Habitual coffee consumption and risk of hypertension: a systematic review and meta-analysis of prospective observational studies1–3

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ABSTRACT
Background: In 2 meta-analyses of randomized controlled trials, increased coffee intake was associated with slightly higher blood pressure. However, these trials were short in duration (<85 d).
Objective: We conducted a systematic review and meta-analyses of long-term prospective studies that examined the association of habitual coffee consumption with risk of hypertension.
Design: We searched electronic databases (MEDLINE, EMBASE, Agricola, and Cochrane Library) through August 2009 with the use of a standardized protocol. Eligible studies were prospective cohort trials that examined the association of coffee consumption with incident hypertension or blood pressure.
Results: From 6 prospective cohort studies, a total of 172,567 participants and 37,135 incident hypertension cases were included. Mean follow-up ranged from 6.4 to 33.0 y. Compared with the lowest consumption (0 cups/d: 0.99; 95% CI: 0.89, 1.10), the pooled relative risks (RRs) for hypertension were 1.09 (95% CI: 1.01, 1.18) for the next higher category (1–3 cups/d), 1.07 (95% CI: 0.96, 1.20) for the second highest category (3–5 cups/d), and 1.08 (95% CI: 0.96, 1.21) for the highest category (>5 cups/d). A dose-response meta-analysis showed an inverse "J-shaped" curve (P for quadratic term < 0.001) with hypertension risk increasing up to 3 cups/d (RR for comparison of 3 with 0 cups/d: 1.07; 95% CI: 0.97, 1.20) and decreasing with higher intakes (RR for comparison of 6 with 0 cups/d: 0.99; 95% CI: 0.89, 1.10).
Conclusion: The results suggest that habitual coffee consumption of >3 cups/d was not associated with an increased risk of hypertension compared with <1 cup/d; however, a slightly elevated risk appeared to be associated with light-to-moderate consumption of 1 to 3 cups/d.

INTRODUCTION
Hypertension continues to be one of the most common and important health problems worldwide. It has been estimated that 29% of the world’s adult population, or ~1.6 billion people, will have hypertension by the year of 2025 (1). Elevated blood pressure (BP) is an established risk factor for coronary artery disease, stroke, kidney disease, all-cause mortality, and shortened life expectancy (1, 2). Furthermore, the relation between BP and subsequent outcomes is direct and progressive throughout the usual range of BP, including the nonhypertensive range. Given these considerations, even a small decrease in BP may have a major public health effect.

It is well established that dietary and other lifestyle factors play an important role in hypertension and BP control. Established risk factors for hypertension include excess intake of salt or alcohol, suboptimal dietary pattern, physical inactivity, and excessive body weight (3, 4). Another dietary factor of much interest is coffee drinking. Coffee is one of the most popular beverages in the world, with a global consumption of 6.7 million tons per year (5). Therefore, whether coffee drinking affects incident hypertension is an important public health question.

A link between coffee drinking and BP was first reported nearly 75 y ago (6), but whether coffee intake is associated with BP or hypertension risk remains controversial (7). In 2 meta-analyses of published randomized controlled trials (RCTs), increased coffee intake was associated with slightly higher BP (8, 9). These RCTs were short in duration (<85 d) and tested a very high dose of coffee in the treatment groups (median: 5 cups/d; 1 cup = ~237 mL). No systematic review or meta-analysis has been conducted to evaluate the long-term effects of habitual coffee intake on the risk of hypertension in free-living populations. The objective of this study was to systematically evaluate available prospective cohort studies on the relation between habitual coffee drinking and hypertension risk.

METHODS
Literature search
A systematic literature search for studies on coffee consumption (total coffee, regular coffee, or decaffeinated coffee) and hypertension risk published from January 1966 to August 2009 was conducted in PubMed (http://www.ncbi.nlm.nih.gov/pubmed), EMBASE (http://www.embase.com/), Agricola (http://agricola.nal.usda.gov/), and the Cochrane Library.
Study selection and data extraction

To be included in our systematic review, a study had to be prospective in design and report quantitative estimates of the association between habitual consumption of coffee (≥6 mo) and incidence of hypertension or measures of BP in humans. Initially, we identified 84 full-text references from the literature search. We excluded articles if they (1) did not have original data (review articles, editorials, meta-analysis) (n = 14), (2) did not assess coffee intake at the individual level (ecologic study) (n = 3), (3) only reported cross-sectional associations (n = 30), (4) had a study duration of <6 mo (n = 19), (5) did not have information on incident hypertension or BP (ie, other cardiovascular event or mortality) (n = 9), (6) did not report the quantitative estimates of hypertension or BP [effect sizes [eg, relative risk (RR), relative hazard, or regression coefficient] and SE of effect size] (n = 2) (10, 11), or (7) were publications of the same study (n = 2) (12, 13). Seven publications from 84 full text articles that were identified during the literature search met the above inclusion criteria and were included in this systematic review, including 6 independent studies with hypertension incidence as an outcome and 4 studies with BP as an outcome (14–20) (Figure 1).

Data were then extracted by 2 independent reviewers following a standardized protocol (ZZ and LC). The results were reported following the MOOSE checklist (21). Information on time period of study, country of origin, participant characteristics, measurement of coffee intake and hypertension/BP, sample size, estimate of the measurement of association, potential confounding factors adjusted for in the analyses were extracted. Disagreements between reviewers were resolved by repeated examination of the original articles until consensus was achieved.

Statistical analysis

For studies that used incident hypertension as an outcome, RR was used to measure effect size. We created 4 levels of coffee...
consumption: lowest (reference), next higher, second highest, and highest. Data from original studies was categorized into the above levels (from low to high) if the consumption of coffee was <1 cup/d, 1–3 cups/d, 3–5 cups/d, or >5 cups/d, respectively. We used random-effects models to estimate the pooled RRs and 95% CIs for highest consumption compared with lowest consumption, second highest consumption compared with lowest consumption, and third highest consumption compared with lowest consumption. To examine the influence of each individual study, we conducted sensitivity analyses by excluding each study from the meta-analyses and comparing the point estimates before and after excluding each specific individual study.

We examined publication bias through funnel plots and tested their symmetry. We also conducted a random-effects, dose-response meta-analysis by using the generalized least-squares estimation and “pool-first” method (22). Both linear and quadratic models were applied to fit the trend of the dose response. \( P < 0.05 \) was considered statistically significant. All analyses were performed by using STATA 10.0 software (Stata Corporation, College Station, TX).

**RESULTS**

**Search results and study characteristics**

We identified 5 articles (15, 17–20) that reported 6 independent prospective cohort studies on coffee consumption and incidence of hypertension. Of these, the Nurses’ Health Study (NHS) I and the NHS II were reported in one article (20). All together, 172,567 participants and 37,135 incident cases of hypertension were included in the 6 studies.

All 6 studies (15, 17–20) were large population-based studies with sample sizes ranging from 1017 to 87,369, and the duration of follow-up ranged from 6.4 to 33.0 y (Table 1). Of the 6 studies, the HARVEST study (18) enrolled individuals with untreated elevated BP at the baseline with drug-treated hypertension as the outcome; the Finnish study included both non-hypertensive and untreated hypertensive individuals (23% in the men and 14.5% in the women) at baseline with drug-treated hypertension as the outcome (15); the other 4 studies included only healthy participants at baseline (15, 17, 19, 20). Of the 6 studies, 3 of them were conducted in the United States (17, 20) (each without a description of race-ethnicity composition), and the other 3 were conducted in Europe, including Finland, Italy, and the Netherlands (15, 18, 19). Both men and women were included in 3 of the 6 studies (15, 18, 19); the remaining 2 studies (NHS I and NHS II) (20) included only women, and one study included only men (Johns Hopkins Precursors Study) (17). The mean age at the study baseline ranged from 26 to 55 y.

Coffee consumption was accessed through structured food-frequency questionnaires (FFQs) in 2 studies (20) and through either a specific question regarding coffee intake or an unspecified questionnaire in the other 4 studies (15, 17–19). Four studies asked the participants to report their most recent coffee consumption (17, 18, 20), and 2 studies asked for baseline coffee consumption (15, 19). The unit of coffee consumption asked for was cups consumed per day in all studies. The classifications of coffee consumption differed between the 6 studies: the Johns Hopkins Precursor Study (17) and HARVEST study (18) did not include decaffeinated coffee; the Doetinchem Cohort Study, NHS I, and NHS II conducted analyses for both regular and decaffeinated coffee (19, 20). The Finnish study did not discriminate between caffeinated and decaffeinated coffee, because the use of the latter is very low in Finland (15): Finnish surveys between 1987 and 2002 found that only 0.8% of the 26,707 coffee drinkers drank decaffeinated or noncaffeinated coffee (23).

Hypertension (endpoint) was ascertained through direct measurement in 2 studies (18, 19), records of antihypertensive drug use in one study (15), and self-report in 3 studies (17, 20). Of the 6 prospective studies included in this analysis, the association of coffee consumption and hypertension risk were all estimated by using multivariate Cox hazard models controlled for potential confounders. All 6 studies controlled for age, body mass index, smoking, and alcohol intake; 5 of the studies additionally controlled for physical activity, 4 of the studies additionally controlled for family history of hypertension, and none of the studies controlled for sodium or potassium intake.

We also indentified 4 independent prospective studies (14, 16, 17, 19) reporting the association between coffee drinking and BP, with the sample size ranging from 340 to 5189 and the follow-up duration ranging from 6 to 33 y. Two of the 4 studies were conducted in the Netherlands (14, 19), one in the United States (17), and one in Australia (16).

**Coffee drinking and risk of hypertension**

Of the 6 studies, 4 reported a nonlinear association between coffee consumption and hypertension (15, 17–19), whereas 2 found no statistically significant association (20). The pooled results of the prospective cohort studies from a meta-analysis stratified by different levels of coffee consumption are shown in Figure 2. Compared with the lowest consumption (<1 cups/d), the pooled RRs (95% CI) for hypertension were 1.09 (1.01, 1.18) for the next higher category (1–3 cups/d), 1.07 (0.96, 1.20) for the second highest category (3–5 cups/d), and 1.08 (0.96, 1.21) for the highest category (>5 cups/d). The \( P \) values for heterogeneity of the \( Q \) test in the above analyses were 0.16, 0.05, and 0.06, respectively, which indicated no significant heterogeneity for the pooled results. The funnel plot for testing publication bias appears symmetric (figure not shown). The Egger test showed that the \( P \) value for the publication bias was 0.61 for the highest, 0.38 for the second highest, and 0.06 for the third highest level of coffee consumption, which suggested no evidence of publication bias in any of the 3 coffee consumption levels. In the sensitivity analyses, exclusion of individual studies did not change the results substantially, with pooled RRs ranging from 1.04 to 1.13 for the next higher level, 1.03 to 1.10 for the second highest level, and 1.04 to 1.08 for the third highest level.

Because the results in the categorical analyses indicated a possible nonlinear association between coffee consumption and hypertension, we further conducted a dose-response meta-analysis with models that tested for both linear and nonlinear trends. All 6 studies were included because they all reported \( \geq 3 \) categories of the frequency of coffee consumption. The best-fitting model showed an inverse “J-shaped” curve (\( P \) for quadratic term < 0.001), with the risk of hypertension increasing up to 3 cups/d (RR for the comparison of 3 with 0 cups/d: 1.07; 95% CI: 0.97, 1.20) and decreasing with higher intakes (RR for the comparison of 6 with 0 cups/d: 0.99; 95% CI: 0.89, 1.10) (Figure 3).
### TABLE 1
Summary of prospective cohort studies on the association between coffee consumption and risk of hypertension (HT)

<table>
<thead>
<tr>
<th>Study name</th>
<th>Country</th>
<th>Project</th>
<th>Population</th>
<th>Total no. of subjects</th>
<th>Total no. of cases</th>
<th>Sex</th>
<th>Age at baseline</th>
<th>Duration of follow-up</th>
<th>HT assessment</th>
<th>Measure of coffee intake</th>
<th>Adjusted covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palatini et al, 2007 (18)</td>
<td>Italy</td>
<td>HARVEST</td>
<td>Individuals with untreated stage 1 hypertension</td>
<td>1107</td>
<td>561</td>
<td>M, F</td>
<td>33 (18–45)²</td>
<td>6.4</td>
<td>Record of HT drug use</td>
<td>Most recent intake, unspecified questionnaire</td>
<td>Age, sex, family history of HT, duration of HT, physical activity, smoking, alcohol consumption, BMI, change in weight, and baseline BP</td>
</tr>
<tr>
<td>Hu et al, 2007 (15)</td>
<td>Finland</td>
<td>WHO MONICA</td>
<td>General population</td>
<td>24,710</td>
<td>2505</td>
<td>M, F</td>
<td>43 (25–64)</td>
<td>13.2</td>
<td>Directly measured</td>
<td>Baseline coffee intake, one specific question</td>
<td>Age, sex, education, physical activity, smoking, alcohol consumption, high cholesterol, BMI, history of diabetes, and intake of tea, fruit, vegetables, sausage, and bread</td>
</tr>
<tr>
<td>Uiterwaal et al, 2007 (19)</td>
<td>Netherlands</td>
<td>Doetinchem Cohort Study</td>
<td>General population</td>
<td>5189</td>
<td>956</td>
<td>M, F</td>
<td>40</td>
<td>11</td>
<td>Directly measured</td>
<td>Baseline coffee intake, FFQ, and one specific question</td>
<td>Age, education, occupation, weight, height, smoking, alcohol consumption, and intake of tea and total energy</td>
</tr>
<tr>
<td>Winkelmaier et al, 2005 (20)</td>
<td>USA</td>
<td>Nurses' Health Study</td>
<td>Female registered nurses</td>
<td>53,175</td>
<td>19,364</td>
<td>F</td>
<td>55</td>
<td>12</td>
<td>Self-reported</td>
<td>Most recent intake, FFQ</td>
<td>Age, family history of HT, physical activity, smoking, alcohol consumption, high cholesterol, and BMI</td>
</tr>
<tr>
<td>Winkelmaier et al, 2005 (20)</td>
<td>USA</td>
<td>Nurses' Health Study II</td>
<td>Female registered nurses</td>
<td>87,369</td>
<td>13,468</td>
<td>F</td>
<td>36 (25–42)</td>
<td>12</td>
<td>Self-reported</td>
<td>Most recent intake, FFQ</td>
<td>Age, family history of HT, physical activity, smoking, alcohol consumption, high cholesterol, BMI, and oral contraceptive use</td>
</tr>
<tr>
<td>Klag et al, 2002 (17)</td>
<td>USA</td>
<td>Johns Hopkins Precursors Study</td>
<td>Medical school students</td>
<td>1017</td>
<td>281</td>
<td>M</td>
<td>26</td>
<td>33</td>
<td>Self-reported</td>
<td>Most recent intake, one specific question</td>
<td>Age, family history of HT, physical activity, smoking, alcohol consumption, and BMI</td>
</tr>
</tbody>
</table>

¹ BP, blood pressure; FFQ, food-frequency questionnaire; WHO, World Health Organization; MONICA, Multinational MONItoring of trends and determinants in CArdiovascular disease.

² Mean; range in parentheses (all such values).
FIGURE 2. Forest plot of relative risks (RRs) and 95% CIs for the association between coffee consumption and hypertension risk in cohort studies. Top: Third highest category of coffee consumption (1–3 cups/d; 1 cup = ~237 mL) compared with the reference category (<1 cup/d). Middle: Second highest category of coffee consumption (3–5 cups/d) compared with the reference category (<1 cup/d). Bottom: Highest category of coffee consumption (>5 cups/d) compared with the reference category (<1 cup/d). NHS, Nurses’ Health Study.
Coffee drinking and blood pressure

With regard to the association between coffee drinking and BP, we identified 4 independent prospective studies (14, 16, 17, 19). Because the Australia study used residuals of BP in their regression models (16) and the Amsterdam Growth and Health Longitudinal Study in the Netherlands used mean arterial BP \[\text{arterial BP} = \frac{2 \times \text{DBP} + \text{SBP}}{3}\] in the analyses (14), we conducted a meta-analysis for a pooled estimation. Instead, we presented key information and results from these 4 studies in Table 2. In summary, varied results have been reported on the association between coffee drinking and BP, with the US study (17) identifying a positive association, the Australia study (16) detecting a negative association, and the 2 Dutch studies (14, 19) finding no association.

DISCUSSION

In our meta-analysis of 172,567 participants and 37,135 incident cases of hypertension, habitual coffee consumption at an amount of >3 cups/d was not associated with an increased risk of hypertension as compared with <1 cup/d; however, a slightly elevated risk (9%) appeared to be associated with light-to-moderate consumption at 1–3 cups/d. A dose-response meta-analysis also indicated an inverse “J-shape” relation with the risk of hypertension, which increased up to 3 cups/d and then slightly decreased at higher consumption amounts.

An important question is whether caffeinated and decaffeinated coffee have different effects on BP. The studies included in this review did not allow us to conduct a stratified analysis based on the type of coffee: the FINMONICA (The Finnish Multinational Monitoring of Trends and Determinants of Cardiovascular Disease) Study (15) did not differentiate the caffeinated and decaffeinated coffee drinking in their analyses, but few people (0.8%) from Finland drink decaffeinated coffee (23), and the Johns Hopkins Precursors Study (17) and the Italy HARVEST Study (18) only included caffeinated coffee. Only the NHS I, NHS II, and Doetinchem Cohort Study reported associations of both caffeinated and decaffeinated coffee with hypertension; however, the risk of hypertension did not differ by...
types of coffee in these studies (19, 20). The Doetinchem Cohort Study in the Netherlands (19) showed a higher hypertension incidence risk of both total coffee drinkers and decaffeinated coffee drinkers, whereas the NHS I and NHS II (20) showed no positive or negative associations between hypertension incidence risk and caffeine and decaffeinated coffee drinking. Another potential caveat for these comparisons is the serving size. Previous reports have shown that the size of standard coffee cups was larger in the United States (250 mL) than in Europe (125–150 mL), but this might be balanced by the usually weaker brew of coffee in the United States than in Europe (24).

The finding that a slightly increased hypertension risk is associated with light-to-moderate coffee intake is biologically plausible. The major ingredient of coffee, caffeine, has an acute pressor effect, particularly in hypertensive subjects (25, 26). This effect may be regulated through many biological mechanisms, including binding to the adenosine receptor, activating the sympathetic nervous system via elevated plasma concentrations of catecholamines, and stimulating the pituitary-adrenocortical response and increasing cortisol production (27, 28). However, tolerance to the caffeine-induced pressor effect develops in habitual coffee drinkers (26, 29). The human body has a complex set of counterregulatory hormones, which maintain BP and may cause tolerance to the humoral and hemodynamic effects of caffeine (30). In addition, ingredients other than caffeine may also have BP-control effects, including chlorogenic acid, flavonoids, melanoids, quinide, magnesium, cafestol, and kahweol (24, 31). Coffee is also rich in potassium, which lowers BP (4). These ingredients could counterbalance caffeine’s pressor effect above a certain level of consumption (9). This may help to explain the observed inverse “J-shape” relation between habitual coffee drinking and hypertension risk. However, our findings should be considered as suggestive, given that only 6 studies were included in the current analysis. Future experimental studies are needed to help elucidate the mechanisms.

Genetic factors should be taken into consideration when studying the association of coffee consumption and BP/hypertension because previous reports have suggested obvious interindividual differences in the sensitivity to the effect of coffee (31–33). Caffeine was mainly metabolized by cytochrome P450 1A2 (CYP1A2) in the liver. Slow caffeine metabolizers carry the *1F allele variant, and rapid caffeine metabolizers carry the A2*A1A gene. In a subgroup of participants from the Italy HARVEST Study, a significant interaction was found between the CYP1A2 genotype and coffee drinking on both SBP and DBP (32). Another study in Japan also found that the NADH dehydrogenase subunit-2 237 (ND2-237) leucine/methionine polymorphism modified the association between coffee drinking and hypertension risk in middle-aged Japanese men (34). Although only a few studies investigated the role of genes in the coffee-BP association, the available evidence suggests that certain genes modify the effects of coffee on BP.

It is important to note that sex, race, and smoking have been considered as factors that may modify the associations between coffee drinking and BP. All 3 studies included in our meta-analysis and that enrolled both men and women did not detect a sex difference (15, 18, 19). In 3 analyses stratified by smoking status, the association between coffee drinking and hypertension was found to be similar between smokers and nonsmokers (15, 17, 19).

Our meta-analysis had limitations. First, there were only 6 cohort studies. Second, all of these studies were observational in nature, and residual confounding cannot be totally ruled out. In particular, no studies controlled for salt intake. Third, information on the pattern of coffee drinking, such as type, time, and brewing method, was limited. Fourth, the studies currently available were all conducted among white populations; therefore, the findings from the present study may not be generalized to other populations.

Our meta-analysis also had several strengths. The available studies appeared to be of good quality. They were well designed and implemented with relatively high follow-up rates, in the range of 62% to 94%. The outcomes of BP and hypertension were either directly measured or self-reported with high validation. The NHS I found that self-reported hypertension was reliable: 100% of the respondents who reported hypertension had documented systolic BP >140 mm Hg and diastolic blood pressure >90 mm Hg (35). The exposure assessments of coffee consumption were also reliable when valid instruments were used. For example, the correlation between coffee consumption from an FFQ and food records was 0.78 (36). All studies conducted appropriate statistical analyses with control of known risk factors for BP.

In summary, in this meta-analysis of pooled results from 6 prospective cohort studies, we found that habitual coffee consumption of >3 cups/d was not associated with an increased risk of hypertension compared with consumption of <1 cup/d; however, a slightly elevated risk appeared to be associated with light- to-moderate consumption (ie, 1–3 cups/d). Future studies using different types of coffee and in nonwhite populations are warranted.

The authors’ responsibilities were as follows—LC: had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; ZZ and LC: conducted the literature search and statistical analyses; and ZZ: prepared the first draft of the manuscript. All authors were responsible for the conception and design of the study, interpretation of the analyses, and revision of the manuscript. None of the authors had any personal or financial conflicts of interest.

REFERENCES


