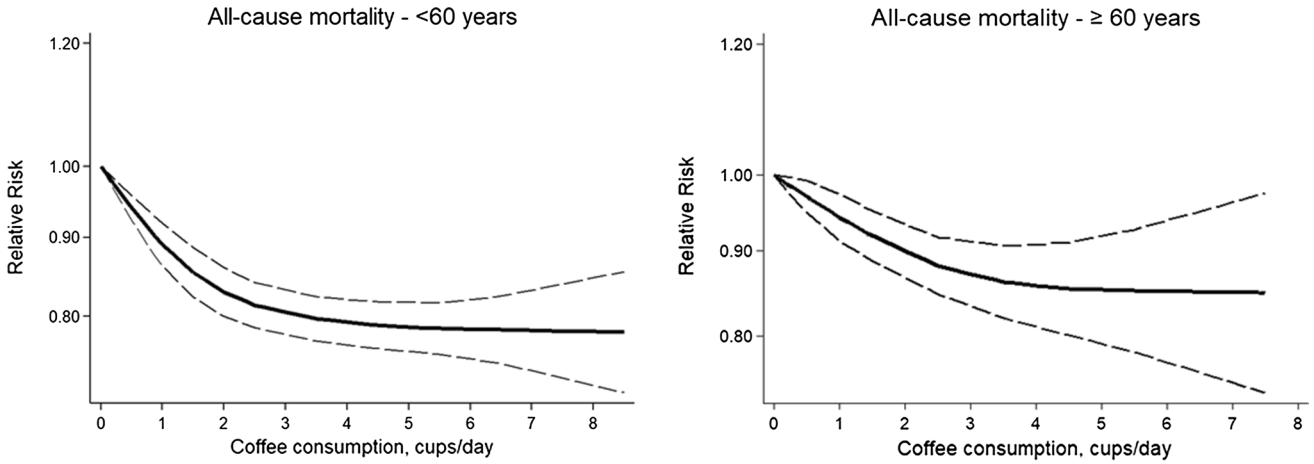
[a] *P* value difference in RR for studies conducted in Europe versus the US

[b] *P* value difference in RR for studies conducted in Asia versus the US

Further dose–response analyses showed nonlinear associations of coffee consumption and all-cause and CVD mortality. The strongest association was observed in 3.5 cups/day of coffee consumption for all-cause mortality (15% lower risk) and 2.5 cups/day of coffee consumption for CVD mortality (17% lower risk), compared with no consumption. Regarding cancer mortality, a non-linear association with the lowest risk in 2–2.5 cups/day of coffee consumption (4% lower risk) was observed, compared with no consumption. We found 24% and 35% lower risks of mortality from diabetes and non-CVD, non-cancer causes in the comparison of highest versus lowest coffee consumption categories. The non-linear relationships were found for mortality from respiratory disease and diabetes, and a linear relationship was found for mortality from non-CVD, non-cancer causes.

The results of the present meta-analysis were consistent with previous results [61] in that the largest decrease in RR of mortality from all causes and CVD was observed at moderate coffee consumption of 2–4 cups/day. However, the results of analysis for cancer mortality differed from those of previous meta-analyses, which reported no significant association between coffee drinking and cancer mortality [61] or found a significant inverse association only in non-smokers [50]. In contrast, we included more studies and found a significant non-linear relationship between coffee consumption and cancer mortality. The strongest inverse association was shown at coffee consumption of 2–2.5 cups/day, but an association was not apparent at higher coffee consumption. One reason why the lower risk disappeared with higher intake could be residual cofounding by smoking because smoking is a very strong risk factor for cancer and is correlated with coffee drinking.

We found some evidence of differences by age in the non-linear dose–response analysis, though not in the analysis of highest versus lowest coffee consumption. Younger people (< 60 years) showed a lower risk (20%) of all-cause mortality than older people (≥ 60 years) (14%) at coffee consumption of 3.5 cups/day. The stronger inverse association between coffee drinking and all-cause mortality in younger



Cups/day	RR	95% CI
0	1.00 (reference)	
0.5	0.94	0.92-0.96
1	0.89	0.86-0.92
1.5	0.85	0.82-0.89
2	0.83	0.80-0.86
2.5	0.81	0.79-0.84
3.5	0.80	0.77-0.82
4.5	0.79	0.76-0.82
5.5	0.79	0.76-0.82
6.5	0.78	0.75-0.82
8.5	0.78	0.71-0.86
$P_{nonlinearity}$	<0.001	
No. of studies	7	

Cups/day	RR	95% CI
0	1.00 (reference)	
1	0.94	0.91-0.97
1.5	0.92	0.88-0.95
2.5	0.88	0.85-0.92
3.5	0.86	0.82-0.91
4.5	0.85	0.80-0.91
5.5	0.85	0.78-0.93
7.5	0.85	0.74-0.98
$P_{nonlinearity}$	0.003	
No. of studies	4	

Fig. 8 Pooled dose-response association between coffee consumption and all-cause mortality stratified by age. Solid lines represent relative risk (RR), dashed lines represent 95% confidence intervals

people than older people was also found in previous studies [8, 33]. Older people are more susceptible to the blood pressure-raising effect of caffeine compared to younger people [47], which may attenuate the inverse association. A stronger inverse association for CVD mortality was shown in younger people compared to older people. However, further study conducting an analysis by age is warranted due to small number of studies included in the analysis by age.

Previous meta-analyses investigating the association between coffee consumption and risk of chronic disease provided the results by some potential modifiers. A stronger inverse association was observed among non-smokers than smokers for type 2 diabetes [62] and CVD [63]. This is similar to our result showing slightly lower mortality in non-smokers. For the results by BMI, on the other hand, we observed a slightly lower risk of death in overweight people, but previous studies have reported higher risks of type 2 diabetes in overweight [62] or obese people [64]. Our results by caffeine content of coffee showed little difference in the risk of death. Unlike our results, some studies suggested lower risk of type 2 diabetes [62] and CVD [63] in people consuming caffeinated coffee than those drinking decaffeinated coffee.

We observed the presence of heterogeneity among the studies. When we excluded outlying studies, the observed heterogeneity reduced, but the inverse association between coffee consumption and risk of mortality did not substantially change. A potential source of heterogeneity may be related to geographic region. We found stronger inverse associations from studies performed in Europe and Asia than those performed in the US. The type of coffee powder, roasting, brewing methods, beverage preparation, sugar and cream added to coffee and cup sizes are different by geographic region and this may affect the association between coffee consumption and mortality. In addition, genetic variants may explain heterogeneities across the studies. The genotype such as cytochrome P-450 1A2 metabolizes caffeine, and thus, is associated with variability in effects of caffeine and coffee consumption [65]. Other possible reasons of heterogeneity could be different distributions of confounding factors and biological differences that Asians are more sensitive to insulin resistance than other races [66, 67].

In the current meta-analysis, we showed the results on mortality from specific causes such as respiratory disease, diabetes, and non-CVD, non-cancer causes. We observed inverse associations between coffee consumption and respiratory disease or diabetes-specific mortality, and these are consistent with the results from previous epidemiological studies examining the association between coffee consumption and disease. Recent review showed that coffee

consumption was associated with decreased prevalence of asthma and could be used as a treatment for persistent cough [68]. Regarding diabetes, a recent meta-analysis from 30 cohort studies found that high coffee consumption is associated with 29% lower risk of type 2 diabetes [69]. For mortality from non-CVD, non-cancer causes, we observed a strong inverse association, but, the results should be interpreted with caution because the number of studies included was relatively small. One study included in the analysis of non-CVD, non-cancer causes showed that suicide and respiratory disease were the major causes of other causes of death [26]. Recent studies reported that coffee intake was associated with lower risk of depression [70] and suicide [71] may be through increasing turnover of serotonin [71]. Also, as mentioned before, we found an inverse association between moderate coffee consumption and respiratory disease-specific mortality. The inverse association between coffee and depression or respiratory disease-specific mortality may have contributed to a strong inverse association between coffee consumption and mortality from non-CVD, non-cancer causes.

Although it is still unclear, several potential mechanisms could explain a beneficial effect of coffee consumption on health. Increased oxidative stress and prolonged inflammation may contribute to premature death by increasing the risk of chronic disease [72, 73]. Coffee contains various antioxidant components such as caffeine, chlorogenic acid, melanoidins, cafestol, kahweol, and trigonelline [74]. Previous experimental studies reported a significant increased level of serum antioxidant enzymes (i.e. glutathione peroxidase and glutathione-S-transferase) [75, 76] and decreased levels of lipid peroxidation [75] and oxidative DNA damage [77, 78] among the subjects who consumed coffee. Many human studies also have shown that coffee intake may be associated with the levels of pro-inflammatory biomarkers including tumor necrosis factor alpha, [79] C-reactive protein [80, 81], and interleukin 18 [82], and increase the levels of anti-inflammatory biomarkers such as adiponectin [81, 83]. These antioxidant and anti-inflammatory properties of coffee compounds may lead to a decreased risk of mortality through slowing the development of some major chronic diseases including diabetes, CVD, and cancers.

There are several strengths in the current meta-analysis. To the best of our knowledge, this is the first meta-analysis to examine the association between coffee drinking and mortality using both high versus low analyses and linear and non-linear dose–response analyses. Compared to previous meta-analyses [50, 51, 84] we added recent studies increasing the number of subjects [10, 13, 23, 28, 30, 38, 41–45]. Due to the large number of studies, we could investigate the association of coffee intake on all-cause mortality in various subpopulations by age, sex, geographic region, overweight status, alcohol consumption, and smoking status. Unlike previous meta-analyses, we performed meta-analyses of coffee consumption and mortality from less common causes, including respiratory disease, diabetes, and non-CVD, non-cancer causes besides all-cause, CVD, and cancer mortality.

The present meta-analysis has several limitations. First, because of the observational design of the included studies, unmeasured or residual confounding is possible. However, most of the studies included in meta-analysis provided estimates that adjusted for various mortality risk factors, and results were observed in stratified meta-analyses by major potential confounders. Second, misclassification of actual coffee amounts consumed might occur because coffee consumption was assessed by self-reported questionnaires and the size of coffee cup varied. However, any misclassification in coffee intake categories is likely to be non-differential and would have probably led to dilute the association rather than to strengthen it, pushing estimates towards the null value in the high versus low analysis. Third, the highest categories of coffee consumption differed across the studies. However, we examined the dose–response relation between coffee consumption and risk of mortality by conducting linear and non-linear dose–response analyses as well as high versus low analysis. Lastly, the quality assessment indicates high qualities of included studies, but most of studies did not provide the details for type of coffee, brewing methods, or preparation which could help to understand the potential effect of coffee intake on risk of mortality.

In conclusion, our findings provide further evidence for a beneficial effect of moderate coffee consumption (e.g. 2–4 cups/day) on the risk of mortality from respiratory disease, diabetes, and all non-CVD, non-cancer causes as well as mortality from all causes, CVD, and cancer. The inverse association between coffee drinking and all-cause mortality was consistent in various subpopulations by overweight status, alcohol consumption, smoking status and by caffeine content of coffee. Future large prospective studies with detailed information of coffee preparation, sugar and cream added to coffee, or genotype of population could provide more definitive conclusion on the potential effects of coffee intake on risk of mortality.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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