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META-ANALYSIS

Coffee consumption and risk of all-cause, cardiovascular, and cancer mortality in smokers and non-smokers: a dose-response meta-analysis

Giuseppe Grosso[1] · Agnieszka Micek[2] · Justyna Godos[1] · Salvatore Sciacca[1] · Andrzej Pajak[2] · Miguel A. Martínez-González[3,4] · Edward L. Giovannucci[5,6,7] · Fabio Galvano[8]

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Abstract Coffee consumption has been associated with several benefits toward human health. However, its association with mortality risk has yielded contrasting results, including a non-linear relation to all-cause and cardiovascular disease (CVD) mortality and no association with cancer mortality. As smoking habits may affect the association between coffee and health outcomes, the aim of the present study was to update the latest dose-response meta-analysis of prospective cohort studies on the association between coffee consumption and mortality risk and conduct stratified analyses by smoking status and other potential confounders. A systematic search was conducted in electronic databases to identify relevant studies, risk estimates were retrieved from the studies, and dose-response analysis was modeled by using restricted cubic splines. A total of 31 studies comprising 1610,543 individuals and 183,991 cases of all-cause, 34,574 of CVD, and 40,991 of cancer deaths were selected. Analysis showed decreased all-cause [relative risk (RR) = 0.86, 95 % confidence interval (CI) = 0.82, 0.89)] and CVD mortality risk (RR = 0.85, 95 % CI = 0.77, 0.93) for consumption of up to 4 cups/day of coffee, while higher intakes were associated with no further lower risk. When analyses were restricted only to non-smokers, a linear decreased risk of all-cause (RR = 0.94, 95 % CI = 0.93, 0.96), CVD

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✉ Giuseppe Grosso
giuseppe.grosso@studium.unict.it

Agnieszka Micek
agnieszka.micek@uj.edu.pl

Justyna Godos
justyna.godos@uj.edu.pl

Salvatore Sciacca
sciacca@unict.it

Andrzej Pajak
mmpajak@cyf-kr.edu.pl

Miguel A. Martínez-González
mamartinez@unav.es

Edward L. Giovannucci
egiovann@hsph.harvard.edu

Fabio Galvano
fgalvano@unict.it

[1] Integrated Cancer Registry of Catania-Messina-Siracusa-Enna, Azienda Policlinico Universitaria "Vittorio Emanuele", Via S. Sofia 85, 95123 Catania, Italy

[2] Department of Epidemiology and Population Studies, Jagiellonian University Medical College, Krakow, Poland

[3] Department of Preventive Medicine & Public Health, School of Medicine, University of Navarra-IDISNA, Pamplona, Spain

[4] CIBER de Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Institute of Health Carlos III, Madrid, Spain

[5] Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, MA, USA

[6] Department of Nutrition, Harvard TH Chan School of Public Health, Boston, MA, USA

[7] Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

[8] Department of Biomedical and Biotechnological Sciences, University of Catania, Catania, Italy

(RR = 0.94, 95 % CI = 0.91, 0.97), and cancer mortality (RR = 0.98, 95 % CI = 0.96, 1.00) for 1 cup/day increase was found. The search for other potential confounders, including dose-response analyses in subgroups by gender, geographical area, year of publication, and type of coffee, showed no relevant differences between strata. In conclusion, coffee consumption is associated with decreased risk of mortality from all-cause, CVD, and cancer; however, smoking modifies the observed risk when studying the role of coffee on human health.

Keywords Coffee · Mortality · Cardiovascular disease · Cancer · Smoking · Prospective cohorts · Meta-analysis

Introduction

A large body of literature points to the health benefits of long-term coffee consumption in relation to diabetes, cardiovascular disease (CVD), and certain cancers [1]. A recent report of the IARC monographs Working Group regarding the possible carcinogenicity of coffee found no conclusive evidence for a carcinogenic effect of drinking coffee, focusing the attention on drinking very hot beverages (as probable cause of esophageal cancer) rather than the drinks themselves [2]. In contrast, coffee contains several biochemically active compounds that may exert beneficial effects on human health [3]. Although the mechanisms of action are not entirely understood, the effects of antioxidant compounds may explain the potential benefit of coffee against those conditions associated with a chronic state of subclinical inflammation, such as CVD and cancer [4–7]. Indeed, coffee has been reported to exert the main anti-oxidant effect among the most commonly consumed foods in the diet [8]. Among the components recently studied as responsible for such action, polyphenols demonstrated anti-oxidant and anti-inflammatory capacity in laboratory studies and their consumption has been associated in prospective cohort studies with reduced risk of diabetes, CVD, and some cancers [9–11].

Studies exploring the relation between coffee consumption and mortality have produced puzzling results. Relatively recent summary analyses of cohort studies provided quantitative evidence that coffee intake might be inversely related to all cause and, probably, CVD mortality [12, 13]. Other studies reported a non-linear dose-response association, pointing out the possibility of unfavorable effects of coffee intake at high concentrations [14, 15]. However, findings across studies are not consistent. Older studies may be affected by methodological issues, such as lack of adjustment for important confounding factors as smoking status. Moreover, some meta-analyses on specific health outcomes for which smoking habit represent a known risk factor, suggested that adjustment by smoking status may not be sufficient to overcome the strong association between coffee drinking and smoking, and reduced the confounding effect by stratifying the analysis for smokers and non-smokers [16, 17]. A major limitation of previous meta-analyses on coffee consumption and mortality risk is lack of stratification by smoking status. The aim of the present study was to perform a dose-response meta-analysis of prospective cohort studies exploring the association of coffee consumption with mortality risk. We also examined the dose-response mortality risk by smoking status in order to compare the shape of association between smokers and non-smokers. Additional analyses were performed to evaluate whether other potential confounders exist.

Methods

Study selection and data extraction

A systematic search on PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and EMBASE (http://www.embase.com/) databases of studies published up to December 2015 was performed with the search terms "coffee" and "mortality". Inclusion criteria were: (1) had a prospective design; (2) evaluated association between coffee intake and risk of mortality; (3) assessed and reported hazard ratios (HRs) and the corresponding 95 % CI for mortality for ≥3 exposure categories; and (4) provided defined amount of coffee consumption (i.e., cups per day) per category of exposure. Exclusion criteria were the following: (1) reported insufficient statistics and (2) assessed composite outcome from which was not possible to derive mortality risk (i.e., incidence of CVD event, including cardiovascular death). Reference lists of studies of interest were also examined for any additional study not previously identified. If more than one study was conducted on the same cohort, only the study including the entire cohort or the longest follow-up was included.

Data were abstracted from each identified study by using a standardized extraction form. The following information was collected: (1) first author name; (2) year of publication; (3) study cohort name and country; (4) number, gender, and age (mean or range) of participants; (5) follow-up period; (6) endpoints and cases; (7) distributions of cases and person-years, HRs and 95 % CIs for all categories of exposure; (8) median intake of coffee per each category of exposure; (9) covariates used in adjustments. This process was independently performed by two authors (G.G. and A.M.) and discrepancies were discussed and resolved by consensus.

Statistical analysis

Outcomes evaluated in the analyses included all-cause, CVD, and cancer mortality. When coffee consumption was reported by ranges of intake, the midpoint of the range was used. When the highest category was open-ended, we assumed the width of the category to be the same as the adjacent category. When the lowest category was open-ended, we set the lower boundary to zero. Two-stage random-effects dose-response meta-analysis was performed to examine linear and non-linear relationship between coffee intake and all-cause, CVD, and cancer mortality. In the first stage the method reported by Greenland and Orsini (generalized least-squares, GLS) was used to calculate study-specific coefficients on the basis of results across categories of coffee intake taking into account the correlation within each set of retrieved HRs [18, 19]. Non-linear dose–response analysis was modeled using restricted cubic splines with 3 knots at fixed percentiles (25, 50, and 75 %) of the distribution [20]. We combined the coefficients that had been estimated within each study by performing random-effects meta-analysis. In linear dose-response meta-analysis the method of DerSimonian and Laird was used and in non-linear dose-response meta-analysis the multivariate extension of the method of moments was used to estimate the relative risks (RRs). We calculated an overall P value by testing that the 2 regression coefficients were simultaneously equal to zero. We then calculated a P value for non-linearity by testing that the coefficient of the second spline was equal to zero. A number of sensitivity analyses were conducted to test stability of results: (a) by grouping studies according the level of adjustment for smoking-related variables; (b) by excluding one study at the time; (c) by excluding studies that did not report the number of cases, individuals, and person-years for each category of exposure; and (d) by converting the volume of cups of coffee into a homogeneous measure (1 cup = 150 ml coffee) in those studies in which volume was given. To test for potential confounders/effect modifiers, dose-response analyses for all-cause, CVD, and cancer mortality were performed according to some variables of interest for which stratified data was available, such as smoking status [smokers (current and former)/non-smokers (never)] and other factors, including gender (men/women), year of publication, geographical area, and type of coffee. Publication bias was assessed with Egger's regression test. Statistical heterogeneity between studies was assessed using the Chi square test (defined as a P value less than 0.10) and quantified through the multivariate generalization of the I^2 statistic: no, low, medium, and high heterogeneity were defined by I^2 values <25, <50, <75, and ≥75 %, respectively. All analyses were performed with R software version 3.0.3, dosresmeta and mvmeta packages (Development Core Team, Vienna, Austria).

Results

Study characteristics

The selection process of studies potentially relevant for the meta-analyses is presented in Fig. 1. Out of 470 screened studies, a total of 31 studies [21–51] involving 1,610,543 individuals and 183,991 cases of all-cause, 34,574 of CVD, and 40,991 of cancer deaths (2 studies [23, 26] did not provide number of cases) were included in the meta-analyses to test the association between coffee consumption and mortality risk. A description of the studies and cohorts included is presented in Table 1. Eleven studies were conducted in US, 14 were settled in Europe, and 7 in Asia (6 in Japan and 1 in Singapore). Follow-up periods ranged

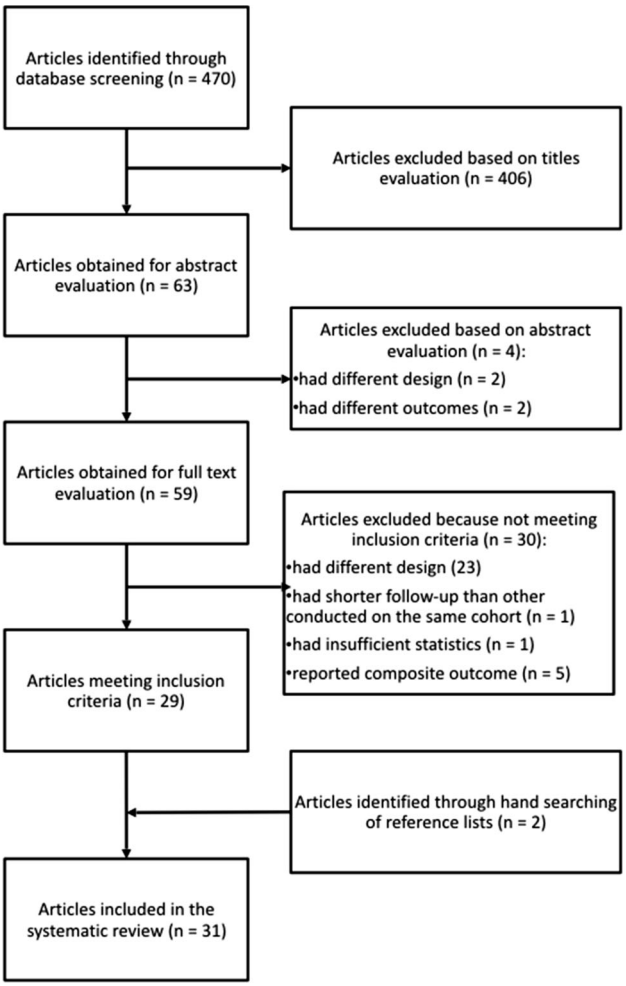

Fig. 1 Process of study selection for inclusion in the meta-analysis on all-cause, CVD, and cancer mortality

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

Author, year	Cohort name (country, baseline year), f-up	No. of participants (age range)	Outcome	No. cases	Adjustments in multivariate analyses	Specific adjustments for smoking
Kahn [21]	California Seventh-day Adventist Study (US, 1960), 21 year	27,530 men and women (30–99)	All-cause	5654	Age, gender, history of major chronic disease	Never, ever
Vandenbroucke [23]	Random sample (Netherlands, 1953–54), 25 year	1583 men and 1508 women (40–65)	All-cause	NA	Age, alcohol use, BMI, living parents, cholesterol level, systolic blood pressure	Current
Jacobsen [22]	Norwegian Prospective Study (Norway, 1967–69), 11.5 year	13,664 men and 2891 women (NA)	All-cause	4032	Gender, age, residence	Never, former, current (1–9, 10–19, ≥20 cigarettes/day)
			Cancer	886		
LeGrady [24]	Chicago Western Electric Company Study (US, 1957–58), 19 year	1910 men (40–56)	All-cause	442	Age, diastolic blood pressure, serum cholesterol	Never, former, current (1-15, 16-24, ≥ 25 cigarettes/d)
			CVD	220		
Rosengren [25]	Multifactor Primary Prevention Trial (Norway, 1970–73), 7.1 year	6765 men (51–59)	All-cause	478	Age, smoking, systolic blood pressure, BMI, diabetes, registration for alcohol abuse, family history of myocardial infarction, mental stress, physical activity, and occupational class	Current
			CVD	169		
Lindsted [26]	California Seventh-day Adventist Study (US, 1960), 15 year	9484 men (50–99)	CVD	NA	BMI, stroke, heart disease, cancer history, hypertension, race, exercise, sleep, marital status, education, diet history	Current
			Cancer	NA		
Klatsky [27]	Hospital cohort (US, 1978–85), 8 year	128,934 men and women (NA)	All-cause	4501	Total serum cholesterol, alcohol consumption, diastolic blood pressure, blood glucose, BMI, educational attainment, tea drinking	Never, former, current
			CVD	1762		
			Cancer	1424		
Hart [28]	Screening examination at workplace (UK, 1970–73), 21 year	2686 men (35–64)	CVD	625	Age, diastolic blood pressure, cholesterol, social class, age leaving full time education, BMI, angina, and ECG ischaemia	Current
Woodward [29]	Scottish Heart Health Study (UK, 1984–87), 7.7 year	5645 men and 5800 women (40–59)	All-cause	372	Age, housing tenure, activity at work, activity in leisure, BMI, Bortner score, cotinine, systolic blood pressure, fibrinogen, total cholesterol, HDL-cholesterol, triglycerides, alcohol, vitamin C, and tea	Never, former, current
			CVD	156		
Kleemola [30]	Independent population surveys (Finland, 1972), 10 year	20,179 men and women (30–59)	All-cause	1645	Age, serum cholesterol level, blood pressure, and history of myocardial infarction	Never, former, current
			CVD	608		

Table 1 continued

Author, year	Cohort name (country, baseline year), f-up	No. of participants (age range)	Outcome	No. cases	Adjustments in multivariate analyses	Specific adjustments for smoking
Iwai [31]	Population-based survey (Japan, 1989), 9.9 year	2855 men and women (40–79)	All-cause Cancer	361 61	Age, history of selected diseases, physical activity level, educational status, and additionally only in men, smoking status, habitual alcohol consumption	Never, former, current (≤20, >20 cigarettes/day)
Jazbec [32]	Investigation of chronic diseases (Croatia, 1969), 10 year	1571 men and 1793 women (35–59)	All-cause CVD	950 435	Age, region, smoking, diastolic blood pressure, feeling of well-being, and history of stomach ulcer	Current ≤20, >20 cigarettes/day
Andersen [33]	Iowa Woman's Health Study (US, 1986), 15 year	41,836 post-menopausal women (55–69)	All-cause CVD Cancer	4265 1411 1733	Age, alcohol intake, 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 and seafood, and total fruit and vegetables	Current (≤15, >15 cigarettes/week), former (≤15, >15 cigarettes/week)
Paganini-Hill [34]	Leisure World Cohort Study (US, 1981), 23 year	8644 men and 4980 women (75 year mean)	All-cause	11,386	Age, sex, exercise, BMI, alcohol intake and histories of hypertension, angina, heart attack, stroke, diabetes, rheumatoid arthritis, and cancer	Never, former, current
Happonen [35]	Home-dwelling individuals (Finland, 1991–92), 14.5 year	311 men and 506 women (70–94)	All-cause CVD Cancer	623 344 101	Gender, current age, calendar period, marital status, educational level, previous occupational group, current smoking, BMI, history of myocardial infarction, presence of diabetes mellitus, cognitive impairment, physical disability, and self-rated health	Current
Laaksonen [36]	Annual nationwide survey (Finland, 1979), 11.9 year	29,065 men and 31,543 women (15–64)	All-cause CVD	2727 1184	Age, age squared, study year and pre-existing chronic diseases	Never, former, current (occasional, daily)
Ahmed [37]	Cohort of Swedish Men (Sweden, 1997), 9 year	37,315 men (45–79)	CVD	94	BMI, total activity score, smoking status, history of high cholesterol, family history of MI before age 60, education level, marital status, aspirin use, alcohol, tea, energy-adjusted fat intake, and energy-adjusted daily sodium intake	Never, former, current
Leurs [39]	Netherlands Cohort Study (Netherlands, 1986), 10 year	120,852 men and women (55–69)	CVD	2497	Age, years of active smoking and total energy intake	Current, number of cigarettes/d

Table 1 continued

Author, year	Cohort name (country, baseline year), f-up	No. of participants (age range)	Outcome	No. cases	Adjustments in multivariate analyses	Specific adjustments for smoking
de Koning Gans [38]	EPIC-NL (Netherlands, 1993–97), 13 year	37,514 men and women (50–69)	All-cause CVD	1405 193	Gender; age; cohort (strata); educational level; physical activity; smoking status; waist circumference; menopausal status; alcohol, tea, and coffee consumption; total energy; and saturated fat, fiber, and vitamin C level	Never, former, current
Sugiyama [40]	Sugiyama Miyagi Cohort Study (Japan, 1990), 10.3 year	18,287 men and 19,455 women (40–64)	All-cause CVD Cancer	2454 426 724	Age, gender, past history of hypertension and diabetes, education level, BMI, walking time, cigarette smoking, consumption of alcohol, green tea, oolong tea, black tea, intake of rice, miso soup, total meat, total dairy products, total fish, total vegetables, total fruits, and energy	Never, former, current (< 20, ≥ 20 cigarettes/day)
Tamakoshi [42]	Japan Collaborative Cohort Study for Evaluation of Cancer Risk (Japan, 1988–90), 16 year	97,753 men and women (40–79)	All-cause Cancer	19,532 6794	Age categories, smoking status, alcohol drinking, walking hours, sleep duration, BMI, consumption of green-leafy vegetables, green tea consumption, education, stress, marital status, past history of cancer, myocardial infarction or stroke	Never, former, current
Mineharu [41]	Japan Collaborative Cohort Study for Evaluation of Cancer Risk (Japan, 1988–90), 13.1 year	76,979 men and women free of CVD (40-79)	CVD	1807	BMI, history of hypertension, history of diabetes, smoking status, alcohol intake, education, walking 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 seaweeds and total daily energy intake	Never, former, current (≤19, 20–29, ≥30 cigarettes/day)
Freedman [43]	National Institutes of Health (NIH)–AARP Diet and Health Study (US, 1995–96), 14 year	229,119 men and 173,141 women (50–71)	All-cause CVD Cancer	52,515 9454 13,402	Age, BMI, race or ethnic group, level of education, alcohol consumption, health status, diabetes, marital status, physical activity, total energy intake, consumption of fruits, vegetables, red meat, white meat, and saturated fat, use or nonuse of vitamin supplements, history of cancer in a first-degree relative	Never, former, current; number of cigarettes/d; use or nonuse of pipes or cigars; time of smoking cessation (<1, 1–4, 5–9, ≥10 year before baseline)
Gardener [44]	Northern Manhattan Study (US, 1993–2001), 11 year	2461 men and women (68 y mean)	All-cause CVD Cancer	863 342 160	Age, sex, race/ethnicity, education, alcohol consumed/day, moderate-heavy physical activity, total daily energy, protein, carbohydrates, total fat, saturated fat, BMI, vascular risk factors (history of cardiac disease, diabetes, hypertension, hypercholesterolemia), other non-water beverage consumption, milk in coffee, cream in coffee, and nondairy creamer in coffee, and tea	Smoking (pack-years)

Table 1 continued

Author, year	Cohort name (country, baseline year), f-up	No. of participants (age range)	Outcome	No. cases	Adjustments in multivariate analyses	Specific adjustments for smoking
Liu [45]	Aerobics Center Longitudinal Study (US, 1987), 17 year	43,727 men and women (20–87)	All-cause	2512	Age, baseline examination year, fitness measures, decaffeinated coffee use, regular tea use, decaffeinated or herbal tea use, physical inactivity, BMI, alcohol consumption, diabetes, hypertension, hypercholesterolemia, and family history of CVD	Current
			CVD	804		
Lof [47]	Swedish Women's Lifestyle and Health Cohort (Sweden, 1991–92), 18 year	49,259 women (30–49)	All-cause	1576	BMI, education, smoking, alcohol, parity and age at first birth	Never, former, current
			CVD	956		
			Cancer	124		
Odegaard [49]	Singapore Chinese Health Study (Singapore, 1993–98), 16 year	52,584 men and women (45–74)	All-cause	10,029	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	Provided risk estimates stratified by smoking status (never, ever)
			CVD	3097		
			Cancer	4092		
Saito [50]	Japan Public Health Center (Japan, 1990–94), 18.7	90,914 men and women (40–69)	All-cause	12,874	Gender, age, and 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; and job status	Never, former, current <20, ≥20 cigarettes/day
			CVD	1264		
			Cancer	5327		
Ding [46]	Nurses' Health Study (US, 1976), 28 year	74,890 women (30–55)	All-cause	31,956	Age, baseline disease status (hypertension, hypercholesterolemia, diabetes), BMI, physical activity, overall dietary pattern, total energy intake, sugar-sweetened beverage consumption and alcohol consumption, menopausal status and postmenopausal hormone use (for women)	Never, former (1–4, 5–14, 15–24, 25–34, 35–44, ≥45, unknown cigarettes/day), current (1–4, 5–14, 15–24, 25–34, 35–44, ≥45, unknown cigarettes/day)
	Nurses' Health Study II (US, 1989), 21 year	93,054 women (25–42)	CVD	2587		
	Health Professionals Follow-up Study (US, 1986), 26 year	40,557 men (40–75)	Cancer	3664		
Loftfield [48]	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (US, 1993–2001), 20 year	90,317 men and women (55–74)	All-cause	8718	Age, sex, 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	Never, former, current (≤ 10, 11–20, 21–40, or ≥ 41); time of smoking cessation (1–4, 5–9 10–19, ≥20 years prior to study entry
			CVD	3226		
			Cancer	1744		

Table 1 continued

Author, year	Cohort name (country, baseline year), f-up	No. of participants (age range)	Outcome	No. cases	Adjustments in multivariate analyses	Specific adjustments for smoking
Grosso [51]	HAPIEE study (Czech Republic, Poland, Russia, 2002–05), 6.1 year	28,561 men and women (45–69)	All-cause	2121	Age, gender, smoking status, BMI, educational level, physical activity, alcohol intake, hypertension, diabetes, hypercholesterolemia, history of CVD or cancer, family history of CVD, family history of cancer, total energy intake, vitamin supplement use, poly-unsaturated, saturated, total n-3 fatty acids, and menopausal status (in women)	Current
			CVD	755		
			Cancer	913		

between 6 and 28 years, providing reasonable time to observe the outcomes studied. Sixteen studies [25, 26, 28–30, 36, 37, 39–43, 45–47, 50] provided gender-specific risk estimates and 6 studies [43, 46, 48–51] reported stratified analysis for smokers and non-smokers. Three studies [22, 24, 25] did not provide 95 % CIs and were excluded from the analyses because they could only be included by deriving missing information as crude risk estimates, which is poorly informative for the purpose of the present study. Moreover, the same studies considered "non-smokers" as "never and former smokers", which did not fit our inclusion criteria for the analyses. All other studies adjusted analyses for potential confounding factors associated with the outcomes of interest, including age, gender, body mass index, and smoking status. Regarding the latter, 8 studies provided adjustment only for current/non-smokers [21, 23, 25, 26, 28, 35, 45, 51], 9 adjusted for current/former/never smokers [27, 29, 30, 34, 36–38, 42, 47], while 12 further adjusted for further information (i.e., number of cigarettes) [22, 24, 31–33, 40, 41, 43, 44, 46, 48, 50]. Adjustment for other covariates was not equal across studies: 8 included evaluation of health parameters (i.e., blood pressure, lipids, etc.) [23–25, 27–30, 32], 18 included prevalence of chronic non-communicable diseases [21, 25, 26, 30, 31, 34–36, 40–46, 48, 50, 51], and 17 included information on other diet-related factors [29, 33, 37–46, 48–51].

All-cause and cause-specific mortality

The dose-response meta-analyses for all-cause (including 24 studies [21, 23, 26, 27, 29–36, 38, 40, 42–51)], CVD (including 23 studies [26–30, 32, 33, 35–41, 43–51]), CHD (including 12 studies [28–30, 36, 38–41, 43, 46, 48, 50]), stroke (including 9 studies [36, 38–41, 43, 46, 48, 50]), and cancer mortality (including 15 studies [26, 27, 31, 33, 35, 40, 42–44, 46–51]) are showed in Fig. 2. Compared with no coffee consumption, the summary RR of all-cause mortality for 4 cups/day of coffee was 0.84 (95 % CI = 0.81, 0.88; $I^2 = 83$ %, $P_{heterogeneity} < 0.001$) and RR of CVD mortality was 0.83 (95 % CI = 0.75, 0.92; $I^2 = 92$ %, $P_{heterogeneity} < 0.001$), while increased intake was associated with no further lower risk (Table 2). Similar risk estimates were found for CHD mortality while risk of stroke was slightly lower (RR = 0.84, 95 % CI = 0.71, 0.99; $I^2 = 95$ %, $P_{heterogeneity} < 0.001$; and RR = 0.72, 95 % CI = 0.6, 0.87; $I^2 = 89$ %, $P_{heterogeneity} < 0.001$). No significant association was found between coffee consumption and cancer mortality risk. Egger's regression test provided no evidence of substantial publication bias. A sensitivity analysis by level of adjustment by smoking status did not change previous findings besides resulting in a stronger association between coffee and CVD mortality

in the model including studies adjustment for additional variables related to smoking status (Supplementary Table 1). Additional sensitivity analyses by excluding one study at the time, by excluding studies due to lack of number of individuals/cases for each category of exposure, and by uniformed converted doses of cup of coffee for those studies reporting the exact amount of coffee per cup did not show differences from main analyses (data not shown).

Stratified dose-response analyses

When performing a dose-response analysis on population stratified by smoking status, heterogeneity was reduced in all models (Table 3). No differences were found between smokers and non-smokers for all-cause and CVD mortality risk (Fig. 3), both significantly reduced for higher compared to no consumption of coffee, with no/small evidence of heterogeneity or publication bias (Table 3); in contrast, cancer mortality was significantly decreased only when considering non-smokers, while increased in smokers (Table 3 and Fig. 3). A sensitivity analysis by level of adjustment for smoking-related variables conducted in all models on smokers showed stable results for all-cause mortality (despite with evidence of heterogeneity in the most adjusted studies), significant decreased risk of CVD mortality when considering the most adjusted studies, and non-significant results for cancer mortality (Supplementary Table 2). When considering non-smokers, all models showed significant decreased risk with no/small evidence of heterogeneity or publication bias: a linear dose-response analysis showed a significant decreased risk by 6 % for each additional cup of coffee per day consumed for all-cause and CVD mortality (RR = 0.94, 95 % CI = 0.93, 0.96 and RR = 0.94, 95 % CI = 0.91, 0.97, respectively) and significant decreased risk of 2 % for cancer mortality (RR = 0.98, 95 % CI = 0.96, 1.00).

Stratified dose-response analyses by gender, year of publication, type of coffee, and geographical area showed less remarkable differences in the association between coffee consumption and the outcomes explored between the strata (Supplementary Table 3). Summary risk estimates for men and women were similar between genders (Supplementary Figure 1). Also the results stratified by geographical area did not show differences for most of the analyses, despite coffee consumption was associated with risk of CVD mortality in a U-shaped, rather than J-shaped manner (Supplementary Figure 2). In contrast, older studies (publication year prior 2010) and consumption of caffeinated, rather than decaffeinated coffee were mostly contributing to the increased risk of cancer mortality associated with increased intake of coffee (Supplementary Figure 3 and Supplementary Figure 4, respectively).

Discussion

After analyzing results from existing cohorts on coffee consumption and stratifying analyses by smoking status, we found evidence of a decreased risk of all-cause, CVD, and cancer mortality among non-smokers. Compared with previous meta-analyses [14, 47], we included a higher number of individuals and we performed dose-response analyses for a number of strata to test for potential confounders/effect modifiers, including smoking status, but also gender, year of publication, geographical area, and type of coffee. In smokers, a J-shaped association with all outcomes was found. The slope for benefit was steeper at the lower range for CVD mortality, but appeared linear for all outcomes. Among other variables of interest, there were no particular findings to be noted.

Previous meta-analyses reported that the association of coffee drinking with mortality risk may not be linear. Potential reasons for any adverse effect of coffee have

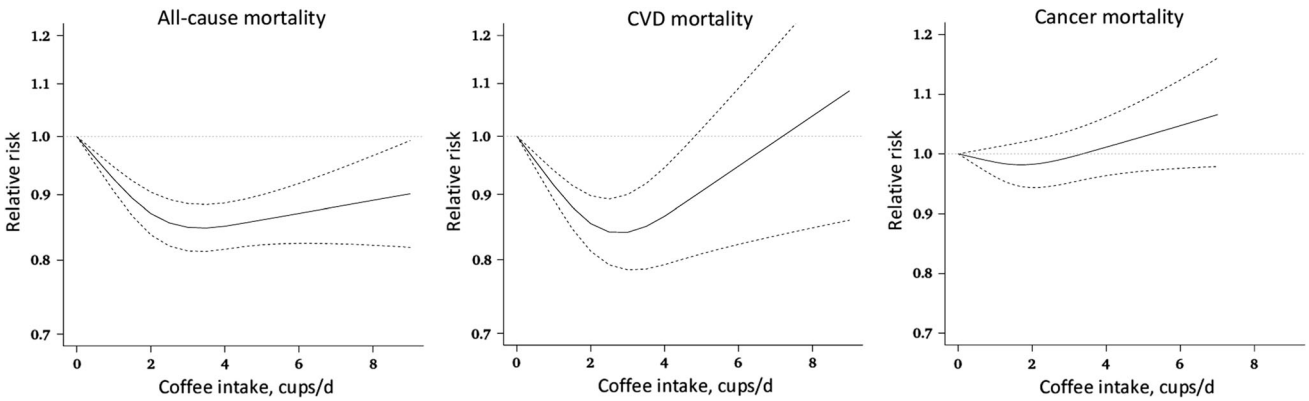

Fig. 2 Dose-response association between coffee consumption and all-cause, CVD, and cancer mortality. *Solid lines* represent relative risk, dashed lines represent 95 % confidence intervals

Table 2 Dose-response meta-analysis of prospective studies on coffee consumption and all-cause, cardiovascular, coronary heart disease, stroke, and cancer mortality

	No. of datasets (no. of studies)	Coffee intake (cups/day)							I^2 (%)	$P_{heterogeneity}$
		0	1	2	3	4	5	6	7		
All-cause mortality	36 (24)	Reference	0.92 (0.89, 0.94)	0.85 (0.82, 0.89)	0.83 (0.79, 0.88)	0.84 (0.81, 0.88)	0.86 (0.82, 0.90)	0.88 (0.84, 0.92)	0.9 (0.85, 0.96)	83	<0.001
CVD mortality	32 (23)	Reference	0.9 (0.85, 0.94)	0.82 (0.75, 0.91)	0.81 (0.72, 0.9)	0.83 (0.75, 0.92)	0.87 (0.78, 0.96)	0.91 (0.81, 1.01)	0.95 (0.84, 1.06)	92	<0.001
CHD mortality	20 (12)	Reference	0.92 (0.86, 0.98)	0.86 (0.76, 0.97)	0.84 (0.71, 0.99)	0.84 (0.68, 1.03)	0.85 (0.67, 1.09)	0.87 (0.66, 1.14)	0.88 (0.65, 1.2)	95	<0.001
Stroke mortality	13 (9)	Reference	0.82 (0.73, 0.93)	0.72 (0.59, 0.88)	0.7 (0.57, 0.86)	0.72 (0.6, 0.87)	0.76 (0.65, 0.90)	0.8 (0.68, 0.95)	0.85 (0.69, 1.03)	89	<0.001
Cancer mortality	19 (15)	Reference	0.99 (0.96, 1.01)	0.98 (0.94, 1.02)	0.99 (0.95, 1.04)	1.01 (0.96, 1.06)	1.03 (0.97, 1.09)	1.05 (0.98, 1.12)	1.07 (0.98, 1.16)	42	0.003

frequently been attributed to a trigger of coronary events induced acutely by high doses or caffeine [52, 53]. However, this hypothesis is not confirmed in pooled analyses of prospective cohort studies on coffee and caffeine intake and risk of atrial fibrillation and heart failure [54, 55]. While caffeine intake may have some acute effects, habitual, rather than occasional intake of coffee has been demonstrated to reduce inflammatory and glycemic markers [7, 56, 57]. Moreover, habitual coffee intake may also lead to desensitization to the acute effects of caffeine [58], and previous investigations showed potential beneficial effects of coffee not related with caffeine intake [59]. Findings from meta-analyses on CVD and mortality risk were in accord on the decreased risk associated with coffee consumption. We confirmed the association, reporting that coffee was associated with decreased risk of all-cause and CVD mortality, with no effect modification from any factor except smoking, which weakens the strength of the association when considering smokers. For cancer mortality, previous studies reported increased risk associated with higher coffee intake. In contrast, some recent studies suggest that coffee may be associated with decreased risk of some cancers, including colorectal, oral, endometrial, prostate, and liver cancers [60–63]. In the present meta-analysis we observed a different pattern for risk of cancer mortality when stratified by smoking: while a suggestive increased risk was observed in smokers, we observed a linear decreased risk of cancer mortality when the analysis was restricted to non-smokers. While it is hardly plausible that any biological effect of coffee causally differs by smoking status, given that coffee drinking and smoking are correlated, and that smoking is the strongest risk factor for cancer, we believe that residual confounding by smoking is the most likely the explanation for such increased risk and that the association between coffee and cancer mortality is difficult to isolate when considering smokers. These findings argue against any adverse effects of coffee on cancer risk, at least among non-smokers, and in contrast are consistent with potential beneficial effects.

The polyphenol content of coffee has been considered as the main biological explanation for coffee's benefits on human health. Coffee is one of the main contributors to polyphenol content in the diet of European individuals, accounting for up to 40 % of the total polyphenol intake [64–68]. The polyphenol mainly represented in coffee are phenolic acids, which have been only recently considered in epidemiological studies showing potential benefits toward metabolic disorders [69]. Chlorogenic acids, the most abundant group of phenolic acids contained in coffee, showed improvements in blood pressure alterations, and the ability to affect some metabolic pathways, for instance by improving glucose metabolism and decreasing inflammation and endothelial dysfunction [70, 71]. This family of

Table 3 Dose-response meta-analysis of prospective studies on coffee consumption and all-cause, cardiovascular, coronary heart disease, stroke, and cancer mortality stratified by smoking status

	No. of datasets (no. of studies)	Coffee intake (cups/day)								I^2 (%)	$P_{heterogeneity}$
		0	1	2	3	4	5	6	7		
All-cause mortality											
Smokers	9 (5)	Reference	0.94 (0.91, 0.97)	0.9 (0.85, 0.95)	0.89 (0.84, 0.94)	0.88 (0.83, 0.94)	0.88 (0.81, 0.95)	0.87 (0.79, 0.96)	0.87 (0.77, 0.98)	79	<0.001
Non-smokers	9 (5)	Reference	0.92 (0.89, 0.95)	0.87 (0.83, 0.91)	0.84 (0.8, 0.88)	0.83 (0.78, 0.87)	0.81 (0.76, 0.87)	0.8 (0.74, 0.87)	0.79 (0.71, 0.87)	29	0.13
CVD mortality											
Smokers	8 (4)	Reference	0.94 (0.89, 0.99)	0.89 (0.82, 0.97)	0.85 (0.77, 0.93)	0.81 (0.74, 0.89)	0.78 (0.69, 0.87)	0.74 (0.65, 0.85)	0.71 (0.61, 0.83)	26	0.16
Non-smokers	10 (5)	Reference	0.89 (0.84, 0.95)	0.81 (0.74, 0.9)	0.77 (0.7, 0.86)	0.76 (0.69, 0.83)	0.75 (0.69, 0.82)	0.75 (0.67, 0.84)	0.74 (0.64, 0.86)	45	0.01
CHD mortality											
Smokers	5 (2)	Reference	0.93 (0.89, 0.98)	0.89 (0.82, 0.96)	0.86 (0.78, 0.95)	0.84 (0.74, 0.96)	0.82 (0.70, 0.98)	0.8 (0.65, 1.00)	0.79 (0.61, 1.02)	58	0.01
Non-smokers	5 (3)	Reference	0.86 (0.77, 0.97)	0.8 (0.69, 0.93)	0.86 (0.81, 0.92)	1.05 (0.75, 1.45)	1.32 (0.67, 2.58)	1.66 (0.6, 4.60)	2.1 (0.54, 8.23)	49	0.046
Stroke mortality											
Smokers	5 (2)	Reference	0.91 (0.81, 1.01)	0.83 (0.71, 0.96)	0.76 (0.65, 0.87)	0.69 (0.60, 0.80)	0.64 (0.54, 0.76)	0.58 (0.47, 0.72)	0.54 (0.41, 0.70)	0	0.91
Non-smokers	5 (3)	Reference	0.88 (0.77, 1.02)	0.82 (0.67, 1.00)	0.82 (0.7, 0.97)	0.86 (0.75, 1.00)	0.92 (0.71, 1.21)	0.99 (0.64, 1.53)	1.06 (0.58, 1.95)	10	0.35
Cancer mortality											
Smokers	8 (4)	Reference	1 (0.96, 1.05)	1.01 (0.95, 1.08)	1.03 (0.97, 1.09)	1.06 (1.01, 1.11)	1.08 (1.03, 1.14)	1.11 (1.04, 1.19)	1.14 (1.04, 1.24)	0	0.52
Non-smokers	8 (5)	Reference	0.99 (0.98, 1.01)	0.98 (0.95, 1.00)	0.94 (0.92, 0.96)	0.9 (0.88, 0.93)	0.86 (0.83, 0.90)	0.83 (0.78, 0.87)	0.79 (0.74, 0.85)	0	0.93

Smokers included current and/or former smokers; non-smokers included never smokers

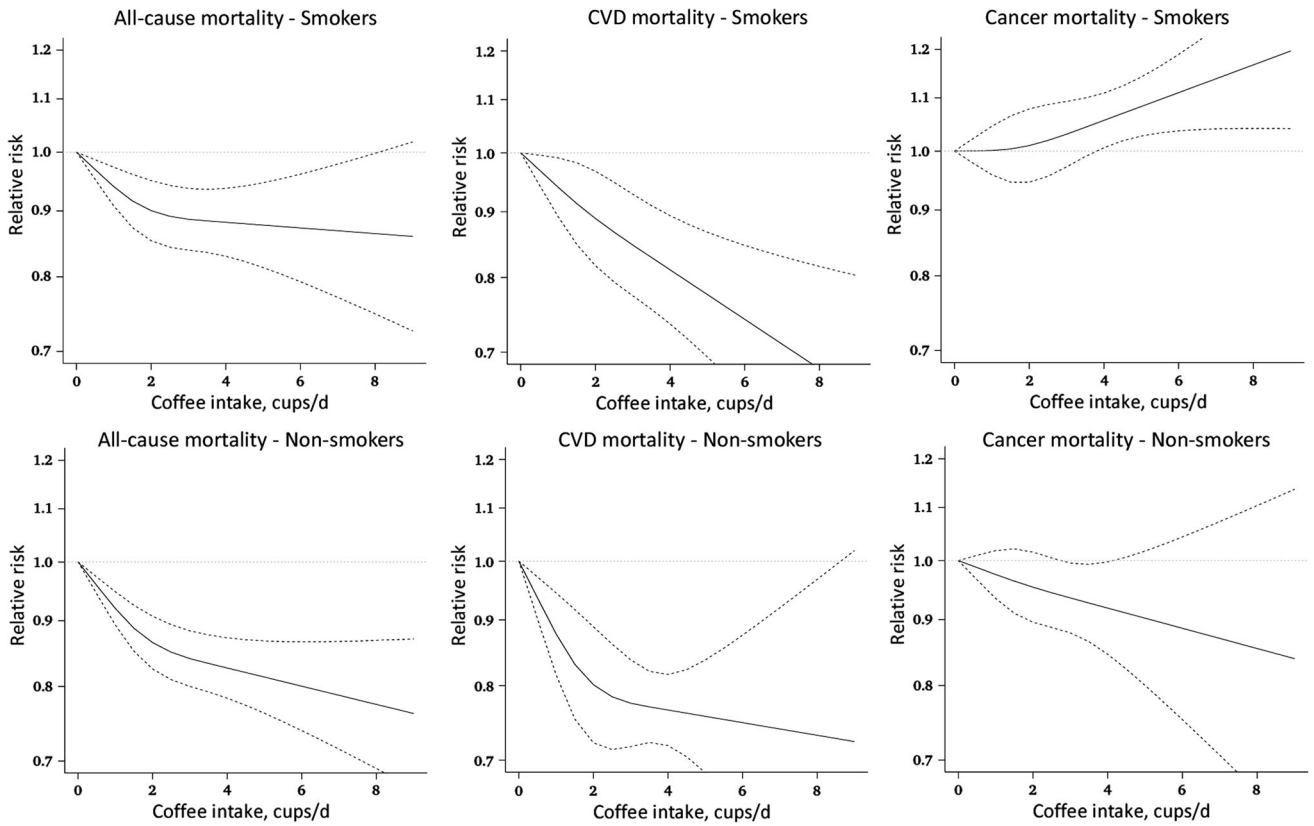

Fig. 3 Dose-response association between coffee consumption and all-cause, CVD, and cancer mortality stratified by smoking status. *Solid lines* represent relative risk, dashed lines represent 95 % confidence intervals

compounds also demonstrated antitumor properties by inhibiting key enzymes involved in tumor genesis and metastasis [72]. Among other components, kaweol and cafestol have been proposed as possible antitumor agents due to their capacity of regulating angiogenesis, apoptosis and inflammation process [73, 74].

Results of the present study should be considered in light of some limitations. First, some analyses reported moderate yet significant heterogeneity. As previously suggested, a number of factors may explain differences across studies, including type of coffee powder (Arabica or Robusta), roasting, and beverage preparation. Moreover, genetic variants associated with caffeine metabolism are not considered in prospective cohort studies included in the meta-analysis and may explain part of the heterogeneity [75]. Second, although most of the included studies reported adjusted measures and we further stratified by the main potential confounding factors, the observational design did not exclude the presence of residual or unmeasured confounding from other mortality risk factors. Because coffee was assessed before outcome, recall bias is unlikely. However, misclassification of the actual amounts consumed may have affected the dose-response relation. Reverse causation may have affected the results if individuals changed coffee intake due to a diagnosed medical condition or disease; however, any such effects would be muted in studies with long duration. Finally, time-related variables, such as period of evaluation (baseline, continuous, etc.) and duration of coffee consumption have not been investigated.

In conclusion, coffee consumption is associated with decreased risk of all-cause, CVD, and cancer mortality when considering non-smokers. The contrasting results for higher intake of coffee among smokers depend most likely on the effect modification of smoking habit and more realistic association with mortality risk is provided in non-smokers. Future studies should also distinguish between smoking-related cancer mortality, in order to add further details to the associations retrieved and confirm those on cancer mortality as well as to explore other potential confounding factors that may justify previous findings (i.e., drinking very hot beverage, including coffee). Moreover, further details related to coffee type and preparation could also provide future insights on the potential effects of coffee consumption on human health. However, from a public health point of view, there is no evidence of harmful

effects of coffee drinking with regard to the outcomes investigated, rather a potential beneficial effect evidenced in non-smokers.

Acknowledgments Author contribution: GG designed the study, performed the study search and wrote the manuscript; AM performed the analyses; JG built the databases and the tables; AP and MAMG provided insights on methodology and content; ELG and FG provided expertise on the topic and drafted the paper (equal contribution). All authors critically revised the paper.

Compliance with ethical standards

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

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