



Systematic Reviews and Meta- and Pooled Analyses

Coffee Consumption and Mortality From All Causes, Cardiovascular Disease, and Cancer: A Dose-Response Meta-Analysis

Alessio Crippa*, Andrea Discacciati, Susanna C. Larsson, Alicja Wolk, and Nicola Orsini

* Correspondence to Alessio Crippa, Institute of Environmental Medicine, Karolinska Institutet, Box 210, SE-171 77 Stockholm, Sweden (e-mail: alessio.crippa@ki.se).

Initially submitted March 11, 2014; accepted for publication July 1, 2014.

Several studies have analyzed the relationship between coffee consumption and mortality, but the shape of the association remains unclear. We conducted a dose-response meta-analysis of prospective studies to examine the dose-response associations between coffee consumption and mortality from all causes, cardiovascular disease (CVD), and all cancers. Pertinent studies, published between 1966 and 2013, were identified by searching PubMed and by reviewing the reference lists of the selected articles. Prospective studies in which investigators reported relative risks of mortality from all causes, CVD, and all cancers for 3 or more categories of coffee consumption were eligible. Results from individual studies were pooled using a random-effects model. Twenty-one prospective studies, with 121,915 deaths and 997,464 participants, met the inclusion criteria. There was strong evidence of nonlinear associations between coffee consumption and mortality for all causes and CVD (P for nonlinearity < 0.001). The largest risk reductions were observed for 4 cups/day for all-cause mortality (16%, 95% confidence interval: 13, 18) and 3 cups/day for CVD mortality (21%, 95% confidence interval: 16, 26). Coffee consumption was not associated with cancer mortality. Findings from this meta-analysis indicate that coffee consumption is inversely associated with all-cause and CVD mortality.

all-cause mortality; cancer mortality; cardiovascular disease mortality; coffee; dose-response relationship; meta-analysis; prospective studies

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; *CYP1A2*, cytochrome P-450 1A2 gene.

Coffee is one of the most commonly consumed beverages around the world. Because of its popularity, even small health effects could have important public health consequences. Coffee has been considered potentially unhealthy, since caffeine intake has been positively associated with blood pressure (1), serum lipid concentration (2), cholesterol levels (3), and insulin resistance (4). Prospective studies, however, have generally not supported adverse health effects associated with coffee consumption. Besides caffeine, coffee contains several bioactive compounds with potentially beneficial properties, such as insulin-sensitizing (5) and antiinflammatory (6) effects.

Several quantitative reviews have indicated that coffee consumption may decrease the incidence of common chronic diseases, including type 2 diabetes (7), heart disease (8), and specific types of cancers (9). Only 2 meta-analyses have

examined the association between coffee and mortality, pooling relative risks for the highest category of coffee consumption versus the lowest (10, 11). A weak inverse association was found for all-cause mortality (10, 11), while an unclear association was found for cardiovascular disease (CVD) and no association was found for cancer mortality (10). A dose-response analysis uses all of the exposure-disease information, including intermediate categories, and is therefore more efficient than the highest-versus-lowest approach. In addition, it is less sensitive to the variability of exposure categories and more flexible in modeling the relationship under investigation. In particular, it provides a detailed description of the risk of death throughout the observed range of exposure, thus allowing identification of those values associated with the highest or lowest risk. Because the shapes of the associations remain uncertain, we conducted a dose-response meta-analysis of

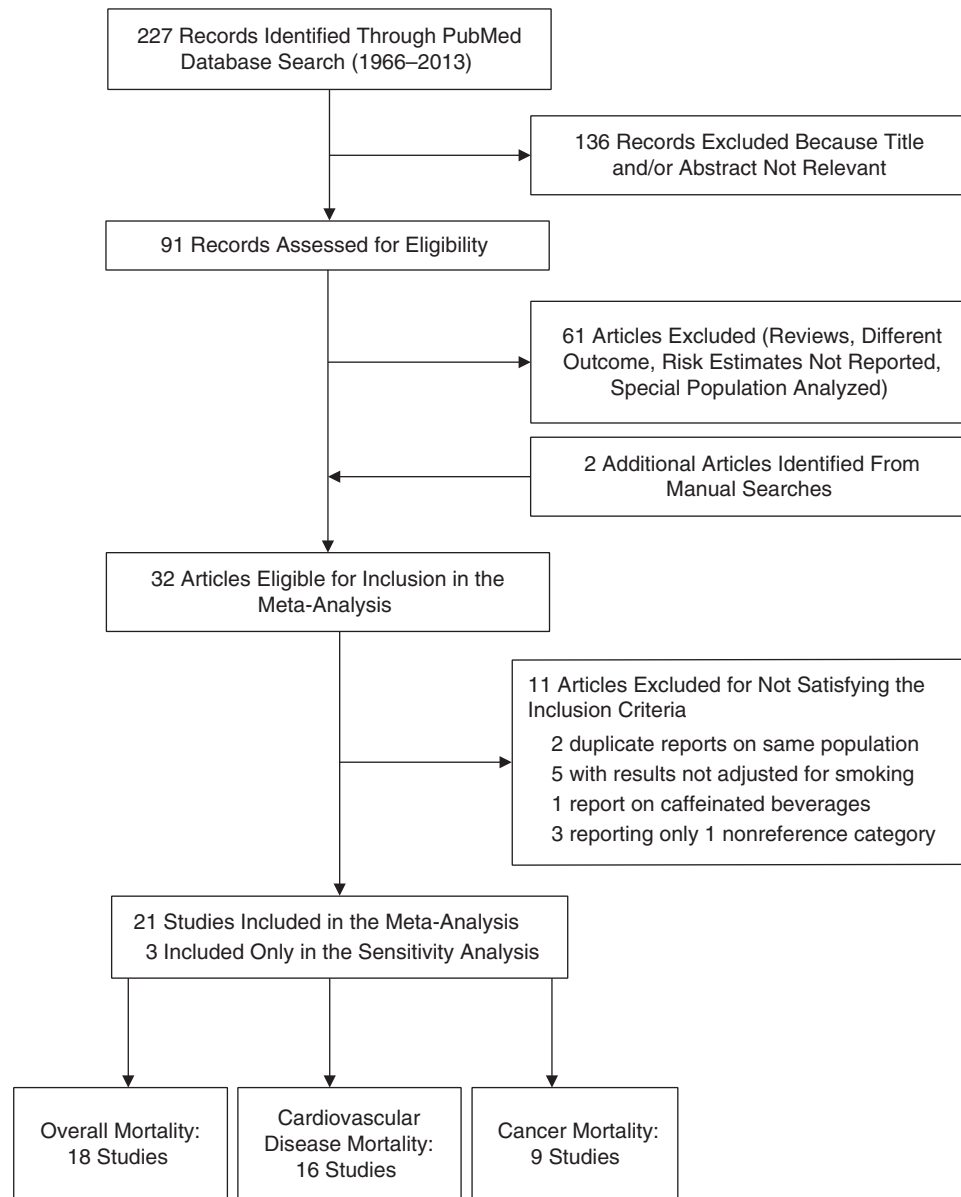


Figure 1. Selection of studies for inclusion in a meta-analysis of coffee consumption and mortality from all causes, cardiovascular disease, and all cancers, 1966–2013.

prospective studies on coffee and mortality to examine the exposure-disease associations between coffee consumption and mortality from all causes, CVD, and cancer.

METHODS

Literature search and selection

We performed a literature search in the PubMed database for articles published from January 1966 through December 2013, using the terms “(prospective or cohort) and (fatal or death or mortality) and (hot beverages or coffee or

caffeine).” The search was limited to studies carried out in humans. We followed the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines for conducting meta-analyses and reporting results (12). Two authors (A.C., A.D.) separately retrieved the studies reporting data on the association between coffee consumption and all-cause mortality, as well as associations for CVD and all-cancer mortality. Discrepancies were discussed and resolved.

Studies were eligible for inclusion in the meta-analysis if they met the following criteria: 1) the study had a prospective design; 2) the exposure of interest was coffee consumption; 3) the outcome was all-cause mortality, CVD mortality, and/

Table 1. Characteristics of Prospective Studies Included in a Meta-Analysis of Coffee Consumption and Mortality From All Causes, Cardiovascular Disease, and Cancer, 1966–2013

| First Author, Year (Reference No.) | Study Name | Country | No. of Cases | | | No. of Noncases | | | Years of Enrollment | Duration of Follow-up, years | Beverage Type | Cause of Death | Adjustment Variables |
|------------------------------------|--|--------------------------|--------------|-------|--------|-----------------|--------|---------|---------------------|------------------------------|-------------------------------|---|---|
| | | | Men | Women | Total | Men | Women | Total | | | | | |
| LeGrady, 1987 (23) | Chicago Western Electric Company Study | United States | 452 | | | 1,910 | | | 1959–1978 | 19 | Coffee | All causes; CHD; all other causes | Age, smoking, blood pressure, and cholesterol |
| Rosengren, 1991 (24) | Multifactor Primary Prevention Trial | Sweden | 478 | | | 6,765 | | | 1974/1977–1983 | 7.1 | Coffee | All causes; CHD; cancer; all other causes | Age, smoking, alcohol abuse, occupational class, BMI, physical activity, blood pressure, diabetes, family history of myocardial infarction, and mental stress |
| Klatsky, 1993 (25) | Northern California Kaiser Permanente Medical Care Program | United States | 2,695 | 1,806 | | | | 128,934 | 1978/1985–1988 | 8 | Coffee + decaffeinated coffee | All causes | Age, sex, race, smoking, alcohol, education, marital status, and BMI |
| Hart, 1997 (41) | | Scotland, United Kingdom | 625 | | | 5,766 | | | 1970/1973–1994 | 21 | Coffee | CHD | Age, smoking, social class, age upon leaving full-time education, BMI, diastolic blood pressure, cholesterol, angina, and electrocardiographic ischemia |
| Woodward, 1999 (26) | Scottish Heart Health Study | Scotland, United Kingdom | 372 | 201 | | 5,754 | 5,875 | | 1984/1987–1993 | 7.7 | Coffee | All causes; CHD | Age, smoking, cotinine, alcohol, housing tenure, BMI, physical activity, blood pressure, fibrinogen, cholesterol, high-density lipoprotein cholesterol, triglycerides, vitamin C, tea drinking, and Bortner score (57) |
| Kleemola, 2000 (27) | | Finland | 1,201 | 444 | | 10,075 | 10,387 | | 1972/1977–1982 | 10 | Coffee | All causes; CHD | Age, smoking, education, BMI, cholesterol, blood pressure, and history of acute myocardial infarction |
| Iwai, 2002 (28) | | Japan | 246 | 115 | | 1,404 | 1,451 | | 1989–1999 | 9.9 | Coffee | All causes; apoplexy; cancer | Age, education (age at final graduation), physical activity, and history of selected diseases |
| Jazbec, 2003 (29) | | Croatia | 568 | 382 | | 1,571 | 1,739 | | 1972–1999 | | Coffee | All causes; CVD | Age, residence, smoking, diastolic blood pressure, history of gastric/duodenal ulcer, and feeling of well-being |
| Andersen, 2006 (30) | Iowa Women's Health Study | United States | | 4,265 | | | 27,312 | | 1986–2001 | 15 | Coffee; decaffeinated coffee | All causes; CVD; cancer; all other causes | Age; smoking; alcohol; education; BMI; waist:hip ratio; physical activity; intake of whole grain, refined grain, red meat, fish and seafood, fruit, vegetables, and energy; use of estrogens; and use of multivitamin supplements |
| Paganini-Hill, 2007 (31) | Leisure World Cohort Study | United States | | | 11,386 | 4,980 | 8,644 | | 1981–2004 | 23 | Coffee; decaffeinated coffee | All causes | Age, sex, smoking, alcohol, BMI, physical activity, hypertension, diabetes, and history of angina, heart attack, stroke, rheumatoid arthritis, and cancer |

Table continues

Table 1. Continued

| First Author, Year (Reference No.) | Study Name | Country | No. of Cases | | | No. of Noncases | | | Years of Enrollment | Duration of Follow-up, years | Beverage Type | Cause of Death | Adjustment Variables |
|--|---|--------------------|--------------|--------|-------|-----------------|--------|-------|------------------------------------|------------------------------------|---|---|---|
| | | | Men | Women | Total | Men | Women | Total | | | | | |
| Lopez-Garcia, 2008 (32) | Nurses' Health Study; Health Professionals Follow-up Study | United States | 6,888 | 11,095 | | 41,736 | 86,214 | | HPFS: 1986–2004; NHS: 1980–2004 | HPFS: 18; NHS: 24 | Caffeinated coffee; decaffeinated coffee | All causes; CVD; cancer; all other causes | Age; smoking; alcohol; BMI; physical activity; intake of n-3, polyunsaturated, saturated, and <i>trans</i> -fats, folic acid, and total energy; glycemic load; use of multivitamin and vitamin E supplements; and family history of myocardial infarction. For women, also menopausal status and hormone replacement therapy. |
| Happonen, 2008 (33) | | Finland | 251 | 372 | | 311 | 506 | | 1991/1992–2005 | 14.5 | Coffee | All causes; cancer; CVD; all other causes | Age, sex, calendar year, smoking, education, previous occupation, marital status, BMI, diabetes, history of acute myocardial infarction, physical disability, cognitive impairment, and self-rated health |
| Ahmed, 2009 (34) | Cohort of Swedish Men | Sweden | | | | 37,315 | | | 1998–2006 | 9 | Coffee | All causes | Age, smoking, alcohol, education, marital status, BMI, physical activity, tea drinking, fat intake, sodium intake, cholesterol, aspirin, and family history of myocardial infarction |
| de Koning Gans, 2010 (35) | EPIC-NL (Prospect-EPIC and MORGEN-EPIC cohorts) | The Netherlands | | | 1,405 | | | | 1993/1997–2006 | 13 | Coffee | All causes; CHD; stroke | Age; sex; study cohort; smoking; alcohol; education; waist circumference; physical activity; intake of tea, saturated fat, fiber, vitamin C, total fluids, and total energy; hypertension; diabetes; and hypercholesterolemia. For women, also menopausal status and hormone replacement therapy. |
| Sugiyama, 2010 (36) | Miyagi Cohort Study | Japan | 1,647 | 807 | | 18,287 | 19,455 | | 1990–2001 | 10.3 | Coffee | All causes; CVD; CHD; stroke; all other causes | Age; sex; smoking; alcohol; education; BMI; walking time; intake of green tea, oolong tea, black tea, rice, miso soup, meat, dairy products, fish, vegetables, fruits, and energy; hypertension; and diabetes |
| Leurs, 2010 (42) | Netherlands Cohort Study | The Netherlands | 1,669 | 828 | | 58,279 | 62,573 | | 1986–1996 | 10 | Coffee | Ischemic heart disease; stroke | Age, smoking and number of cigarettes smoked per day, and total energy intake |
| Tamakoshi, 2011 (37) | Japan Collaborative Cohort Study for Evaluation of Cancer Risk | Japan | 11,178 | 8,354 | | 40,672 | 57,081 | | 1988/1990–2006 | 16 | Coffee | All causes; cancer | Age; smoking; alcohol; education; marital status; BMI; daily walking; intake of green leafy vegetables and green tea; sleep length; stress; and history of cancer, myocardial infarction, and stroke |

Table continues

Table 1. Continued

| First Author, Year (Reference No.) | Study Name | Country | No. of Cases | | | No. of Noncases | | | Years of Enrollment | Duration of Follow-up, years | Beverage Type | Cause of Death | Adjustment Variables |
|--|---|---------------|--------------|--------|-------|-----------------|---------|-------|---------------------|------------------------------------|---|---|---|
| | | | Men | Women | Total | Men | Women | Total | | | | | |
| Mineharu, 2011 (43) | Japan Collaborative Cohort Study for Evaluation of Cancer Risk | Japan | 1,681 | 1,436 | | 34,345 | 48,310 | | 1988–2003 | 13.1 | Coffee | CVD; CHD; stroke | Age; smoking; alcohol; education; BMI; walking hours; sports participation; intake of fruit, vegetables, beans, meat, fish, seaweed, and energy; multivitamin and vitamin E supplement use; hypertension; diabetes; and mental stress |
| Freedman, 2012 (38) | NIH-AARP Diet and Health Study | United States | 33,731 | 18,784 | | 229,119 | 173,141 | | 1995–2008 | 13.6 | Coffee | All causes; cancer; heart disease; stroke | Age; race; smoking; alcohol; education; marital status; BMI; physical activity; intake of fruits, vegetables, meat, saturated fats, and total energy; use of vitamin supplements; health status; and diabetes. For cancers, also family history of cancer. For women, also hormone replacement therapy. |
| Liu, 2013 (39) | Aerobics Center Longitudinal Study | United States | 2,198 | 314 | | 33,900 | 9,827 | | 1971–2002 | 17 | Coffee | 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, parental history of CVD, and cardiorespiratory fitness |
| Gardener, 2013 (40) | Northern Manhattan Study | United States | | | 863 | | | 2,461 | 1993–2001 | 11 | Caffeinated coffee; decaffeinated coffee | | Age, sex, race/ethnicity, education, demographic factors, smoking, behavioral risk factors, diet, BMI, previous cardiac disease, diabetes, hypertension, and hypercholesterolemia |

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; EPIC, European Prospective Investigation into Cancer and Nutrition; EPIC-NL, EPIC Netherlands; HPFS, Health Professionals Follow-up Study; MORGEN, Monitoring Project on Risk Factors for Chronic Diseases; NHS, Nurses' Health Study; NIH, National Institutes of Health.

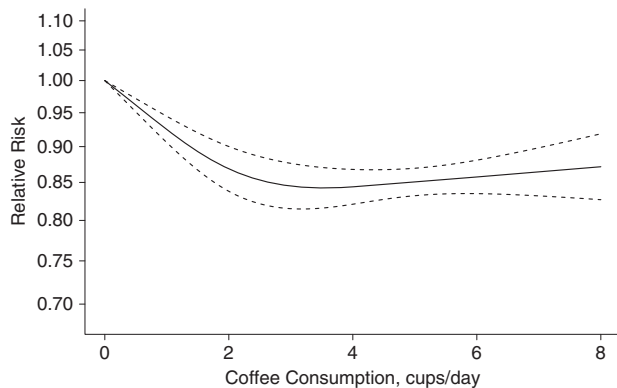


Figure 2. Pooled dose-response association between coffee consumption and all-cause mortality (solid line) in a meta-analysis, 1966–2013. Coffee consumption was modeled with restricted cubic splines in a multivariate random-effects dose-response model. The relative risks are plotted on the log scale. Dashed lines represent the 95% confidence intervals for the spline model. No coffee consumption (0 cups/day) served as the referent group.

or all-cancer mortality; 4) the investigators reported relative risks with 95% confidence intervals for 3 or more quantitative categories of coffee consumption; and 5) the reported relative risks had been adjusted at least for smoking status.

Data extraction

The following information was extracted from each study: first author's surname, publication year, study location, study period, duration of follow-up (years), sex, number of subjects (total number of deaths and total cohort size *or* total number of deaths and person-years of follow-up), mortality outcomes, coffee consumption categories, type of coffee, covariates adjusted for in the multivariable analysis, and relative risks (with their 95% confidence intervals) for all categories of coffee consumption. We extracted the relative risks that reflected the greatest degree of adjustment for potentially confounding variables. If investigators reported the adjusted relative risks but not the corresponding confidence intervals, we calculated the confidence intervals for the crude relative risks and related them to the adjusted relative risks. For studies that presented data separately on both coronary heart disease and stroke, we combined the results as indicated by Hamling et al. (13).

For each study, the median or mean coffee consumption within each exposure interval was assigned the corresponding relative risk. When median or mean consumption per category was not reported, we assigned the midpoint of the upper and lower boundaries for each category as the average consumption. If the upper bound for the highest category was not provided, we assumed that the category had the same amplitude as the adjacent one.

Statistical analysis

We performed a 2-stage random-effects dose-response meta-analysis to examine a potential nonlinear relationship

between coffee consumption and 3 different outcomes: all-cause mortality, CVD mortality, and cancer mortality (14, 15). This was done by modeling coffee consumption using restricted cubic splines with 3 knots at fixed percentiles (25%, 50%, and 75%) of the distribution (15). In the first stage, a restricted cubic spline model with 2 spline transformations (3 knots minus 1) was fitted taking into account the correlation within each set of published relative risks (14, 15). In the second stage, we combined the 2 regression coefficients and the variance/covariance matrices that had been estimated within each study, using the multivariate extension of the method of moments in a multivariate random-effects meta-analysis (16). We calculated an overall *P* value by testing that the 2 regression coefficients were simultaneously equal to zero. We calculated a *P* value for nonlinearity by testing that the coefficient of the second spline was equal to zero (17).

We excluded from the main analysis those studies that did not report the number of subjects (total number of deaths and total cohort size *or* total number of deaths and person-years of follow-up) in order to avoid biases in the estimates for the variances (15). We considered the excluded studies in a sensitivity analysis.

We performed stratified analysis by study location, sex, type of smoking adjustment (smoking status, categories of cigarette smoking, or number of cigarettes smoked per day (continuous variable)), and alcohol adjustment. Statistical heterogeneity among studies was assessed using the χ^2 test and was defined as a *P* value less than 0.10. Statistical heterogeneity was further quantified through the multivariate generalization of the I^2 statistic (18). Low heterogeneity is defined by I^2 values less than 25%, while values greater than 75% are indicative of high heterogeneity. Publication bias was assessed with Egger's regression test (19). All statistical analyses were conducted with the *dosresmeta* (20) and *metafor* (21) packages in R (R Foundation for Statistical Computing, Vienna, Austria) (22). *P* values less than 0.05 were considered statistically significant.

RESULTS

Study characteristics

The search strategy identified 227 articles on humans, 136 of which were excluded after review of the title or abstract (Figure 1). Of the 91 publications selected, 61 were not included, for at least one of the following reasons: 1) the article did not report original results from the study (9 articles); 2) the article did not provide relative risks and corresponding confidence intervals (10 articles); 3) disease incidence and mortality were combined (18 articles); 4) the study analyzed subpopulations (e.g., persons with diabetes or hypertension) (8 articles); and 5) the study investigated relationships with specific types of cancer (22 articles). The reference lists of the remaining 30 articles were checked to obtain other pertinent publications, and 2 additional reports were identified. We further excluded 11 studies: 2 represented duplicate publication; 5 did not adjust for smoking; 1 considered only total caffeine intake; and 3 analyzed only 2 coffee consumption categories. The Web Appendix (available at <http://aje.oxfordjournals.org/>) details the reasons for exclusion of individual studies.

Table 2. Adjusted Relative Risk of All-Cause Mortality According to Coffee Consumption (Versus No Consumption) in Prospective Studies, by Study Location, Sex, Type of Smoking Adjustment, and Alcohol Use, 1966–2013

| | Coffee Consumption, cups/day | | | | | | | | | | | | | | | |
|--|------------------------------|------------|------|------------|------|------------|------|------------|------|------------|------|------------|------|------------|------|------------|
| | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | | 8 | |
| | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI |
| All studies (<i>n</i> = 15) | 0.92 | 0.91, 0.94 | 0.87 | 0.84, 0.90 | 0.85 | 0.82, 0.88 | 0.84 | 0.82, 0.87 | 0.85 | 0.83, 0.87 | 0.86 | 0.83, 0.88 | 0.86 | 0.83, 0.90 | 0.87 | 0.83, 0.92 |
| Inclusion of 3 excluded articles ^a (<i>n</i> = 18) | 0.91 | 0.88, 0.94 | 0.84 | 0.80, 0.89 | 0.82 | 0.78, 0.87 | 0.82 | 0.78, 0.86 | 0.84 | 0.80, 0.87 | 0.85 | 0.81, 0.89 | 0.86 | 0.81, 0.92 | 0.88 | 0.81, 0.95 |
| Study location | | | | | | | | | | | | | | | | |
| Europe (<i>n</i> = 6) | 0.90 | 0.86, 0.95 | 0.83 | 0.76, 0.91 | 0.79 | 0.71, 0.88 | 0.78 | 0.70, 0.86 | 0.78 | 0.71, 0.86 | 0.78 | 0.70, 0.86 | 0.77 | 0.70, 0.86 | 0.77 | 0.69, 0.87 |
| United States (<i>n</i> = 6) | 0.94 | 0.92, 0.96 | 0.89 | 0.85, 0.92 | 0.87 | 0.83, 0.91 | 0.86 | 0.83, 0.90 | 0.87 | 0.83, 0.91 | 0.87 | 0.83, 0.92 | 0.88 | 0.82, 0.93 | 0.88 | 0.82, 0.95 |
| Japan (<i>n</i> = 3) | 0.85 | 0.76, 0.94 | 0.75 | 0.64, 0.88 | 0.75 | 0.67, 0.85 | 0.82 | 0.75, 0.90 | 0.92 | 0.73, 1.14 | | | | | | |
| Sex | | | | | | | | | | | | | | | | |
| Men (<i>n</i> = 10) | 0.91 | 0.87, 0.95 | 0.85 | 0.79, 0.91 | 0.83 | 0.77, 0.89 | 0.83 | 0.79, 0.88 | 0.86 | 0.83, 0.89 | 0.88 | 0.84, 0.91 | 0.90 | 0.85, 0.96 | 0.92 | 0.84, 1.01 |
| Women (<i>n</i> = 8) | 0.91 | 0.89, 0.93 | 0.85 | 0.82, 0.88 | 0.82 | 0.79, 0.84 | 0.81 | 0.78, 0.83 | 0.81 | 0.76, 0.85 | 0.80 | 0.74, 0.88 | 0.80 | 0.71, 0.91 | 0.80 | 0.69, 0.94 |
| Both sexes (<i>n</i> = 4) | 0.96 | 0.93, 0.98 | 0.92 | 0.88, 0.96 | 0.90 | 0.86, 0.95 | 0.90 | 0.85, 0.95 | 0.90 | 0.84, 0.97 | 0.90 | 0.82, 1.00 | 0.91 | 0.80, 1.03 | 0.91 | 0.77, 1.06 |
| Type of smoking adjustment ^b | | | | | | | | | | | | | | | | |
| Status (<i>n</i> = 12) | 0.90 | 0.87, 0.94 | 0.83 | 0.77, 0.88 | 0.80 | 0.74, 0.86 | 0.80 | 0.74, 0.86 | 0.81 | 0.74, 0.87 | 0.81 | 0.74, 0.89 | 0.82 | 0.74, 0.92 | 0.83 | 0.73, 0.95 |
| Categories (<i>n</i> = 7) | 0.90 | 0.85, 0.96 | 0.83 | 0.74, 0.93 | 0.80 | 0.72, 0.89 | 0.80 | 0.75, 0.85 | 0.81 | 0.77, 0.85 | 0.82 | 0.75, 0.90 | 0.83 | 0.71, 0.97 | | |
| Continuous (<i>n</i> = 3) | 0.94 | 0.92, 0.96 | 0.90 | 0.86, 0.94 | 0.88 | 0.83, 0.93 | 0.87 | 0.82, 0.93 | 0.87 | 0.81, 0.94 | 0.87 | 0.80, 0.95 | 0.87 | 0.79, 0.96 | 0.87 | 0.78, 0.97 |
| Alcohol adjustment | | | | | | | | | | | | | | | | |
| No (<i>n</i> = 4) | 0.82 | 0.69, 0.97 | 0.70 | 0.52, 0.94 | 0.66 | 0.49, 0.89 | 0.68 | 0.54, 0.85 | 0.71 | 0.60, 0.84 | 0.74 | 0.61, 0.90 | 0.78 | 0.59, 1.02 | 0.81 | 0.56, 1.19 |
| Yes (<i>n</i> = 11) | 0.93 | 0.91, 0.94 | 0.87 | 0.84, 0.90 | 0.85 | 0.82, 0.88 | 0.84 | 0.81, 0.87 | 0.85 | 0.82, 0.88 | 0.85 | 0.82, 0.88 | 0.85 | 0.82, 0.89 | 0.86 | 0.82, 0.89 |

Abbreviations: CI, confidence interval; RR, relative risk.

^a Includes 3 studies that did not provide information about the number of subjects.^b Smoking status, category of cigarette smoking, or number of cigarettes smoked per day (continuous variable).

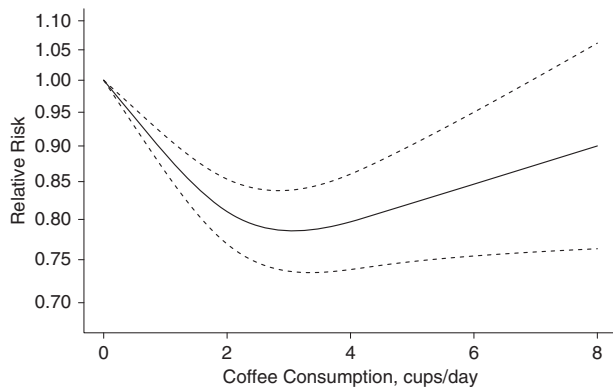


Figure 3. Pooled dose-response association between coffee consumption and cardiovascular disease mortality (solid line) in a meta-analysis, 1966–2013. Coffee consumption was modeled with restricted cubic splines in a multivariate random-effects dose-response model. The relative risks are plotted on the log scale. Dashed lines represent the 95% confidence intervals for the spline model. No coffee consumption (0 cups/day) served as the referent group.

Thus, the meta-analysis included 21 independent prospective studies, the main characteristics of which are described in Table 1. Eighteen studies provided estimates for all-cause mortality (23–40), 16 provided estimates for CVD mortality (23, 24, 26, 27, 29, 30, 32, 33, 35, 36, 38–43), and 9 provided estimates for all-cancer mortality (24, 28, 30, 32, 33, 36–38, 40). Three studies (23, 24, 26) did not provide confidence intervals for the adjusted relative risks but reported sufficient data to back-calculate them. Three studies (35, 38, 42) provided results for coronary heart disease and stroke mortality separately. Three studies (29, 39, 40) did not report information about the distribution of cases and noncases across exposure levels, and therefore they were included only in the sensitivity analysis.

Combined, these studies included 121,915 deaths and 997,464 study participants. Nine studies were conducted in Europe, 8 in the United States, and 4 in Japan (Table 1). One study considered only elderly people (33), while the remaining studies included persons from the general population. All of the studies but 5 included male and female participants, but only 11 reported sex-specific results. The included studies provided relative risk estimates adjusted for age (all 21 studies), body mass index (15 studies), alcohol consumption (14 studies), hypertension or blood pressure (11 studies), physical activity (11 studies), and history of diabetes (8 studies).

Association between coffee consumption and all-cause mortality

We found strong evidence of a nonlinear association between coffee consumption and all-cause mortality (overall $P < 0.001$; P for nonlinearity < 0.001) based on 15 studies (Figure 2). Compared with no coffee consumption, the pooled relative risks for all-cause mortality were 0.92 (95% confidence interval (CI): 0.91, 0.94) for 1 cup/day, 0.87 (95%

CI: 0.84, 0.90) for 2 cups/day, 0.85 (95% CI: 0.82, 0.88) for 3 cups/day, 0.84 (95% CI: 0.82, 0.87) for 4 cups/day, and 0.86 (95% CI: 0.83, 0.88) for 6 cups/day. There was between-study heterogeneity ($I^2 = 58.1\%$; $P < 0.001$). Egger's regression test provided no evidence of substantial publication bias ($P = 0.26$).

The associations were similar for men and women (P for heterogeneity = 0.19), although at high levels of coffee consumption the inverse association was more pronounced in women. Moreover, the associations were similar across strata of type of smoking adjustment (P for heterogeneity = 0.99) and alcohol adjustment (P for heterogeneity = 0.13). There was evidence of differences according to geographical region (P for heterogeneity < 0.001); in particular, the inverse relationship was slightly stronger among studies conducted in Europe than among those conducted in the United States. In the 3 studies conducted in Japan, the association was statistically significant only for moderate coffee consumption (< 4 cups/day) (Table 2).

Association between coffee consumption and CVD mortality

Similar to all-cause mortality, we found strong evidence of a nonlinear association between coffee consumption and CVD mortality (overall $P < 0.001$; P for nonlinearity < 0.001) based on 13 studies (Figure 3). Compared with no coffee consumption, the pooled relative risks of CVD mortality were 0.89 (95% CI: 0.86, 0.91) for 1 cup/day, 0.81 (95% CI: 0.77, 0.85) for 2 cups/day, 0.79 (95% CI: 0.74, 0.84) for 3 cups/day, 0.80 (95% CI: 0.74, 0.86) for 4 cups/day, and 0.85 (95% CI: 0.75, 0.95) for 6 cups/day. There was evidence of moderate between-study heterogeneity ($I^2 = 58.8\%$; $P < 0.001$). Egger's regression test provided no evidence of substantial publication bias ($P = 0.29$).

No relevant differences were found by sex (P for heterogeneity = 0.60) or alcohol adjustment (P for heterogeneity = 0.99) (Table 3). Differences were found for geographical region (P for heterogeneity < 0.001); in particular, studies conducted in Japan showed an inverse association only for low coffee consumption (2 cups/day), while studies conducted in Europe and the United States provided similar results. The associations differed across strata of type of smoking adjustment, with non-statistically significant results for studies that adjusted only for smoking status.

Association between coffee consumption and cancer mortality

Coffee consumption was not statistically significantly associated with cancer mortality (overall $P = 0.07$; P nonlinearity = 0.06) based on 8 studies (Figure 4). Compared with no coffee consumption, the pooled relative risks for total cancer mortality were 0.98 (95% CI: 0.96, 1.01) for 1 cup/day, 0.97 (95% CI: 0.93, 1.01) for 2 cups/day, 0.98 (95% CI: 0.93, 1.02) for 3 cups/day, 0.99 (95% CI: 0.95, 1.03) for 4 cups/day, and 1.03 (95% CI: 0.99, 1.08) for 6 cups/day. There was low between-study heterogeneity ($I^2 = 1\%$; $P = 0.45$). Egger's regression test provided no evidence of publication bias ($P = 0.52$).

Table 3. Adjusted Relative Risk of Cardiovascular Disease Mortality According to Coffee Consumption (Versus No Consumption) in Prospective Studies, by Study Location, Sex, Type of Smoking Adjustment, and Alcohol Use, 1966–2013

| | Coffee Consumption, cups/day | | | | | | | | | | | | | | | |
|--|------------------------------|------------|------|------------|------|------------|------|------------|------|------------|------|------------|------|------------|------|------------|
| | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | | 8 | |
| | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI |
| All studies (<i>n</i> = 13) | 0.89 | 0.86, 0.91 | 0.81 | 0.77, 0.85 | 0.79 | 0.74, 0.84 | 0.80 | 0.74, 0.86 | 0.82 | 0.75, 0.90 | 0.85 | 0.75, 0.95 | 0.87 | 0.76, 1.00 | 0.90 | 0.76, 1.06 |
| Inclusion of 3 excluded articles ^a (<i>n</i> = 16) | 0.88 | 0.83, 0.94 | 0.80 | 0.72, 0.90 | 0.78 | 0.69, 0.88 | 0.80 | 0.70, 0.90 | 0.83 | 0.73, 0.93 | 0.86 | 0.75, 0.98 | 0.89 | 0.77, 1.04 | 0.93 | 0.78, 1.10 |
| Study location | | | | | | | | | | | | | | | | |
| Europe (<i>n</i> = 7) | 0.89 | 0.83, 0.95 | 0.81 | 0.72, 0.92 | 0.78 | 0.68, 0.90 | 0.78 | 0.68, 0.91 | 0.80 | 0.68, 0.93 | 0.81 | 0.69, 0.97 | 0.83 | 0.68, 1.01 | 0.84 | 0.68, 1.05 |
| United States (<i>n</i> = 4) | 0.88 | 0.84, 0.91 | 0.79 | 0.73, 0.85 | 0.76 | 0.71, 0.81 | 0.76 | 0.72, 0.81 | 0.78 | 0.72, 0.85 | 0.81 | 0.72, 0.91 | 0.83 | 0.70, 0.97 | | |
| Japan (<i>n</i> = 2) | 0.82 | 0.72, 0.93 | 0.75 | 0.60, 0.94 | 0.91 | 0.62, 1.35 | 1.36 | 0.66, 2.80 | | | | | | | | |
| Sex | | | | | | | | | | | | | | | | |
| Men (<i>n</i> = 10) | 0.90 | 0.86, 0.94 | 0.83 | 0.76, 0.90 | 0.81 | 0.74, 0.90 | 0.83 | 0.75, 0.92 | 0.87 | 0.77, 0.98 | 0.90 | 0.78, 1.04 | 0.94 | 0.78, 1.12 | 0.98 | 0.79, 1.21 |
| Women (<i>n</i> = 8) | 0.88 | 0.84, 0.92 | 0.79 | 0.73, 0.86 | 0.76 | 0.67, 0.85 | 0.76 | 0.65, 0.88 | 0.77 | 0.63, 0.94 | 0.78 | 0.61, 1.00 | 0.79 | 0.59, 1.06 | 0.80 | 0.57, 1.13 |
| Both sexes (<i>n</i> = 2) | 1.03 | 0.85, 1.23 | 1.04 | 0.75, 1.44 | 1.03 | 0.71, 1.49 | 1.00 | 0.70, 1.42 | 0.96 | 0.69, 1.34 | 0.93 | 0.66, 1.30 | 0.89 | 0.62, 1.28 | | |
| Type of smoking adjustment ^b | | | | | | | | | | | | | | | | |
| Status (<i>n</i> = 11) | 0.92 | 0.86, 0.99 | 0.87 | 0.77, 0.99 | 0.87 | 0.74, 1.03 | 0.90 | 0.74, 1.09 | 0.95 | 0.75, 1.20 | 1.00 | 0.75, 1.32 | 1.05 | 0.75, 1.47 | 1.10 | 0.74, 1.64 |
| Categories (<i>n</i> = 5) | 0.88 | 0.79, 0.96 | 0.78 | 0.67, 0.92 | 0.75 | 0.63, 0.88 | 0.74 | 0.65, 0.84 | 0.74 | 0.65, 0.85 | 0.75 | 0.62, 0.90 | 0.75 | 0.58, 0.98 | | |
| Continuous (<i>n</i> = 4) | 0.87 | 0.85, 0.90 | 0.78 | 0.75, 0.82 | 0.75 | 0.71, 0.79 | 0.76 | 0.72, 0.80 | 0.78 | 0.72, 0.84 | 0.80 | 0.72, 0.88 | 0.82 | 0.72, 0.93 | | |
| Alcohol adjustment | | | | | | | | | | | | | | | | |
| No (<i>n</i> = 5) | 0.89 | 0.81, 0.97 | 0.81 | 0.68, 0.95 | 0.78 | 0.64, 0.96 | 0.79 | 0.64, 0.98 | 0.82 | 0.66, 1.02 | 0.84 | 0.66, 1.07 | 0.87 | 0.66, 1.13 | 0.89 | 0.66, 1.21 |
| Yes (<i>n</i> = 8) | 0.89 | 0.86, 0.92 | 0.81 | 0.76, 0.86 | 0.78 | 0.73, 0.84 | 0.79 | 0.72, 0.86 | 0.81 | 0.72, 0.91 | 0.84 | 0.72, 0.97 | 0.86 | 0.72, 1.03 | 0.88 | 0.71, 1.10 |

Abbreviations: CI, confidence interval; RR, relative risk.

^a Includes 3 studies that did not provide information about the number of subjects.^b Smoking status, category of cigarette smoking, or number of cigarettes smoked per day (continuous variable).

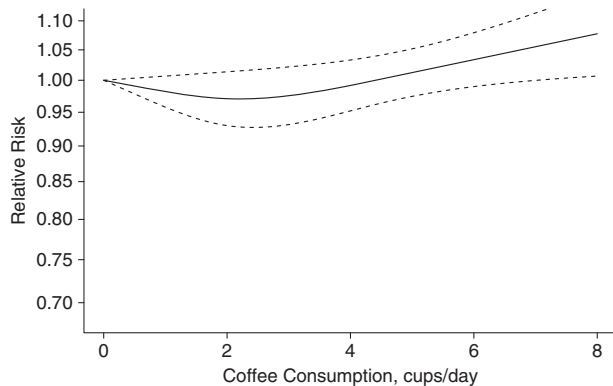


Figure 4. Pooled dose-response association between coffee consumption and cancer mortality (solid line) in a meta-analysis, 1966–2013. Coffee consumption was modeled with restricted cubic splines in a multivariate random-effects dose-response model. The relative risks are plotted on the log scale. Dashed lines represent the 95% confidence intervals for the spline model. No coffee consumption (0 cups/day) served as the referent group.

Subgroup analysis was limited by the small number of studies. We found weak suggestions of differences according to sex (P for heterogeneity = 0.11); in particular, results for men suggested a more pronounced positive association, although the finding was significant only for high consumption (≥ 5 cups/day). Results were similar across geographical areas (P for heterogeneity = 0.39), by type of smoking adjustment (P for heterogeneity = 0.76), and by adjustment for alcohol intake (P for heterogeneity = 0.87).

Sensitivity analysis

Inclusion of the 3 studies that did not report information about the number of subjects by category of coffee consumption did not materially change the results (Tables 2–4). We obtained similar results when we removed data points above 6 cups of coffee per day, and there was still evidence of nonlinearity ($P < 0.001$) for the associations between coffee consumption and all-cause and CVD mortality. For cancer mortality, the association was still not statistically significant (overall $P = 0.26$).

DISCUSSION

Findings from the current meta-analysis, including 21 prospective studies, indicate that coffee consumption may be inversely associated with all-cause and CVD mortality. Nonlinear dose-response relationships were found, with the strongest association being observed for 4 cups/day for all-cause mortality (16% lower risk) and 3 cups/day for CVD mortality (21% lower risk). The results for the association between coffee consumption and all-cause mortality were comparable to those reported in the previous 2 published meta-analyses (10, 11), where no further risk reduction was observed for high coffee consumption (≥ 4 cups/day) as compared with moderate coffee consumption (2–4 cups/day). No

association between coffee consumption and cancer mortality was found. It is still unclear how coffee consumption may have an effect on mortality. Coffee is a composite brew with several bioactive compounds whose health effects are contradictory. In the past, coffee consumption was considered unhealthy because of its content of caffeine, which has been related to increased blood pressure (4), insulin resistance (44), and serum lipid concentration (2). Nonetheless, habitual coffee consumers seem to develop a partial tolerance to the acute effect of caffeine (45). In addition, other bioactive compounds besides caffeine may play an important role; indeed, the phenolic compounds make coffee a major source of antioxidants, with potential beneficial health effects (46). Moreover, several epidemiologic studies have indicated an inverse relationship between coffee consumption and risk of suicide (47), Parkinson's disease (48), and gallstones (49). Further studies have found that coffee consumption is inversely associated with specific markers of inflammation (50) that are responsible for progression of atherosclerosis (51), coronary heart disease (52), and cancer (53). Cardiovascular disease and cancer are some of the most frequent causes of mortality; thus, the beneficial compounds in coffee may lead to a reduction in mortality by slowing the progression of disease.

Strengths of this meta-analysis include the dose-response analysis, which provides a comprehensive description of the shape of the studied association. Another strength is the prospective design of the included studies, which should have eliminated potential selection and recall biases that can affect the results of retrospective case-control studies. The relatively large total number of cases provided high statistical power, which contributes to stable risk estimates. The large number of studies enabled us to conduct several subgroup analyses to assess potential sources of heterogeneity. Lastly, we did not find evidence of publication bias, which could affect the results of a meta-analysis.

Our meta-analysis also had several potential limitations. First, the observational design of the studies did not exclude the presence of residual or unmeasured confounding from other mortality risk factors. However, all of the included studies adjusted for smoking and age, and some of them (11 out of 21) also adjusted for other important confounders, including body mass index, alcohol intake, and physical activity. In particular, the analysis stratified according to type of smoking adjustment indicated the presence of some residual confounding for the association between coffee consumption and CVD mortality, suggesting that the relationship may be even stronger, especially for high coffee consumption. Another potential limitation is misclassification of exposure, which was inevitable since coffee consumption was self-reported. Nevertheless, results from validation studies suggest that coffee consumption can be assessed with relatively high validity (54). Third, we found the presence of heterogeneity among studies, which may be related to geographical area. We observed a stronger inverse relationship between coffee consumption and all-cause mortality among studies conducted in Europe than among those conducted in the United States. Because coffee composition can vary substantially, differences in the association across countries may be related to different types of coffee powder, different methods of preparation, and different serving sizes (4). In addition,

Table 4. Adjusted Relative Risk of All-Cancer Mortality According to Coffee Consumption (Versus No Consumption) in Prospective Studies, by Study Location, Sex, Type of Smoking Adjustment, and Alcohol Use, 1966–2013

| | Coffee Consumption, cups/day | | | | | | | | | | | | | | | |
|--|------------------------------|------------|------|------------|------|------------|------|------------|------|------------|------|------------|------|------------|------|------------|
| | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | | 8 | |
| | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI |
| All studies (<i>n</i> = 8) | 0.98 | 0.96, 1.01 | 0.97 | 0.93, 1.01 | 0.98 | 0.93, 1.02 | 0.99 | 0.95, 1.03 | 1.01 | 0.97, 1.05 | 1.03 | 0.99, 1.08 | 1.06 | 1.00, 1.11 | 1.08 | 1.01, 1.15 |
| Inclusion of 1 excluded article ^a (<i>n</i> = 9) | 0.98 | 0.95, 1.00 | 0.96 | 0.92, 1.00 | 0.96 | 0.92, 1.01 | 0.98 | 0.93, 1.03 | 0.99 | 0.95, 1.05 | 1.01 | 0.96, 1.07 | 1.03 | 0.97, 1.10 | 1.05 | 0.98, 1.13 |
| Study location | | | | | | | | | | | | | | | | |
| Europe (<i>n</i> = 2) | 1.04 | 0.83, 1.30 | 1.07 | 0.71, 1.60 | 1.08 | 0.67, 1.73 | 1.07 | 0.67, 1.71 | 1.05 | 0.67, 1.65 | 1.04 | 0.67, 1.61 | 1.02 | 0.66, 1.59 | 1.01 | 0.64, 1.59 |
| United States (<i>n</i> = 3) | 0.99 | 0.97, 1.00 | 0.98 | 0.95, 1.01 | 0.98 | 0.95, 1.02 | 1.00 | 0.96, 1.03 | 1.01 | 0.97, 1.06 | 1.03 | 0.98, 1.08 | 1.05 | 0.99, 1.12 | | |
| Japan (<i>n</i> = 3) | 0.94 | 0.84, 1.06 | 0.91 | 0.74, 1.11 | 0.92 | 0.75, 1.14 | 0.98 | 0.79, 1.21 | 1.05 | 0.81, 1.36 | | | | | | |
| Sex | | | | | | | | | | | | | | | | |
| Men (<i>n</i> = 6) | 1.00 | 0.97, 1.02 | 0.99 | 0.95, 1.04 | 1.01 | 0.96, 1.06 | 1.03 | 0.98, 1.08 | 1.05 | 1.00, 1.10 | 1.08 | 1.01, 1.14 | 1.10 | 1.02, 1.18 | 1.13 | 1.03, 1.23 |
| Women (<i>n</i> = 5) | 0.96 | 0.91, 1.01 | 0.93 | 0.86, 1.01 | 0.93 | 0.86, 1.01 | 0.95 | 0.89, 1.01 | 0.98 | 0.93, 1.03 | 1.00 | 0.93, 1.08 | | | | |
| Type of smoking adjustment ^b | | | | | | | | | | | | | | | | |
| Status (<i>n</i> = 4) | 0.95 | 0.88, 1.03 | 0.91 | 0.79, 1.05 | 0.90 | 0.76, 1.07 | 0.90 | 0.74, 1.09 | 0.91 | 0.71, 1.15 | 0.91 | 0.68, 1.23 | 0.92 | 0.64, 1.32 | 0.93 | 0.61, 1.43 |
| Categories (<i>n</i> = 6) | 0.98 | 0.93, 1.03 | 0.96 | 0.88, 1.06 | 0.96 | 0.88, 1.05 | 0.97 | 0.91, 1.04 | 0.98 | 0.91, 1.06 | 1.00 | 0.90, 1.11 | 1.01 | 0.87, 1.18 | | |
| Continuous (<i>n</i> = 2) | 0.99 | 0.97, 1.01 | 0.99 | 0.95, 1.03 | 1.00 | 0.95, 1.04 | 1.02 | 0.97, 1.06 | 1.04 | 0.99, 1.08 | 1.06 | 1.01, 1.11 | 1.08 | 1.01, 1.15 | | |
| Alcohol adjustment | | | | | | | | | | | | | | | | |
| No (<i>n</i> = 2) | 1.04 | 0.82, 1.31 | 1.07 | 0.71, 1.61 | 1.07 | 0.67, 1.72 | 1.06 | 0.66, 1.72 | 1.05 | 0.62, 1.76 | 1.03 | 0.56, 1.89 | 1.01 | 0.49, 2.09 | 1.00 | 0.42, 2.35 |
| Yes (<i>n</i> = 6) | 0.98 | 0.96, 1.01 | 0.97 | 0.93, 1.01 | 0.97 | 0.93, 1.02 | 0.99 | 0.95, 1.03 | 1.01 | 0.97, 1.05 | 1.03 | 0.99, 1.08 | 1.06 | 1.00, 1.12 | 1.08 | 1.01, 1.16 |

Abbreviations: CI, confidence interval; RR, relative risk.

^a Includes 1 study that did not provide information about the number of subjects.^b Smoking status, category of cigarette smoking, or number of cigarettes smoked per day (continuous variable).

different genotypes and gene-environment interactions may partially explain the observed variation among studies. For example, cytochrome P-450 1A2 (*CYP1A2*) genotype has been shown to be responsible for 95% of caffeine metabolism and thus for the effect of coffee (55). Another limitation could be related to reverse causation, since persons with chronic disease and poor health might abstain from coffee drinking. However, we considered only studies that targeted the general population, excluding all studies that analyzed specific subpopulations (e.g., persons with diabetes or hypertension). Additionally, 3 different reports (31, 37, 50) evaluated reverse causation by excluding subjects with a history of cancer or CVD or deaths that occurred during the first few years of follow-up. With these exclusions, the estimates showed no remarkable alteration of the associations. A similar result was obtained in a sensitivity analysis in a recent meta-analysis of the relationship between coffee and all-cause mortality (11). Finally, the shape of the observed associations might have been influenced by observations in high-dose categories (56). However, removal of data points above 6 cups of coffee per day did not substantially change the results.

In summary, results from this dose-response meta-analysis indicate that coffee consumption is inversely associated with all-cause and CVD mortality but not with cancer mortality. People who regularly drink a moderate amount of coffee (3–4 cups/day) may have lower risks of death from all causes and CVD than persons who rarely drink coffee. It is unclear whether the nonlinear association between coffee and CVD mortality is related to the harmful effects of caffeine or is due to other risk factors related to coffee consumption.

ACKNOWLEDGMENTS

Author affiliations: Unit of Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden (Alessio Crippa, Andrea Discacciati, Susanna C. Larsson, Alicja Wolk, Nicola Orsini); and Unit of Biostatistics, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden (Alessio Crippa, Andrea Discacciati, Nicola Orsini).

This work was partly supported by a Young Scholar Award from the Karolinska Institutet's Strategic Program in Epidemiology.

The funders played no role in the study design, data collection, or analysis, the decision to publish, or manuscript preparation.

Conflict of interest: none declared.

REFERENCES

- Noordzij M, Uiterwaal CSPM, Arends LR, et al. Blood pressure response to chronic intake of coffee and caffeine: a meta-analysis of randomized controlled trials. *J Hypertens*. 2005;23(5):921–928.
- Hartley TR, Lovallo WR, Whitsett TL. Cardiovascular effects of caffeine in men and women. *Am J Cardiol*. 2004;93(8):1022–1026.
- Jee SH, He J, Appel LJ, et al. Coffee consumption and serum lipids: a meta-analysis of randomized controlled clinical trials. *Am J Epidemiol*. 2001;153(4):353–362.
- Rebello SA, van Dam RM. Coffee consumption and cardiovascular health: getting to the heart of the matter. *Curr Cardiol Rep*. 2013;15(10):403.
- van Dam RM, Feskens EJM. Coffee consumption and risk of type 2 diabetes mellitus. *Lancet*. 2002;360(9344):1477–1478.
- Kempf K, Herder C, Erlund I, et al. Effects of coffee consumption on subclinical inflammation and other risk factors for type 2 diabetes: a clinical trial. *Am J Clin Nutr*. 2010;91(4):950–957.
- Ding M, Bhupathiraju SN, Chen M, et al. Caffeinated and decaffeinated coffee consumption and risk of type 2 diabetes: a systematic review and a dose-response meta-analysis. *Diabetes Care*. 2014;37(2):569–586.
- Ding M, Bhupathiraju SN, Satija A, et al. Long-term coffee consumption and risk of cardiovascular disease: a systematic review and a dose-response meta-analysis of prospective cohort studies. *Circulation*. 2014;129(6):643–659.
- Yu X, Bao Z, Zou J, et al. Coffee consumption and risk of cancers: a meta-analysis of cohort studies. *BMC Cancer*. 2011;11:96.
- Malerba S, Turati F, Galeone C, et al. A meta-analysis of prospective studies of coffee consumption and mortality for all causes, cancers and cardiovascular diseases. *Eur J Epidemiol*. 2013;28(7):527–539.
- Je Y, Giovannucci E. Coffee consumption and total mortality: a meta-analysis of twenty prospective cohort studies. *Br J Nutr*. 2014;111(7):1162–1173.
- Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA*. 2000;283(15):2008–2012.
- Hamling J, Lee P, Weitkunat R, et al. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. *Stat Med*. 2008;27(7):954–970.
- Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. *Stata J*. 2006;6(1):40–57.
- Orsini N, Li R, Wolk A, et al. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. *Am J Epidemiol*. 2012;175(1):66–73.
- Jackson D, White IR, Thompson SG. Extending DerSimonian and Laird's methodology to perform multivariate random effects meta-analyses. *Stat Med*. 2010;29(12):1282–1297.
- Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. *Stat Med*. 2010;29(9):1037–1057.
- Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539–1558.
- Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629–634.
- Crippa A. *Dosresmeta: Performing Multivariate Dose-Response Meta-Analysis*. Vienna, Austria: R Foundation for Statistical Computing; 2013. <http://CRAN.R-project.org/package=dosresmeta>. Accessed January 20, 2014.
- Viechtbauer W. *metafor: Meta-Analysis Package for R*. Vienna, Austria: R Foundation for Statistical Computing; 2010. <http://CRAN.R-project.org/package=metafor>. Accessed January 20, 2014.
- R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for

- Statistical Computing; 2009. <http://www.R-project.org>. Accessed January 20, 2014.
23. LeGrady D, Dyer AR, Shekelle RB, et al. Coffee consumption and mortality in the Chicago Western Electric Company Study. *Am J Epidemiol*. 1987;126(5):803–812.
 24. Rosengren A, Wilhelmsen L. Coffee, coronary heart disease and mortality in middle-aged Swedish men: findings from the Primary Prevention Study. *J Intern Med*. 1991;230(1):67–71.
 25. Klatsky AL, Armstrong MA, Friedman GD. Coffee, tea, and mortality. *Ann Epidemiol*. 1993;3(4):375–381.
 26. Woodward M, Tunstall-Pedoe H. Coffee and tea consumption in the Scottish Heart Health Study follow up: conflicting relations with coronary risk factors, coronary disease, and all cause mortality. *J Epidemiol Community Health*. 1999;53(8):481–487.
 27. Kleemola P, Jousilahti P, Pietinen P, et al. Coffee consumption and the risk of coronary heart disease and death. *Arch Intern Med*. 2000;160(22):3393–3400.
 28. Iwai N, Ohshiro H, Kurozawa Y, et al. Relationship between coffee and green tea consumption and all-cause mortality in a cohort of a rural Japanese population. *J Epidemiol*. 2002;12(3):191–198.
 29. Jazbec A, Simić D, Corović N, et al. Impact of coffee and other selected factors on general mortality and mortality due to cardiovascular disease in Croatia. *J Health Popul Nutr*. 2003;21(4):332–340.
 30. Andersen LF, Jacobs DR Jr, Carlsen MH, et al. Consumption of coffee is associated with reduced risk of death attributed to inflammatory and cardiovascular diseases in the Iowa Women's Health Study. *Am J Clin Nutr*. 2006;83(5):1039–1046.
 31. Paganini-Hill A, Kawas CH, Corrada MM. Non-alcoholic beverage and caffeine consumption and mortality: the Leisure World Cohort Study. *Prev Med*. 2007;44(4):305–310.
 32. Lopez-Garcia E, van Dam RM, Li TY, et al. The relationship of coffee consumption with mortality. *Ann Intern Med*. 2008;148(12):904–914.
 33. Happonen P, Läärä E, Hiltunen L, et al. Coffee consumption and mortality in a 14-year follow-up of an elderly northern Finnish population. *Br J Nutr*. 2008;99(6):1354–1361.
 34. Ahmed HN, Levitan EB, Wolk A, et al. Coffee consumption and risk of heart failure in men: an analysis from the Cohort of Swedish Men. *Am Heart J*. 2009;158(4):667–672.
 35. de Koning Gans JM, Uiterwaal CSPM, van der Schouw YT, et al. Tea and coffee consumption and cardiovascular morbidity and mortality. *Arterioscler Thromb Vasc Biol*. 2010;30(8):1665–1671.
 36. Sugiyama K, Kuriyama S, Akhter M, et al. Coffee consumption and mortality due to all causes, cardiovascular disease, and cancer in Japanese women. *J Nutr*. 2010;140(5):1007–1013.
 37. Tamakoshi A, Lin Y, Kawado M, et al. Effect of coffee consumption on all-cause and total cancer mortality: findings from the JACC Study. *Eur J Epidemiol*. 2011;26(4):285–293.
 38. Freedman ND, Park Y, Abnet CC, et al. Association of coffee drinking with total and cause-specific mortality. *N Engl J Med*. 2012;366(20):1891–1904.
 39. Liu J, Sui X, Lavie CJ, et al. Association of coffee consumption with all-cause and cardiovascular disease mortality. *Mayo Clin Proc*. 2013;88(10):1066–1074.
 40. Gardener H, Rundek T, Wright CB, et al. Coffee and tea consumption are inversely associated with mortality in a multiethnic urban population. *J Nutr*. 2013;143(8):1299–1308.
 41. Hart C, Smith GD. Coffee consumption and coronary heart disease mortality in Scottish men: a 21 year follow up study. *J Epidemiol Community Health*. 1997;51(4):461–462.
 42. Leurs LJ, Schouten LJ, Goldbohm RA, et al. Total fluid and specific beverage intake and mortality due to IHD and stroke in the Netherlands Cohort Study. *Br J Nutr*. 2010;104(8):1212–1221.
 43. Mineharu Y, Koizumi A, Wada Y, et al. Coffee, green tea, black tea and oolong tea consumption and risk of mortality from cardiovascular disease in Japanese men and women. *J Epidemiol Community Health*. 2011;65(3):230–240.
 44. Heckman MA, Weil J, Gonzalez de Mejia E. Caffeine (1, 3, 7-trimethylxanthine) in foods: a comprehensive review on consumption, functionality, safety, and regulatory matters. *J Food Sci*. 2010;75(3):R77–R87.
 45. van Dam RM. Coffee consumption and coronary heart disease: paradoxical effects on biological risk factors versus disease incidence. *Clin Chem*. 2008;54(9):1418–1420.
 46. Natella F, Scaccini C. Role of coffee in modulation of diabetes risk. *Nutr Rev*. 2012;70(4):207–217.
 47. Lucas M, O'Reilly EJ, Pan A, et al. Coffee, caffeine, and risk of completed suicide: results from three prospective cohorts of American adults. *World J Biol Psychiatry*. 2014;15(5):377–386.
 48. Hernán MA, Takkouche B, Caamaño-Isorna F, et al. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. *Ann Neurol*. 2002;52(3):276–284.
 49. Leitzmann MF, Willett WC, Rimm EB, et al. A prospective study of coffee consumption and the risk of symptomatic gallstone disease in men. *JAMA*. 1999;281(22):2106–2112.
 50. Lopez-Garcia E, van Dam RM, Qi L, et al. Coffee consumption and markers of inflammation and endothelial dysfunction in healthy and diabetic women. *Am J Clin Nutr*. 2006;84(4):888–893.
 51. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation*. 2002;105(9):1135–1143.
 52. Roivainen M, Viik-Kajander M, Palosuo T, et al. Infections, inflammation, and the risk of coronary heart disease. *Circulation*. 2000;101(3):252–257.
 53. Shacter E, Weitzman SA. Chronic inflammation and cancer. *Oncology (Williston Park)*. 2002;16(2):217–226, 229.
 54. Ferraroni M, Tavani A, Decarli A, et al. Reproducibility and validity of coffee and tea consumption in Italy. *Eur J Clin Nutr*. 2004;58(4):674–680.
 55. Cornelis MC, El-Sohemy A, Kabagambe EK, et al. Coffee, CYP1A2 genotype, and risk of myocardial infarction. *JAMA*. 2006;295(10):1135–1141.
 56. Bagnardi V, Zambon A, Quatto P, et al. Flexible meta-regression functions for modeling aggregate dose-response data, with an application to alcohol and mortality. *Am J Epidemiol*. 2004;159(11):1077–1086.
 57. Bortner RW, et al. A short rating scale as a potential measure of pattern A behavior. *J Chronic Dis*. 1969;22(2):87–91.