

Coffee consumption and risk of fractures: a meta-analysis

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Abstract

Introduction: Recent studies have indicated higher risk of fractures among coffee drinkers. To quantitatively assess the association between coffee consumption and the risk of fractures, we conducted this meta-analysis.

Material and methods: We searched MEDLINE and EMBASE for prospective studies reporting the risk of fractures with coffee consumption. Quality of included studies was assessed with the Newcastle Ottawa scale. We conducted a meta-analysis and a cumulative meta-analysis of relative risk (RR) for an increment of one cup of coffee per day, and explored the potential dose-response relationship. Sensitivity analysis was performed where statistical heterogeneity existed.

Results: We included 10 prospective studies covering 214,059 participants and 9,597 cases. There was overall 3.5% higher fracture risk for an increment of one cup of coffee per day (RR = 1.035, 95% CI: 1.019-1.052). Pooled RRs were 1.049 (95% CI: 1.022-1.077) for women and 0.910 (95% CI: 0.873-0.949) for men. Among women, RR was 1.055 (95% CI: 0.999-1.114) for younger participants, and 1.047 (95% CI: 1.016-1.080) for older ones. Cumulative meta-analysis indicated that risk estimates reached a stabilization level (RR = 1.035, 95% CI: 1.019-1.052), and it revealed a positive dose-response relationship between coffee consumption and risk of fractures either for men and women combined or women specifically.

Conclusions: This meta-analysis suggests an overall harm of coffee intake in increasing the risk of fractures, especially for women. But current data are insufficient to reach a convincing conclusion and further research needs to be conducted.

Key words: coffee, caffeine, fracture, meta-analysis, cohort study.

Introduction

Observational studies relating coffee intake to the risk of fractures have given inconsistent results [1-11]. With the first prospective study indirectly referring to it, Holbrook *et al.* [12] reported an increase in incidence of hip fracture in women with high caffeine intake and an inverse relation in men. However, neither association was statistically significant. And the Study of Osteoporotic Fractures Research Group [3] revealed that rel-

ative risk for hip fracture was 1.2 (95% CI: 1.0-1.4) per 190 mg caffeine intake. It was adjusted for a substantial number of covariates, including bone mineral density (BMD).

Coffee consumption is the major source of dietary caffeine intake, and it is one of the most popular beverages consumed worldwide. Its effects on bone metabolism and fractures have been explored extensively but the conclusion is still controversial [10, 11, 13-23]. Because of the aging of the world's population and at least half of all white women more than 50 years old will be affected by osteoporotic fractures [24], it has already become one of the most invisible killers worldwide. Moreover, following a fracture, medical and hospitalization costs were 1.6-6.2 times higher than pre-fracture costs and 2.2-3.5 times higher than those for matched controls [25], let alone the decreased quality of life [26]. So the association between coffee consumption and the risk of fractures should be emphasized. In 1989 a randomized cross-over trial [27] conducted among 16 women indicated that 400 mg/day of caffeine had no effect on the calcium economy of premenopausal women. This study, with high quality of study design, could not cease the debate. It was not only because of its specific population setting and small sample size, but because its target intervention was caffeine rather than coffee. Furthermore it cannot rule out deleterious effects of caffeine for postmenopausal women or women with lower calcium intakes. On the other hand, results from prospective studies referring to the specific association have not yet been summarized. Thus to quantitatively assess the relationship, we conducted this meta-analysis.

Material and methods

Literature search and selection

Pertinent studies were identified by a literature search up until June 2012 using the PubMed and Embase databases with the string '(coffee OR caffeine) AND fracture', following the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines [28]. Full texts were reviewed if studies reported the association between coffee consumption and fracture in humans. Reference lists from original research and review articles were also scrutinized for further relevant studies. When multiple reports were published on the same population or subpopulation, we included only the most recent or informative one. No studies were excluded a priori for weakness of design or data quality.

Studies eligible for inclusion in this meta-analysis were required to meet the following criteria: 1) a prospective design; 2) the exposure of interest was coffee or caffeine consumption (when both were provided, we extracted data specifically relat-

ed to coffee); 3) the outcome was incident fracture; and 4) the investigators reported risk estimates with 95% confidence intervals (or data to calculate them).

Data extraction and assessment of study quality

Two investigators (Huifang Liu, Wenjie Zhang) independently extracted the data and assessed the quality of studies included using a standardized data-collection form and the Newcastle-Ottawa scale. Discrepancies were resolved by discussion with a third investigator (Jun Zhou).

To explore possible reasons for discrepancies among study findings, we extracted the following information whenever possible: first author's last name, publication year, study location, follow-up period, mean duration of follow-up, population, sample size, participant characteristics, measurement of coffee consumption, coffee intake categories, the number of cases over the follow-up period and the number of total exposed population at baseline for each category of coffee intake, risk estimates adjusted for the greatest degree of control for potential confounders with corresponding 95% CIs (or data to calculate them) for each category, and lists of corresponding confounding factors.

The Newcastle-Ottawa scale proposed by the Cochrane Collaboration was used for assessing the quality of the included studies. It was applied by judging on three domains:

1. Selection of study groups:
 - a) Representativeness of the average community-dwelling resident who has access to coffee;
 - b) Selection of patients who do not drink coffee even with access to it;
 - c) Ascertainment of coffee consumption;
 - d) Demonstration that fractures were not present at baseline.
2. Comparability of patients: comparability of patients on the basis of the study design or analysis.
3. Outcome of interest (incident fracture):
 - a) Assessment of fractures;
 - b) Was followed up long enough;
 - c) Adequacy of follow-up of the patients.

Each item was allocated 'stars' for a quantitative appraisal of overall quality of the individual studies. The maximum number of stars a study may receive in each of these 3 categories is 4, 2 and 3, respectively. A study can be considered to have a low risk of bias if it was allocated the maximum number of stars. Studies with a score of 7 stars or greater were considered to be of high quality, and studies with a score of 3 stars or lower were deemed to be of low quality. Disagreement was settled as described above.

Statistical analysis

The measures of interest were the relative risk (RR) and the corresponding 95% CIs. When RRs were not available from the published article, they were computed based on the exposure distributions. Where RRs are provided corresponding to caffeine consumption, we get an estimated RR with regard to coffee drinking with the conversion method adopted from the study conducted by Conen *et al.* [39]. To combine RRs on the same scale in the pooled analysis, we prefer to calculate the study-specific RR for 1 cup per day increment of coffee consumption. It assumed a log-linear association of coffee consumption and risk of fractures, and RRs within each study depend on a common reference group.

Whenever possible we adopted a method proposed by Greenland [40, 41] to estimate study-specific slopes. It was regarded as an estimate of RR for the increment of one unit of exposure, from the natural logarithm of the RR across exposure categories. Each category was assigned with the corresponding midpoint of the range, and for the open-ended upper category we considered it of the same amplitude as the preceding one. Then we obtained the study-specific RRs for an increment of one cup of coffee per day and pooled them with random-

effects models or fixed-effects models, using the inverse of the corresponding variances as weights. We also conducted a cumulative meta-analysis and explored the potential dose-response relationship.

Statistical heterogeneity among studies was estimated using *Q* and *I*² statistics. For the *Q* statistic, heterogeneity was considered present for a *p* value < 0.05. And with regard to the *I*² statistic, it indicated low heterogeneity with a value < 25%, moderate heterogeneity with a value ranging between 25% and 75%, and high heterogeneity with a value > 75%. Sensitivity analysis was performed to identify whether the results could have been affected markedly by a single study. Possible publication bias was evaluated by funnel plot visual analysis and with Begg's and Egger's tests [42]. All statistical analyses were performed with STATA (version 11.0; Stata Corp, College Station, TX).

Results

Search results and study characteristics

The detailed process of study selection from the initial search to final inclusion is shown in Figure 1. Ten studies [1-9, 43] with 214,059 participants and 9,597 cases were included.

All studies except two [1, 2] made coffee intake assessment only once, at baseline. The study conducted by van Geel *et al.* [7] consisted of participants with a history of fracture at the start of follow-up. With regard to outcome assessment, subjects sustaining fractures due to high-energy trauma in three studies [5-7] were not excluded in their analysis. And fractures are not all clinically confirmed but partially identified by self-report in two [2, 5] studies.

Quality assessment of included studies

The median score (the number of stars awarded) was 8 (out of 9) for the included studies with a range of 6 to 9 points (Table I). One of the two studies with moderate risk of bias was part of the Nurses Health Study. The exposed cohort was drawn from the selected group of individuals (nurses) who are not truly representative of the average women in the community. And the ascertainment of outcome relied upon self-report by the participants, although the validity of self-reported fractures was demonstrated. The other one was deemed to be with moderate risk of bias for the following reasons: first of all, participants with previous fractures were included at the start of the study. Second, risk estimate was calculated based on univariate Cox regression rather than a multivariate Cox regression. Finally, the follow-up rate was lower than 80% and non-participants were on average 3.5 years older than participants.

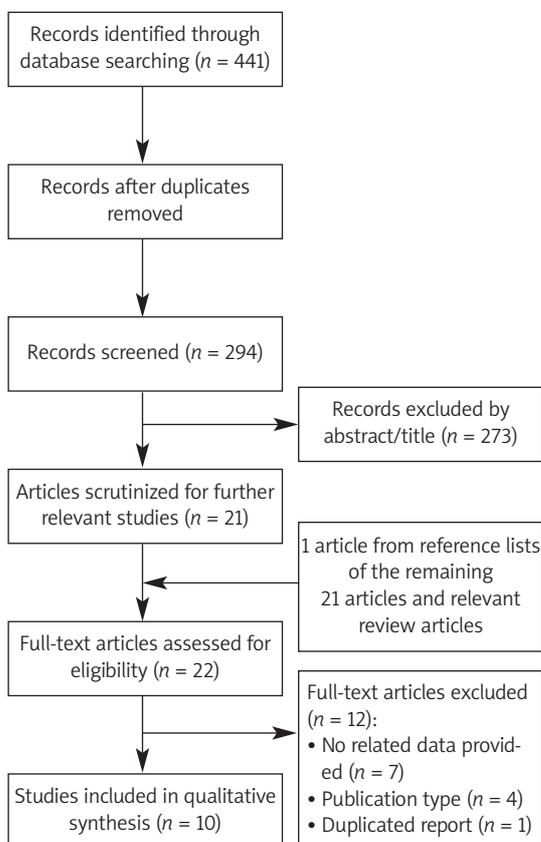


Figure 1. QUOROM flow diagram of the process of article selection for meta-analysis

Primary analysis

The estimated RRs for an increment of one cup of coffee per day from each study and all studies combined are presented in Figure 2. Five [1, 2, 4, 6, 8] of the ten study-specific RRs are obtained by using the method proposed by Greenland [40, 41]. The others are calculated with the logit-linear regression method or extracted from original data. Because the risk of fracture is low, odds ratios [9] and hazard ratios [6-8] in four studies were used to estimate relative risks [44, 45].

Meta-analysis of all the ten studies found a slightly increased risk of fracture (RR = 1.026, 95% CI: 0.996-1.057) for an increment of one cup of coffee per day (Figure 2). But the heterogeneity ($Q = 52.29$, $p < 0.0001$, $I^2 = 80.9\%$) cannot be ignored. To explore possible reasons for it, sensitivity analysis was conducted by removing one study at a time and analyzing the rest studies. The result was strongly influenced by two studies conducted by Hansen *et al.* [5] and Trimpou *et al.* [8]. Without them there was a higher fracture risk (RR = 1.035; 95% CI: 1.019-1.052), and the heterogeneity was acceptable ($Q = 15.38$, $p = 0.052$, $I^2 = 48\%$).

Gender-specific analysis indicated risk elevation for female coffee drinkers and reduction for male drinkers (Figures 3, 4). To access the heterogeneity detected among women, we did sensitivity analysis similarly, and the result was influenced by the study conducted by Hansen *et al.* [5]. After excluding it, heterogeneity is still significant ($Q = 56.88$, $p < 0.0001$, $I^2 = 87.7\%$). Then we further excluded two studies [1, 3] with caffeine as the exposure factor rather than coffee and got insignificant heterogeneity ($Q = 6.54$, $p = 0.162$, $I^2 = 38.8\%$), with slightly lower combined RR for women (RR = 1.049, 95% CI: 1.022-1.077).

Table I. Risk of bias assessment

Study	Selection	Comparability	Outcome	NOS score
Kiel 1990 [1]	****	**	***	9
Hernandez-Avila 1991 [2]	***	**	*	6
Cummings 1995 [3]	****	**	***	9
Meyer 1997 [4]	***	**	***	8
Hansen 2000 [5]	****	**	**	8
Hallström 2006 [6]	****	**	***	9
van Geel 2006 [7]	***	*	**	6
Trimpou 2010 [8]	****	*	***	8
Jokinen 2010 [9]	***	**	***	8
Trimpou 2011 [43]	****	**	***	9

By excluding the three studies [1, 3, 5] mentioned above, five studies providing separate data for women left. When stratified by age at baseline, pooled RRs per cup of coffee were 1.055 (95% CI: 0.999-1.114) for studies including subjects younger than 40 years old, and 1.047 (95% CI: 1.016-1.080) for studies with all participants older than 40 years old. Because the two studies with younger participants were heterogeneous ($Q = 4.09$, $p = 0.043$, $I^2 = 75.6\%$), and the heterogeneity test between subgroups was likely to be invalid, we chose not to perform the analysis.

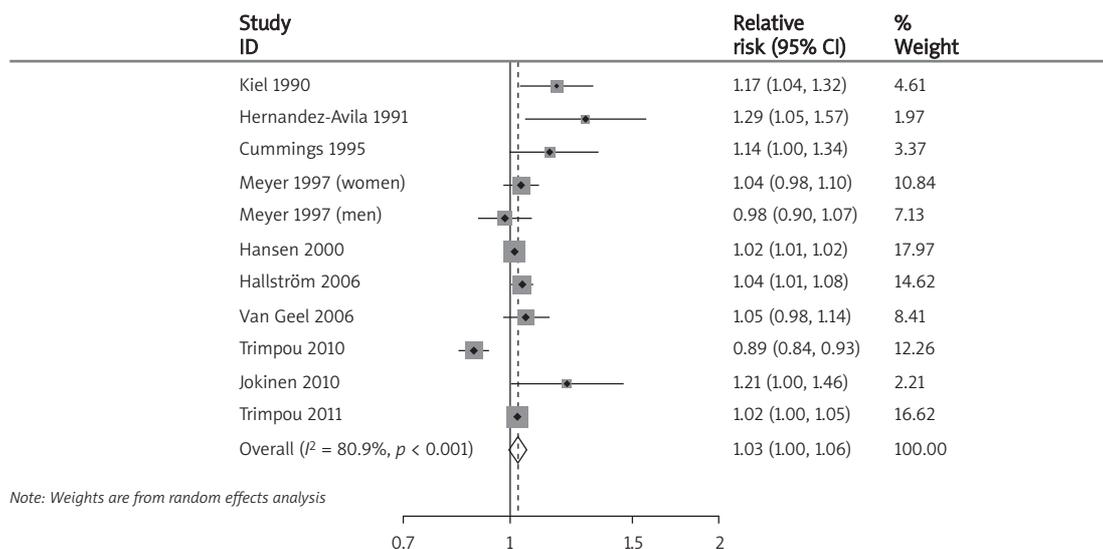


Figure 2. Forest plot for relative risks of fractures for an increment of one cup of coffee per day

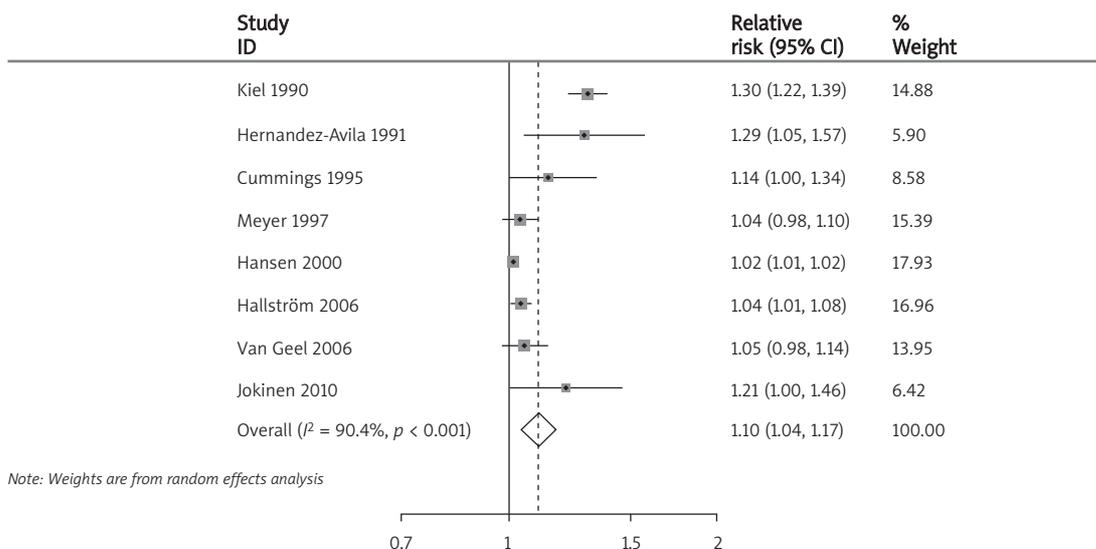


Figure 3. Forest plot for relative risks of fractures for an increment of one cup of coffee per day among women

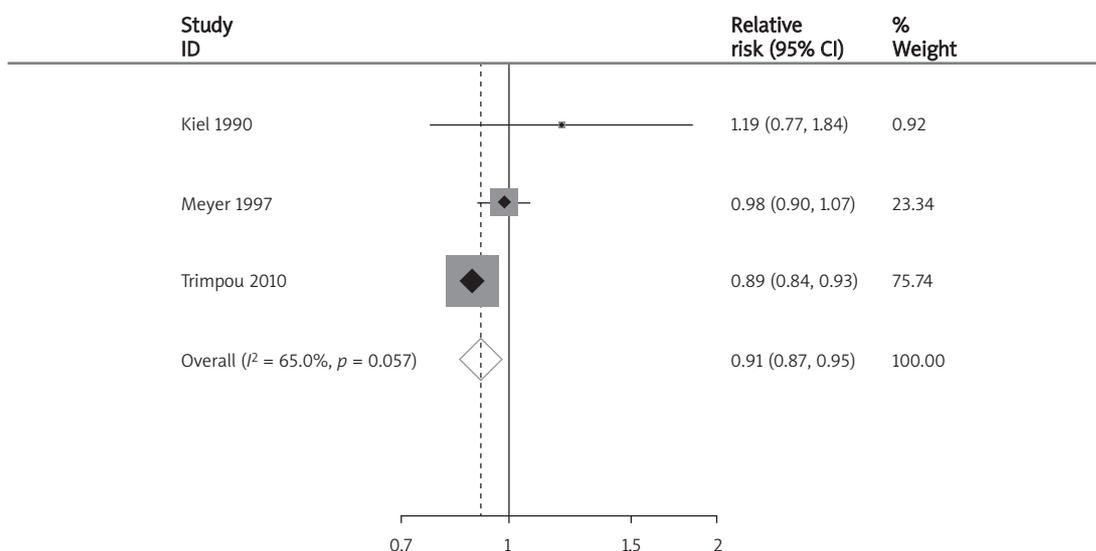


Figure 4. Forest plot for relative risks of fractures for an increment of one cup of coffee per day among men

Cumulative random effects meta-analysis was conducted for men, women, and men and women combined (figures not shown). These analyses were conducted on condition that studies causing inconsistent pooled RR were excluded as mentioned above. Studies on this topic increased steadily over time. Pooled RR for the increment of one cup of coffee per day was becoming consistent, which was illustrated by the narrowing confidence interval. Taking the summary result for men and women combined for example, it was 1.057 (95% CI: 1.014-1.102) at the end of 1997 and is currently 1.035 (95% CI: 1.019-1.052), with no meaningful variation in heterogeneity ($Q = 15.38$, $p = 0.052$, $I^2 = 48\%$).

The dose response relation was assessed by scatter plot illustrating the RR (on a log scale) with

corresponding exposure levels, and quantified by restricted maximum likelihood estimation (figures not shown). All the RR estimates (for each level of exposure) obtained from the eight studies (studies [5, 8] causing inconsistent pooled RR were excluded as mentioned above) were plotted and added to the regression model. Corresponding exposure levels were assigned by the mean of the upper and lower bounds in each category. And it was assumed that the open-ended upper category had the amplitude of the preceding stratum. The results revealed that fracture risk increased with the exposure level either among all participants combined or within women specifically. Because there were limited data available pertaining to men, we did not do such an analysis for them.

Funnel plots (Figure 5) analysis showed evidence of publication bias towards positive studies, further confirmed by Egger's regression asymmetry test ($p = 0.018$) and the Begg adjusted rank correlation test ($p = 0.016$).

Discussion

Our findings indicate that for incident fracture, each additional cup of coffee per day is associated with a risk elevation of 4.9% for women and a risk reduction of 9% for men. The risk estimates have reached a stabilization level. And there was a positive dose-response relationship between coffee consumption and risk of fractures either for men and women combined or women specifically.

Coffee may exert different effects for men and women, which is supported by the sensitivity analysis when removing the study [8] conducted among male participants only. Meyer *et al.* [4] reported that an increased fracture risk was seen in female coffee drinkers but not in men. And it was the study by the National Health Screening Service of Norway [8] that reported a decreased fracture risk among coffee-drinking men for the first time. But they assumed that some adverse characteristics with those who do not drink coffee may lead to the observed preventive effect of coffee. Because related data pertaining to men are limited, the inverse association detected may be attributed to chance. So this finding should be interpreted with caution, and more investigations specially conducted in men are warranted.

For female coffee drinkers, the risk of fracture was not higher within older participants when compared with younger ones. It conflicted with the report [29] that the elderly may be more susceptible to caffeine administration. And studies [30, 31] demonstrated that caffeine intake by young adult women is safe with respect to bone health. But on the other hand, according to Massey [32], caffeine affects metabolic and neurological responses similarly in both young and elderly individuals. Because the subgroup heterogeneity test was likely to be invalid, we do not know whether the difference in pooled RR by strata of age was significant.

Cumulative meta-analysis showed that the risk estimates declined over time and reached a stabilization level. One possible explanation for the tendency observed is that we are more health conscious [33]. People tend to eat healthy food, exercise regularly, and turn to the more and more convenient health care services. All these can be essential confounding factors, but they were not all controlled in the original studies. So from this point of view, pooled RR may be underestimated.

The results indicated a linear dose-response relationship for both men and women combined and

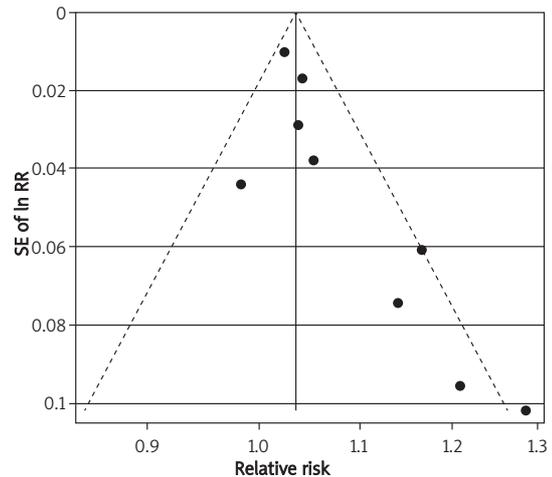


Figure 5. Funnel plots assessing publication bias without studies causing inconsistent pooled result

for women specifically. The more coffee consumed per day, the higher is the risk of fracture. And when someone drinks more than two cups of coffee per day, he or she was considered to have significantly higher RR, which was consistent with the Framingham Study [1].

Also we should note that there was publication bias towards positive results, which means they are more likely to be published. So the findings in our meta-analysis may be partially explained by it.

The biological plausibility of the association between coffee consumption and risk of fracture has been investigated for several decades. Proposed mechanisms are as follows: 1) caffeine, the primary ingredient in coffee, increases urinary and faecal calcium excretion [29] and decreases intestinal calcium absorption efficiency [34, 35], which may produce a negative calcium balance. 2) Caffeine exerts a direct effect on bone mediated by cyclic adenosine monophosphate [36], and teratogenic effects on ossification [37]. This was supported by Jokinen *et al.* [9], who found that the trochanteric region, with more trabecular bone, is more susceptible to caffeine intake. 3) Caffeine (or its confounders) might influence factors other than bone mass, such as bone quality or the risk of falling, because the effect of caffeine intake on hip fracture was still present after adjustment for calcaneal bone density [3].

Our study has several limitations. First of all, original studies included were all observational studies, so associations detected could be attributed to some other factors linked to both coffee consumption and the risk of fracture. For example, milk intake (or calcium intake from any source), one of the most important confounding factors, was adjusted in only four included studies. Smoking is also known to be associated with coffee consumption [38], and evidence showed that of all hip fractures,

one in eight was attributable to smoking [46]. But not all original data extracted have been adjusted for it. Moreover, assessment of coffee intake only at baseline could have neglected its introduction at a later date, affecting accuracy of ascertainment of exposure. Another fact we should pay attention to is that coffee is a complex mixture. Phenolic compounds in coffee, for example, have strong antioxidant activity, which may have an effect on fracture prevention [47]. Also coffee consumption is only a surrogate measure for caffeine intake, and coffee varies widely in caffeine content. There are many other sources of caffeine, such as habitual tea, which should be investigated separately in this regard. It was found that [48] tea drinkers had significantly greater (approximately 5%) mean BMD measurements. And as for outcome assessment, studies with fractures due to high-energy trauma and subsequent fractures were not excluded. But these may not be significant confounders because a distinction could not be made between fractures due to minimal versus high impact trauma [5]. And fracture risks with decreasing bone density in the elderly are comparably caused by low and high trauma [6, 49]. Moreover, sensitivity analysis by removing study [7] with subsequent fractures indicated that pooled RR was not strongly influenced. Nonetheless, we cannot deny the possibility that it happened out of chance. So caution should be exercised when interpreting the summary statistics and clinical decision making.

The strength of our research is that we considered studies with a prospective design only. The potential recall bias was greatly reduced. And within included studies, only a small proportion of participants was lost to follow-up. Highlights of our studies are that we performed sensitivity analysis wherever statistical heterogeneity existed and we adopted the method proposed by Greenland [40, 41] to estimate study-specific RR per cup of coffee whenever possible to get more accurate results.

In conclusion, our results support an overall harm of coffee intake in increasing the risk of fractures, especially for women. But considering the reporting bias and many crucial confounding factors, the findings should be interpreted with caution and further research needs to be conducted.

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