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Coffee consumption and risk of fractures: A systematic review and dose–response meta-analysis

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ABSTRACT

Purpose: The data on the association between coffee consumption and the risk of fractures are inconclusive. We performed a comprehensive literature review and meta-analysis to better quantify this association.
Methods: We identified all potentially relevant articles by searching MEDLINE, EMBASE, Cochrane Library, Web of Science, SCOPUS, and CINAHL (until February 2013). The keywords "coffee," "caffeine," "drink," and "beverage" were used as the exposure factors, and the keyword "fracture" was used as the outcome factor. We determined the overall relative risk (RR) and confidence interval (CI) for the highest and lowest levels of coffee consumption. A dose–response analysis was performed to assess the risk of fractures based on the level of coffee consumption.
Results: We included 253,514 participants with 12,939 fracture cases from 9 cohort and 6 case–control studies. The estimated RR of fractures at the highest level of coffee consumption was 1.14 (95% CI: 1.05–1.24; $I^2 = 0.0\%$) in women and 0.76 (95% CI: 0.62–0.94; $I^2 = 7.3\%$) in men. In the dose–response analysis, the pooled RRs of fractures in women who consumed 2 and 8 cups of coffee per day were 1.02 (95% CI: 1.01–1.04) and 1.54 (95% CI: 1.19–1.99), respectively.
Conclusions: Our meta-analysis suggests that daily consumption of coffee is associated with an increased risk of fractures in women and a contrasting decreased risk in men. However, future well-designed studies should be performed to confirm these findings.

Introduction

Coffee is one of the most widely consumed beverages globally. In addition to caffeine, coffee contains more than 1000 different chemical compounds, including carbohydrates, lipids, nitrogenous compounds, vitamins, minerals, alkaloids, and phenolic compounds [1]. Consumption of coffee is known to have potential health benefits, such as prevention of type 2 diabetes mellitus, cardiovascular disease, cancer, and Parkinson's disease [2–5]; however, it can also have harmful effects on health, such as increased blood pressure, serum total and low-density lipoprotein cholesterol concentrations, and plasma homocysteine concentrations [6–8].

The association between coffee consumption and the risk of fractures is important because osteoporosis and osteoporosis-related fractures are major public health problems worldwide [9]. Moreover, as the global population continues to age [10], the prevalence of osteoporosis and osteoporosis-related fractures will likely continue to increase, contributing to a rapid growth in the social and economic burden in the near future [11].

Several epidemiological studies have been conducted to quantify the relationship between coffee consumption and the risk of fractures [12–20], but the findings were inconclusive. In a recently published meta-analysis, Liu et al. noted that the risk of fractures among coffee drinkers was higher, particularly among women [21]. However, this meta-analysis had some limitations: (1) it included incomplete studies that provided only unadjusted results [22]; (2) it included studies that did not fully discriminate between consumption of coffee and

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consumption of other caffeinated drinks [23,24]; and (3) it showed evidence of publication bias toward studies reporting positive findings.

Thus, we aimed to better quantify the association between coffee consumption and the risk of fractures through a comprehensive systematic literature review and dose–response meta-analysis that avoided the aforementioned limitations of the meta-analysis by Liu et al. [21].

Materials and methods

Data sources and searches

The meta-analysis was performed in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines [25]. We identified all potentially relevant articles, without any language restriction, by searching MEDLINE, EMBASE, Cochrane Library, Web of Science, SCOPUS, and CINAHL from the dates of their respective inceptions to February 2013. The searches were enhanced by scanning the bibliographies of all identified original articles and reviews. The following keywords or corresponding Medical Subject Heading (MeSH) terms were used: "coffee," "caffeine," "drink," and "beverage" as the exposure factors and "fracture" as the outcome factor. Two of the authors (DRL and JL) independently evaluated all the retrieved articles for inclusion in the meta-analysis. Any discrepancy between the 2 authors was solved by discussion with the senior investigator (SMP). To be included in our meta-analysis, studies had to (1) be observational studies (case–control or cohort), (2) investigate the association between coffee consumption and the risk of fractures, and (3) provide adjusted relative risks (RRs) with 95% confidence intervals (CIs). We defined "osteoporotic fractures" as fractures of the proximal femur (i.e., hip fracture), pelvis, vertebrae, distal forearm, and proximal humerus that occurred with low-energy trauma. We excluded studies investigating pathologic fractures due to bone metastasis.

For each study, we obtained data on the study design, location (city and country), number of subjects (cases, controls, or cohort size), duration of follow-up (for cohort studies), age at screening, gender, variables adjusted for in the analysis, RR estimates for each level of coffee consumption and the corresponding 95% CIs, and – when available – the number of cases and non-cases for each level of coffee consumption. When this information could not be extracted from the published reports, we contacted the investigators by e-mail to request any missing data.

If a study reported more than one set of RR estimates, we used the maximally adjusted RRs. If a study provided multiple RR estimates on different outcomes (e.g., forearm and hip fractures), we used the RRs derived from the outcome with the largest number of events. We considered gender-specific estimates in cases where a study reported data separately for men and women. When a study analyzed data with different regression techniques (i.e., Cox and Poisson regressions), we used the results derived from the Cox model because this was the most commonly used regression method among all the studies included in the meta-analysis. If multiple reports had been published on the same study, we selected the most recent or informative one.

Quality assessment was performed using the Newcastle–Ottawa Quality Assessment Scale [26]. This scale has a range of 0 to 9; low quality was defined as a Newcastle–Ottawa Scale score <8 and high quality was defined as a score ≥ 8.

Statistical analysis

The RR was used to measure the association between coffee consumption and the risk of fractures. We assumed that odds ratios (ORs) adequately approximate the RR in case–control studies [27]. We computed a pooled RR and the CI for the highest category of coffee consumption compared with the lowest category using random-effects models, which allow for the consideration of both within- and between-study variations [28].

Statistical heterogeneity across studies was assessed using Q statistics; a P value of <0.10 was considered statistically significant [27]. Potential inconsistency was quantified using the Higgins I^2 statistic, which represents the proportion of the total variation contributed by between-study variance [29]. Heterogeneity was considered to be significant when the I^2 statistic was $\geq 50\%$. We performed stratified analyses by study design (cohort or case–control), gender, age at screening (≥ 19 years, ≥ 50 years, and ≥ 65 years), methodological quality (high vs. low), level of adjustment (high vs. low), latitude ($\geq 37°$ vs. $<37°$) [30], study location (United States, Canada, and Europe vs. Asia-Pacific), duration of follow-up (≥ 10 years vs. <10 years), and fracture site (hip/femur or forearm/wrist). The level of adjustment (high vs. low) was defined according to the number of variables (≥ 4 vs. <4) adjusted for in the analyses, as selected from the following: age, gender, body mass index, alcohol consumption, smoking, calcium intake, physical activity, menopause, bone density, sun exposure or vitamin D intake, estrogen therapy, glucocorticoid therapy, previous fractures, grip strength, and functional mobility [10]. In addition, summary estimates were calculated in specific subgroups (postmenopausal women and those with osteoporotic fractures).

A dose–response analysis was performed using both linear and non-linear random-effects models. The linear model was fitted to the data according to the method proposed by Greenland and Longnecker [31], which allows for consideration of correlations among estimates for separate categories of coffee consumption. The non-linear analysis was performed by fitting a class of two-term fractional polynomial models to the data [32], allowing us to simultaneously address the correlations among reported estimates in the same study, the heterogeneity between studies, and the non-linear trend component of the dose–response relationship. To determine the dose–response relationship, we included studies reporting at least 3 categories of coffee consumption and providing the number of cases and controls for each category. Because coffee consumption is often given as a range, we assigned the value of exposure as the midpoint between the upper and lower boundaries for each category of coffee consumption; for the highest open-ended category, the value of exposure was assigned by keeping the same amplitude of range categories. The best-fitting model was defined as the one achieving the lowest Akaike information criterion (AIC) and was selected as the final dose–response model.

To evaluate the included studies for publication bias, we visually explored funnel plots for asymmetry. In addition, Begg's test [33] and Egger's test [34] were performed. All analyses were performed using Stata software version 10 (StataCorp LP, College Station, Texas, USA).

Results

Literature search and study characteristics

Fig. 1 shows the strategy used to identify the relevant studies for inclusion in the meta-analysis. The search strategy identified a total of 5913 reports, of which 1461 were duplicate studies. After reviewing the abstracts of the 4452 remaining reports, 47 reports were selected for full review. Of these, we excluded 2 studies that were letters or reviews, 15 studies that had not been conducted on coffee consumption, 6 studies that reported insufficient data for analysis, 2 studies for which only univariate analyses were performed, 4 studies that did not discriminate between coffee and other caffeinated drinks, 2 studies conducted on the same study population of other included studies, and 1 study that used the same study results of another study already included in the meta-analysis.

Fifteen reports, including 9 cohort studies [12–20] and 6 case–control studies [35–40], were included in the meta-analysis. The main characteristics are summarized in Table 1 for the cohort studies and in Table 2 for the case–control studies. The study by Meyer et al. [17] was considered as 2 studies because it presented the results separately by gender.

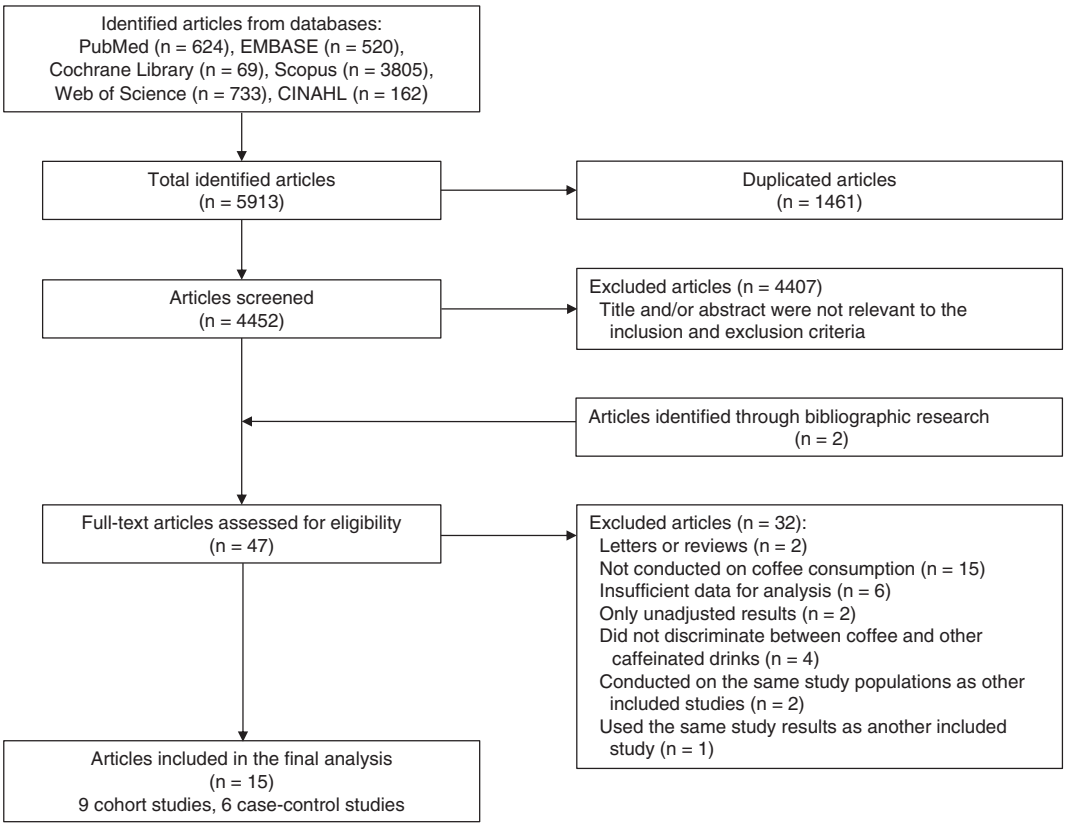

Fig. 1. Flowchart for the identification of studies that were included in the meta-analysis.

Table 1
Summary characteristics of the 9 cohort studies included in the meta-analysis of coffee consumption and the risk of fractures.

First author Year of publication	Location	Follow-up period (year)	Age at screening (year)	Study population		Coffee		Relative risk	Adjusted for
				No. of cases	Size of cohort	Lowest	Highest		
Hernandez-Avila [21] 1991	US	6	34–59	Forearm 593 (F) Hip 65 (F)	F 98,462	Almost never	≥4 cups/day	Forearm 1.10 (0.85–1.44) Hip 3.35 (1.32–8.49)	Age, BMI, menopause status, estrogen-replacement therapy, calcium intake, and alcohol intake
Meyer [24] 1997	Norway	11.4	35–49	Hip 56 (M), 157 (F)	F 19,752 M 20,035	≤2 cups/day	≥9 cups/day	M 1.04 (0.37–2.94) F 1.94 (0.96–3.91)	Age, height, BMI, physical activity, DM, smoking, disability, marital status
Hansen [20] 2000	US	6.5	55–69	Multiple 4378 (F)	F 34,703	<1/month	≥6 cups/day	1.11 (0.97–1.26)	Age
Hallstrom [19] 2006	Sweden	10.3	40–76	Multiple 3279 (F)	F 31,527	<1 cup/day	≥4 cups/day	1.22 (1.04–1.43)	Age, height, weight, total caloric intake, vitamin D intake, vitamin A intake, calcium intake, phosphorous intake, alcohol intake, education, marital status
Trimpou [25] 2010	Sweden	30	46–56	Hip 451 (M)	7495	None	Drinker	0.64 (0.49–0.85)	Age, height, BMI, physical activity, smoking, alcohol intemperance, stroke, dementia
van Lenthe [27] 2011	Netherlands	13	25–74	Hip 192 (M + F)	16,578	None	≥3 cups/day	0.75 (0.42–1.36)	Age, sex, height, father's occupation, adult occupation, education, income
Ma [22] 2011	US	6	71–93	Hip 33 (M) Spine 43 (M)	2737	<1 cup/day	≥1 cup/day	Hip 0.53 (0.24–1.18) Spine 0.62 (0.32–1.22)	Age, education, BMI, grip strength, Upper arm girth, standing height, alcohol, smoking, dietary calcium, physical activity, glucose, diabetic medication, milk
Trimpou [26] 2011	Sweden	20	25–64	Multiple 143 (M + F)	1396	None	2–3 cups/day	1.07 (1.01–1.13)	Age, sex
Maatta [23] 2012	Finland	13	70–73	Femur neck 39 (F)	1222	<3 cups/day	≥3 cups/day	0.30 (0.19–0.79)	Age, BMI, functional mobility, hypertension

Table 2
Summary characteristics of the 6 case–control studies included in the meta-analysis of coffee consumption and the risk of fractures.

First author, Year of publication	Location	Age range (year)	Type of control	Study population		Coffee		Odds ratio	Adjusted for
				No. of cases	No. of control	Lowest	Highest		
Kreiger [30] 1992	Canada	50–84	Hospital	Hip 102 (F) Wrist 54 (F)	277	<3	≥3 cups/day	Hip 1.18 (0.64–2.18) Wrist 0.90 (0.55–1.47)	Age, estrogen replacement, ovariectomy, smoking, calcium intake, tea drinking, Quetelet index[a]
Nieves [31] 1992	US	50–103	Hospital	Hip 162 (F)	168	None	≥3 cups/day	1.87 (0.74–4.69)	Age, BMI, smoking, chronic disease, education
Johnell [28] 1995	Portugal, Spain, France, Greece, Italy, Turkey	≥50	Community	Hip 2086 (F)	3532	<1 cup/day	≥3 cups/day	1.01 (0.82–1.23)	Age, center, BMI
Tavani [33] 1995	Italy	19–74	Hospital	Hip 279 (F)	1061	None	≥5 cups/day	1.2 (0.5–2.7)	Age, education, BMI, smoke, total alcohol drinking, calcium intake, menopausal status, estrogen replacement therapy
Suzuki [32] 1997	Japan	65–89	Community	Hip 249 (M + F)	498	Never	≥3 cups/day	3.59 (1.46–8.85)	Age, sex, BMI, physical activity, living area in the past, main work activity, sleep disturbance during the past six months, past history of stroke with hemiplegia diabetes, alcohol intake, milk consumption, drinking Japanese green tea, fish eating, sun exposure, physical exercise, immobilized or bedridden condition, type of bedding, and ADL for bathing (washing and drying)
Kanis [29] 1999	Portugal, Spain, France, Greece, Italy, Turkey	50–100	Community	Hip 730 (M)	1132	<1 cup/day	≥3 cups/day	0.91 (0.67–1.22)	Age, center, BMI, recreational physical activity, milk intake, cheese intake, consumption of tea, consumption of alcohol

[a] Quetelet index: quantified bone mass (g/cm^2).

The majority of the studies included in the meta-analysis were from Western countries (United States, Canada, and Europe), although 2 studies were from Asia-Pacific countries [15,39]. Six of the 16 studies [12–20,35–40] – 4 studies conducted in women [12,14,17,38], 1 study conducted in men [17], and 1 study conducted in both men and women [39] – fulfilled the definition of osteoporotic fracture. The average duration of follow-up in the 9 cohort studies included in the meta-analysis was 12.9 years (range, 6–30 years). The cohort studies achieved relatively high scores on the quality assessment (7–9 in total) except for the studies by Hansen et al. [13] and Trimpou et al. [19]. Conversely, the case–control studies achieved low quality assessment scores (6–7 in total) (Table 3).

Main analysis

Fig. 2 summarizes the comparisons between the highest and lowest categories of coffee consumption. A total of 12,939 fracture cases and 253,514 participants from the 16 studies were included in this analysis. The summary RR was 1.03 (95% CI: 0.91–1.16, $I^2 = 61.4\%$, P = 0.001) for all studies combined, 0.99 (95% CI: 0.86–1.14, $I^2 = 68.9\%$, P = 0.001) for the cohort studies, and 1.18 (95% CI: 0.89–1.57, $I^2 = 49.5\%$, P = 0.078) for the case–control studies.

Subgroup analysis

We examined the possible differences in risk estimates using several study characteristics (study design, gender, age at screening, methodological quality, level of adjustment, latitude, location, duration of follow-up, and fracture site). A significant interaction was noted between gender and coffee consumption (P < 0.001). The summary RR was significant only among men (RR: 0.76, 95% CI: 0.62–0.94, $I^2 = 7.3\%$, P = 0.36) (Table 4). On sensitivity analysis, this association disappeared when the study by Trimpou et al. [18] or the study by Ma et al. [15] was omitted. For women, the RR was marginally significant (RR: 1.11, 95% CI: 0.97–1.28, $I^2 = 43.5\%$, P = 0.08). However, the study by Maatta et al. [16] provided selective information for specific fracture location (femoral neck) and did not report results that would have been more informative for hip fracture (e.g., total hip). By replacing the results of this study with those of another cohort study conducted in the same population with a similar duration of follow-up (Jokinen et al. [41]; RR of trochanteric fractures: 2.58, 95% CI: 1.01–6.56), the heterogeneity decreased greatly from an I^2 of 43.5% (P = 0.08) to an I^2 of 6.5% (P = 0.38) and a significant association was observed (RR: 1.15, 95% CI: 1.05–1.26) in the female population. Furthermore, a similar result was found (RR: 1.14, 95% CI: 1.05–1.24, $I^2 = 0.0\%$, P = 0.58) when excluding the study by Maatta et al. [16]. Moreover, sensitivity analyses excluding each study in turn showed the robustness of the pooled RR in women.

Additional stratified analyses showed that coffee consumption was unrelated to the risk of fractures in postmenopausal women (RR: 0.98, 95% CI: 0.76–1.25, $I^2 = 64.2\%$, P = 0.04). The pooled RR was 1.35 (95% CI: 1.06–1.73, $I^2 = 41.9\%$, P = 0.13) when we considered the 6 studies that fulfilled the definition of osteoporotic fracture. Furthermore, when the analysis was restricted to the 4 studies investigating osteoporotic fractures in women, the pooled RR was 1.29 (95% CI: 1.05–1.57, $I^2 = 27.4\%$, P = 0.24). However, additional stratified analyses were not performed for the male population because of a lack of data (Table 4).

Dose–response relationship

The dose–response analysis was restricted to the female population because only 1 study reported estimates for the male population. Of the 9 studies reporting RR estimates for the female population, 5 studies [12,14,17,38,40] were included in the dose–response analysis. Based on the AIC, a non-linear model was selected (AIC for the best non-linear model: −78.7, AIC for the linear model: −10.9). The dose–risk

Table 3
Quality assessment of cohort and case–control studies included in the meta-analysis of coffee consumption and the risk of fractures according to the Newcastle–Ottawa Scale.[a]

Cohort studies	Selection				Comparability	Outcome			Overall quality score (Total = 9)
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Control for important factors or additional factors	Assessment of outcome	Follow-up was long enough for outcomes to occur	Adequacy of follow up of cohorts	
Hernandez-Avila [21] 1991	1	1	1	1	2	1	0	0	7
Meyer [24] 1997	1	1	0	1	2	1	1	1	8
Hansen [20] 2000	1	1	0	1	1	0	0	0	4
Hallstrom [19] 2006	1	1	1	1	2	1	1	1	9
Trimpou [25] 2010	1	1	0	1	2	1	1	0	7
van Lenthe [68] 2011	1	1	0	1	2	1	1	1	8
Ma [22] 2011	1	1	0	1	2	1	1	0	7
Trimpou [26] 2011	1	1	0	1	1	1	1	0	6
Maatta [23] 2012	1	1	0	1	2	1	1	0	7
Case–control studies	Selection				Comparability	Exposure			Overall quality score (Total = 9)
	Adequate definition of cases	Representativeness of cases	Selection of controls	Definition of Controls	Control for important factors or additional factors	Ascertainment of exposure (blinding)	Same method of ascertainment for subjects	Non-response rate	
Kreiger [29] 1992	1	1	0	1	2	0	1	0	6
Nieves [30] 1992	1	1	0	1	2	0	1	1	7
Johnell [27] 1995	1	1	1	1	2	0	1	0	7
Tavani [32] 1995	1	1	0	1	2	0	1	0	6
Suzuki [31] 1997	1	1	1	1	2	0	1	0	7
Kanis [28] 1999	1	1	1	1	2	0	1	0	7

[a] A study can be awarded a maximum of 1 point for each numbered item in the selection and outcome categories. A maximum of 2 points can be given for comparability.

function for the female population showed an RR of 1.02 (95% CI: 1.01–1.04) for 2 cups/day of coffee, 1.12 (95% CI: 1.04–1.21) for 4 cups/day, 1.31 (95% CI: 1.13–1.52) for 6 cups/day, and 1.54 (95% CI: 1.19–1.99) for 8 cups/day (Fig. 3).

Publication bias

Fig. 4 presents the funnel plot of log RR versus variance of log RR for all the studies included in the meta-analysis (n = 16). Publication bias was not suspected from visualization of the funnel plot or from Begg's test (P = 0.96) or Egger's test (P = 0.93).

Discussion

In the present meta-analysis, we found that coffee consumption was associated with an increased risk of fractures in women in a dose-dependent fashion. We showed that consumption of 2 and 8 cups/day of coffee was associated with a 2% and 54% higher risk of fractures in women compared with that in those who didn't drink coffee, respectively. Interestingly, however, the risk of fractures was 24% lower in men with the highest level of coffee consumption.

Our meta-analysis addressed some of the limitations of a recently published meta-analysis on the association between coffee consumption and the risk of fractures [21]. First, we included only studies investigating coffee consumption, whereas Liu et al. [21] included studies of both caffeine intake and coffee consumption. Second, we excluded studies reporting only an unadjusted RR of fractures to rule out a confounding effect. Third, we performed a more recent and comprehensive literature review that included both cohort and case–control studies and identified 8 additional reports compared with the meta-analysis by Liu et al. [21]. Therefore, we could examine the dose–response relationship between coffee consumption and the risk of fractures with greater statistical power, while avoiding publication bias and performing additional subgroup analyses.

Effects of caffeine on bone

Although the mechanism responsible for the association between coffee consumption and the risk of fractures is unclear, most studies have implicated caffeine – one of the major ingredients of coffee – as the key to the association. Several prospective cohort studies have found that increased caffeine intake was associated with an increased risk of hip fracture [14,24,42], first vertebral fracture [43], and wrist fracture [13], especially in women. Therefore, high levels of caffeine intake may be a risk factor for osteoporosis in women, as shown by our meta-analysis. Biological evidence also supports this finding. In animal models, caffeine intake resulted in negative calcium balance through increased calcium excretion in urine and feces [44]. Caffeine also enhanced osteoclast differentiation from bone marrow hematopoietic cells and reduced bone mineral density in growing rats [45]. Altered mechanical properties of the bone were also observed in young ovariectomized rats [46]. In human studies, caffeine has been shown to similarly influence calcium metabolism by impairing the efficiency of calcium absorption [47], increasing calcium excretion in urine [47,48], and decreasing vitamin D receptor protein expression and $1,25(OH)_2$ vitamin D_3-stimulated alkaline phosphatase activity of osteoblasts [49]. Based on epidemiological and experimental evidence, the increased risk of fractures with increasing coffee consumption in women, as seen in our study, may be at least partly attributed to the effects of caffeine.

Gender effects on the association between coffee (or caffeine) consumption and the risk of fractures

Previous epidemiological studies have shown a gender difference in the association between caffeine intake and bone health. Yano et al. [50] found an inverse relationship between caffeine intake and bone density

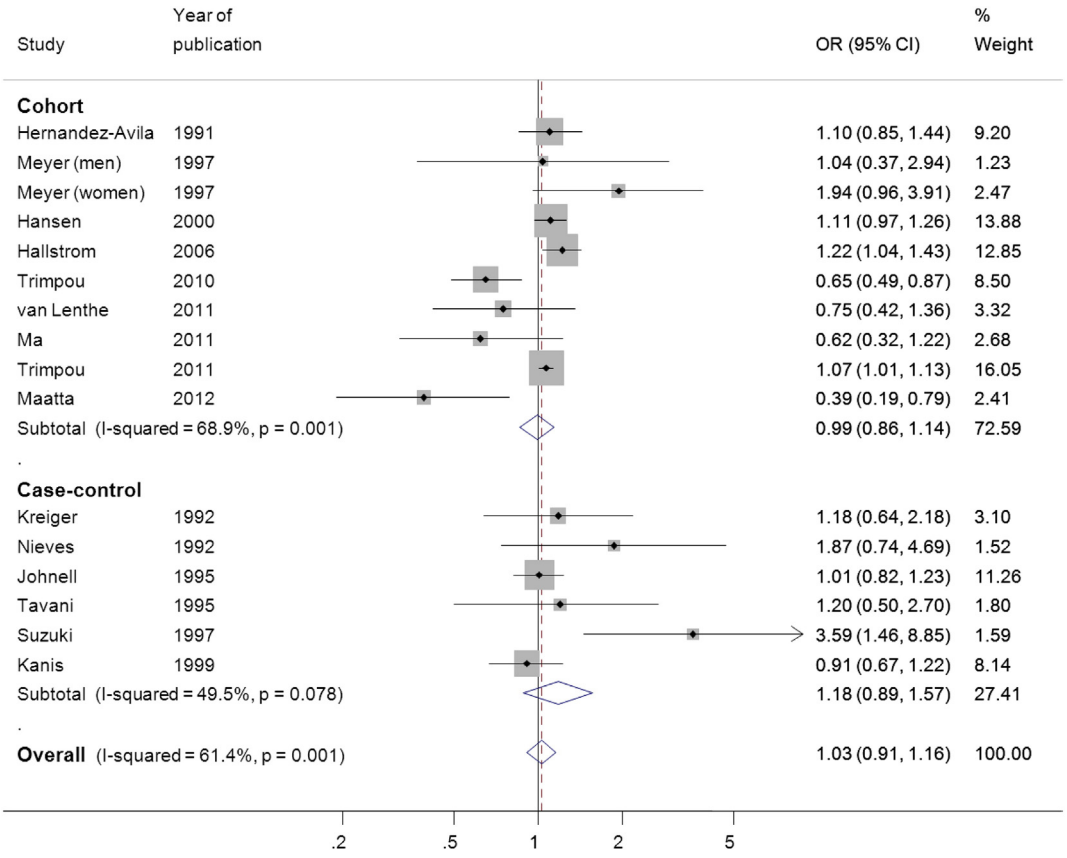

Fig. 2. Study-specific and pooled relative risks (RRs) along with 95% confidence intervals (CIs) of fractures for the highest and lowest categories of coffee consumption. Pooled RRs and their respective 95% CIs were calculated using random-effects models.

in women but not in men. This gender difference was also noted in a case–control study [24] and in a cohort study [51], and both of which examined the effect of caffeine intake on the risk of fractures. These results suggest that the effects of caffeine on bone may be different in men and women. Not surprisingly, gender is a critical factor affecting bone mass and fracture. Young men have larger bones and thicker trabeculae than young women [52], and periosteal bone formation, which offsets age-related bone loss, is greater in men [53]. Furthermore, a rapid decline in estrogen production at menopause and a longer life span contribute to the prevalence of osteoporosis in elderly women [54]. Thus, it seems likely that women would be more vulnerable to extrinsic factors such as caffeine intake. In addition, physiological, hormonal, and behavioral disparities between genders may also affect or confound the relationship between caffeine and bone. These possibilities require further investigation.

Similar to the case of caffeine, a gender difference was also suspected in the association between coffee consumption and the risk of fractures. In our study, coffee consumption was associated with an increased risk of fractures in women but a decreased risk of fractures in men with the highest level of coffee consumption. Given that the association between caffeine intake and bone health is not evident in men, as discussed in the preceding text, it is not surprising that the association between coffee consumption and the risk of fractures in men differed from that in women. However, our results are interesting because we found an opposite tendency, and not merely a lack of tendency, in men. Although the same result was reported in the meta-analysis conducted by Liu et al. [21], the investigators suggested that the effect may have been a chance occurrence. This inference was based on the fact that the pooled estimate of the previous meta-analysis among men was influenced by a large-scale study by Trimpou et al. [18] in which the investigators assumed that the possible favorable effect of coffee might be confounded by characteristics of participants who do not drink coffee. Based on the sensitivity analysis, however, no single study in our meta-analysis exclusively decided the significance of the result in the male population. In this respect, a relationship between coffee consumption and the decreased risk of fracture observed in our study may not be a chance occurrence and seems to be clinically relevant. Interestingly, a 5-year follow-up study of 70 adult male monozygotic twins showed that 1 cup/day of coffee increased bone mineral density in the femoral neck [55]. Furthermore, several components of coffee other than caffeine have been shown to exert favorable effects on bone metabolism, as discussed in the following section.

Effects of non-caffeine components of coffee on bone metabolism

Several studies have indicated that polyphenols from tea may exert beneficial effects on bone mineral density [35,36,56,57]. Coffee also contains polyphenols (e.g., caffeic acid, *p*-coumaric acid, ferulic acid, and kahweol) and provides 4 times the amount of polyphenols (per volume) compared to that found in tea [58]. *P*-coumaric acid (*P*-hydroxycinnamic acid) has been shown to decrease bone resorptive activity in a rat model [59], and other phenolic acids (caffeic acid and ferulic acid) may also have favorable effects on bone metabolism [60,61]. Kahweol, a coffee-specific diterpene, inhibits osteoclastogenesis and prevents the bone-resorbing activity of osteoclasts [62]. Based on these findings, coffee may exert beneficial effects on bone health due to its high polyphenol composition; the effects may be especially prominent in men, who are resistant to caffeine-induced bone loss [24,50,51]. Although evidence is lacking to support the protective effect of coffee on bone in men, we need to acknowledge the homogeneity of the results and recognize that the issue warrants further investigation. In summary, a decreased risk of fractures among coffee-drinking men

Table 4
Pooled relative risks (RRs) and 95% confidence intervals (CIs) for coffee consumption and the risk of fractures in the strata of selected covariates.

Included studies[a]	No. of studies	RR (95% CI)	I^2 (%)	P for heterogeneity
Gender				
Men	4	0.76 (0.62–0.94)	7.3	0.36
Women[b]	8	1.14 (1.05–1.24)	0.0	0.58
Age at screening (year)				
≥19	8	1.03 (0.88–1.22)	62.1	0.01
≥50	5	1.07 (0.97–1.18)	0.0	0.52
≥65	3	0.92 (0.28–3.06)	86.8	0.001
Methodological quality[c]				
High (≥8)	4	0.99 (0.86–1.14)	65.3	0.001
Low (<8)	12	1.18 (0.87–1.59)	31.3	0.22
Level of adjustment[d]				
High (≥4)	10	1.07 (0.85–1.36)	64.0	0.001
Low (<4)	6	1.03 (0.90–1.17)	63.9	0.05
Latitude[e]				
≥37°	13	1.02 (0.90–1.15)	59.1	0.004
<37°	2	1.45 (0.26–8.11)	89.4	0.002
Location				
USA, Canada, Europe	14	1.03 (0.92–1.14)	55.7	0.006
Asia-Pacific[f]	2	1.45 (0.26–8.11)	89.4	0.002
Duration of follow-up				
≥10 years	7	0.94 (0.75–1.18)	76.9	<0.001
<10 years	3	1.07 (0.90–1.27)	28.8	0.25
Fracture Site[g]				
Hip/femur	11	0.96 (0.73–1.26)	66.8	0.001
Forearm/wrist	2	1.05 (0.83–1.33)	0.0	0.48
Osteoporotic fracture				
Men or women	6	1.35 (1.06–1.73)	49.9	0.13
Women	4	1.29 (1.05–1.57)	27.4	0.24
Postmenopausal women	4	0.98 (0.76–1.25)	64.2	0.04

[a] The study by Meyer et al. [17] was considered 2 studies because it presented the results separately according to the gender.
[b] The study by Maatta et al. [16] was not considered.
[c] Assessed using the Newcastle–Ottawa Scale (maximum score, 9).
[d] Defined according to the number of important variables that were adjusted in the analyses (age, gender, body mass index, alcohol, smoking, calcium intake, physical activity, menopausal status, bone density, sun exposure or vitamin D intake, estrogen therapy, glucocorticoid use, grip strength, functional mobility).
[e] The study by Hernandez-Avila et al. [14] was not considered since latitude was not classifiable.
[f] The study by Ma et al. [15] was classified as the Asia-Pacific region considering the ethnicity of the study population (Hawaiian Japanese).
[g] The study by Kreiger et al. [37] was included in the forearm/wrist fracture analysis due to the scarcity of studies on forearm/wrist fractures.

might be explained by the (1) ambiguous detrimental effects of caffeine on bone, (2) possible confounding factors that have not been fully considered, and (3) beneficial effects of non-caffeine components in coffee

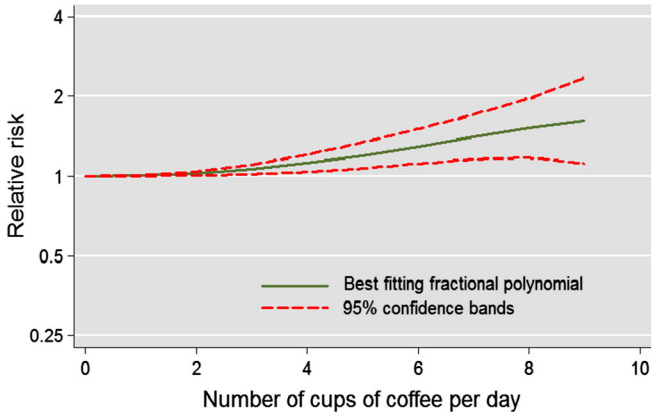

Fig. 3. Relative risk function (solid green line) along with the corresponding 95% confidence interval (dashed red lines) describing the best-fitting dose–response relationship between coffee consumption and the risk of fractures in women. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

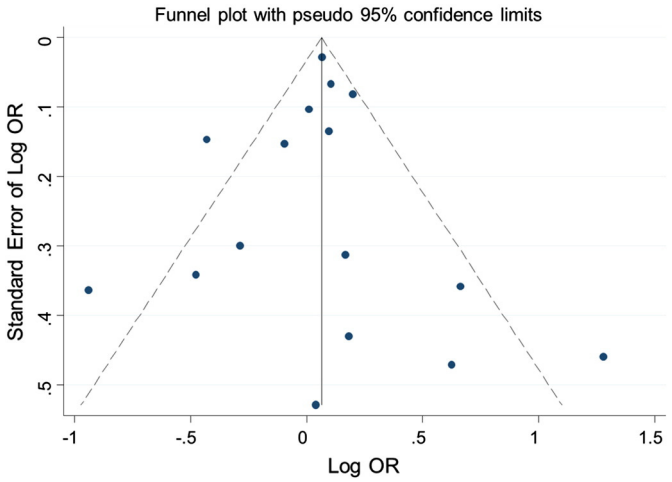

Fig. 4. Funnel plot for studies included in the meta-analysis of coffee consumption and the risk of fractures.

on bone health. However, further studies are required on whether, why, and how caffeine and other compounds (e.g., polyphenols) exert differential effects on bone metabolism according to gender.

Strengths and limitations

Our study has some limitations. First, there may have been recall bias in the case–control studies and information bias in the cohort studies. Second, the included studies either did not seek to quantify total lifetime coffee consumption or did not consider the type of coffee bean used, the brewing time, or the preparation method, all of which may affect the quantities of caffeine in the consumed drink. Additionally, coffee can be consumed in a variety of ways (e.g., decaffeinated, with or without milk or cream), and this aspect was not considered in most studies. Third, although baseline bone mineral density is an important factor, only one study considered its effects on the results. Fourth, many other possible confounders, such as smoking and alcohol consumption, which are commonly associated with coffee consumption and can contribute to the risk of falling, were not fully accounted for in several studies. Fifth, because of limited data, the interactions between coffee and other factors (e.g., calcium intake) were not examined.

Despite these limitations, our study has several strengths. First, we performed the most comprehensive literature search to date, without language restriction, on the effect of coffee consumption on the risk of fractures. Second, our analysis included studies with adjusted results. Third, there was little evidence of publication bias revealed by visual inspection and statistical analyses. Fourth, we examined the associations in detail according to various stratifying factors. Fifth, the included studies had large sample sizes and long durations of follow-up. Thus, we had adequate statistical power to clarify the effects of even low levels of coffee consumption on the risk of fractures. Lastly, we quantified the association between coffee consumption and the risk of fractures by creating flexible non-linear dose–response models. Along with these strengths, there were low levels of heterogeneity among studies for the main results, which also make our study noteworthy.

Conclusions

In summary, coffee consumption was associated with a slightly increased risk of fractures in women in a dose-dependent fashion. Conversely, coffee consumption was associated with a decreased risk of fractures in men. Given the potential limitations in the designs of the included studies and possible uncontrolled confounding effects, prospective well-designed studies should be performed to confirm these findings. Further efforts are also required to understand the gender

difference that may exist in the effects of coffee on the risk of fractures. In addition, the mechanisms and active components of coffee that may be responsible for these associations remain under investigation.

Conflict of interest

None.

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