Long-Term Coffee Consumption and Risk of Cardiovascular Disease

A Systematic Review and a Dose–Response Meta-Analysis of Prospective Cohort Studies

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Background—Considerable controversy exists on the association between coffee consumption and cardiovascular disease (CVD) risk. A meta-analysis was performed to assess the dose–response relationship of long-term coffee consumption with CVD risk.

Methods and Results—PubMed and EMBASE were searched for prospective cohort studies of the relationship between coffee consumption and CVD risk, which included coronary heart disease, stroke, heart failure, and CVD mortality. Thirty-six studies were included with 1,279,804 participants and 36,352 CVD cases. A nonlinear relationship of coffee consumption with CVD risk was identified (P for heterogeneity=0.09, P for trend <0.001, P for nonlinearity <0.001). Compared with the lowest category of coffee consumption (median, 0 cups per day), the relative risk of CVD was 0.95 (95% confidence interval, 0.87–1.03) for the highest category (median, 5 cups per day) category, 0.85 (95% confidence interval, 0.80–0.90) for the second highest category (median, 3.5 cups per day), and 0.89 (95% confidence interval, 0.84–0.94) for the third highest category (median, 1.5 cups per day). Looking at separate outcomes, coffee consumption was nonlinearly associated with both coronary heart disease (P for heterogeneity=0.001, P for trend <0.001, P for nonlinearity <0.001) and stroke (P for heterogeneity=0.07, P for trend <0.001, P for nonlinearity <0.001; P for trend differences >0.05) risks.

Conclusions—A nonlinear association between coffee consumption and CVD risk was observed in this meta-analysis. Moderate coffee consumption was inversely significantly associated with CVD risk, with the lowest CVD risk at 3 to 5 cups per day, and heavy coffee consumption was not associated with elevated CVD risk. (Circulation. 2014;129:643-659.)

Key Words: cardiovascular diseases ☐ coffee ☐ meta-analysis

Coffee is one of the most widely consumed beverages around the world; thus, investigating whether coffee consumption is associated with chronic disease risk has important public health implications. The relationship between coffee consumption and risk of coronary heart disease was first studied in the 1960s, given that the prevalences of both coffee drinking and coronary heart disease (CHD) were high in Western countries.1 Short-term metabolic studies found that caffeine ingestion acutely induces cardiac arrhythmias and increases plasma renin activity, catecholamine concentrations, and blood pressure.2,3 In the 1980s, cross-sectional studies found a positive association between coffee consumption and serum total cholesterol concentrations, which might be related to the coffee brewing method (ie, boiled or unfiltered coffee).4 A later randomized trial showed that boiled coffee consumption increased serum cholesterol.5 From the 1980s to the 2000s, many case-control studies, which are prone to recall and selection bias, showed a positive association between coffee consumption and CHD risk.6-8 In contrast, meta-analyses of prospective cohort studies tended to find no association, although results varied substantially across studies.9,10

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Since 2000, the associations between coffee consumption and other cardiovascular disease (CVD) outcomes such as stroke, heart failure, and total CVD mortality have also been more frequently studied.11-13 Meta-analyses have been published to summarize the association between coffee and risk of CHD,14 stroke,15 and heart failure.16 These meta-analyses did not support an association between coffee consumption and...
a higher CVD risk, but the shape of the association remains uncertain. Moreover, a number of additional studies have been published since the publication of these meta-analyses, and 1 recent meta-analysis showed that heavy coffee consumption was not associated with risk of CVD mortality. To examine the dose–response association of coffee consumption with CVD risk, we conducted a systematic review and meta-analysis of coffee consumption and incidence of total CVD outcomes, including incidence of CHD, stroke, heart failure, and CVD mortality.

**Methods**

We followed the Meta-Analysis of Observational Studies in Epidemiology protocol throughout the design, implementation, analysis, and reporting of our meta-analysis.

**Search Strategy and Selection Criteria**

We searched the PubMed and EMBASE databases for prospective studies that had evaluated the association between coffee consumption and risk of CVD between January 1966 and March 2013. The computer-based searches included the key words “coffee,” “cardiovascular disease,” “coronary heart disease,” “stroke,” “mortality,” “heart failure,” “myocardial infarction,” “ischemic heart disease,” “sudden cardiac arrest,” and “acute coronary syndrome.” Reference lists of retrieved articles were scanned manually for all relevant additional studies and review articles. We restricted the search to studies on humans that were written in English.

**Study Selection**

Studies were included in this meta-analysis if they met the following criteria: (1) The study was a prospective cohort study, including case-cohort studies and nested case-control studies with a prospective design; (2) the exposure was coffee consumption, including total coffee, decaffeinated coffee, coffee; and (3) the outcome was risk of CVD, including incidence of CHD, stroke, heart failure, and CVD mortality. Studies were excluded if (1) the study had a retrospective design; (2) the estimates were presented without standard errors or other information that allowed calculation of standard errors; (3) the outcome was atrial fibrillation, atherosclerosis, hypertension, aortic stiffness, or venous thrombus; or (4) no confounders were adjusted for.

**Data Extraction and Quality Assessment**

One author (M.D.) assessed study eligibility and extracted the data; another author (A.S.) independently double-checked the available data. The following data were extracted from each study: first author’s name, year of publication, geographical location, follow-up time, sex, age, number of CVD events, number of participants/ person-years of follow-up, categories of coffee consumption, mean/ median coffee consumption in each category, CVD assessment method, covariates adjusted for in the multivariable analysis, and relative risks (RRs) and the associated measure of variance for all categories of coffee consumption. For cohorts with published data on several CVD outcomes, we chose CVD incidence instead of mortality or heart failure results. For studies with data on both CHD and stroke as the outcome, we included both in the meta-analysis. The correlation of CHD and stroke was accounted for in the main analysis (see below). In a sensitivity analysis, we analyzed 1 of the 2 outcomes. The Newcastle-Ottawa quality assessment scale (NOS) was used to evaluate the quality of the included studies. Two authors (M.D. and S.B.) developed the evaluation criteria (Table I in the online-only Data Supplement). The score ranges from 0 to 9 points, with a higher score indicating higher study quality.

To perform a dose–response meta-analysis, we assigned the median coffee consumption in each category of consumption to the corresponding RR for each study. We used means for this purpose if medians were not reported. If neither the mean nor the median consumption per category was reported, the midpoint of the upper and lower boundaries in each category was used to estimate median consumption. We used both semiparametric and parametric methods. For the semiparametric method, 4 coffee consumption groups were generated, namely lowest, third highest, second highest, and highest. For each study that was included, the lowest and the highest coffee consumption categories corresponded to the lowest and highest groups, respectively. For studies with 4 exposure categories, the second and third categories corresponded to the second and third highest groups, respectively. For studies with 3 exposure categories, the middle category corresponded to either the second or the third highest group in the meta-analysis, depending on the similarity of the median coffee consumption to either the second or the third highest group of the meta-analysis. If the study had >4 exposure categories, 2 consumption groups, other than the lowest and highest, were chosen on the basis of their similarity of the amount of coffee consumption in that category to the second and third highest groups of the meta-analysis. For each group, we computed correlation coefficients (ρ) between CHD and stroke outcomes in the same cohort. We imputed ρ=1 initially to obtain the most conservative effect estimates. A random-effects model was used first and was changed to a fixed-effects model if a between-study heterogeneity was found for the random-effects model (τ<1). Sensitivity analysis was conducted by imputing different ρ (0<ρ≤1) to evaluate the robustness of the effect estimates. We used the STATA command ROBOMET to obtain the effect estimates.

For the parametric method, a dose–response meta-analysis was performed. The number of cases and participants in each coffee consumption category was extracted to estimate the covariance of the RR in each study. Together with the observed adjusted variance of the RR, we estimated the variance/covariance matrix of the data. The weight of each study was calculated as the inverse of the variance/covariance matrix. We used generalized least-squares models with the maximum likelihood method to estimate the coefficients for each study. We fit a fixed-effects generalized linear model first and changed to a random-effects generalized linear model if the P value for the goodness of fit/heterogeneity of the previous model was <0.05. Additionally, we tested for potential nonlinearity in the association between coffee consumption and CVD risk using a fixed/random-effects restricted cubic spline model with 3 knots. In sensitivity analysis, we used 2-stage fixed-effects/random-effects dose–response models to combine studies that reported results for categorized coffee consumption and studies with reported results for continuous coffee consumption. Specifically, the RR of CVD per unit increase of coffee consumption for each study was first estimated separately by generalized least-squares models, and then the RRs from all of the studies were pooled together by a fixed-effects/random-effects model. We used the STATA command GLST for model fitting, and the command LINCOM to obtain effect estimates for the fitted model.

We performed stratified analyses by baseline hypertension or myocardial infarction of the study population, smoking status, publication year, NOS study quality score, dietary assessment method, evaluation of stroke or CHD as the outcome, country, sex, and type of coffee (caffeinated coffee or decaffeinated coffee). The interaction between categorized coffee consumption and the stratifying variable with the risk of CVD was tested by a likelihood ratio test comparing the models derived using generalized least-squares method with and without the interaction terms. We assessed the potential for publication bias using the Egger regression symmetry test. All analyses were conducted with STATA version 11.2 (STATA Corp, College Station, TX).
Results

Characteristics of Studies
Our initial search identified 2587 potentially relevant citations. After screening titles and abstracts, we identified 53 studies for further evaluation. Of the 53 initially included studies, we excluded 14 studies because of duplicate publication, 1 study with point estimates without standard errors, and 1 nested case-control study with a retrospective design. Thirty-six studies remained in the meta-analysis (Figure 1). The included studies comprised 1283685 study participants and 47779 CVD cases, including 28347 CHD cases, 12030 stroke cases, and 7402 other CVD cases. Characteristics of these 36 studies are shown in the Table. One study had a nested case-control study design, 1 had a case-cohort study design, and the rest of the studies were cohort studies. Duration of follow-up for incident CVD ranged from 6 to 44 years, with a median follow-up of 10 years. Twenty-one studies were conducted in Europe, 12 in the United States, and 3 in Japan. Three studies assessed coffee consumption repeatedly during the course of the follow-up, and the rest of the studies assessed coffee consumption at baseline. Thirteen studies assessed coffee consumption without using a specific dietary assessment method, and the rest of the studies assessed coffee consumption by diet recalls, diet records, or food frequency questionnaires. One study modeled coffee consumption as a continuous variable, and the remaining studies modeled coffee consumption categorically. Nine studies assessed the association of caffeinated coffee consumption with CVD risk, and 4 studies assessed the association of decaffeinated coffee consumption with CVD risk. The outcome in 17 studies was risk of stroke, whereas the outcome in 22 studies was risk of CHD. The scores of the NOS quality assessment ranged from 3 to 8, and 31 studies had scores of ≥5. The corresponding results of each criteria of the NOS quality assessment for our meta-analysis are shown in Table I in the online-only Data Supplement. The study modeling coffee as a continuous exposure was excluded in the following analysis because of the difficulty of combining the risk estimate with those of other studies and was included only in the sensitivity analysis.26 All remaining 35 studies were included in the main analysis, and 29 studies were included in the dose–response analysis between coffee consumption and risk of CVD.

Coffee Consumption and Risk of CVD
The RRs for CVD with different coffee consumption categories relative to the lowest category are shown in Figure 2. Of the 35 studies, 6 cohorts presented the outcome of stroke and CHD simultaneously. Compared with the lowest category of coffee consumption (median and mean, 0 cups per day), the pooled RR for incident CVD was 0.89 (95% confidence interval [CI], 0.84–0.94) for the third highest (median, 1.5 cups per day; mean, 1.48 cups per day), 0.85 (95% CI, 0.80–0.90) for the second highest (median,: 3.5 cups per day; mean, 3 cups per day), and 0.95 (95% CI, 0.87–1.03) for the highest (median, 5 cups per day; mean, 5.5 cups per day) category of coffee consumption (Figure 2). Low between-study variances of CVD risk were found for each category of coffee consumption (τ^2=0.00 for the random-effects models), and the imputed correlation coefficient between the risks of stroke and CHD within the same cohort (0<ρ≤1) did not have an effect on the RR of CVD for each category of coffee consumption.

Stratified Analyses
Stratified analyses were conducted according to baseline hypertension or myocardial infarction of the study population, smoking status, publication year, NOS study quality score, dietary assessment method (24-hour diet recall/diet record/food frequency questionnaire versus other methods), stroke versus CHD as the outcome, country, sex, and type of coffee (caffeinated coffee or decaffeinated coffee). No interactions between categorized coffee consumption and stratification variables in relation to CVD risk were observed (all P for interactions >0.05; Figure 3). Only 4 studies provided the stratified results by age.27–30 The summarized results showed that, comparing the highest with the lowest intakes, the RR of CVD was 0.96 (95% CI, 0.65–1.42) for age <65 years and 0.91 (95% CI, 0.59–1.40) for age ≥65 years.
### Table. Basic Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Author, Year, Country, Special Annotation</th>
<th>Sex</th>
<th>Age at Start of Follow-Up, y</th>
<th>Cases/Total Participants, n/N</th>
<th>Exposure (cup/d) Relative Risk (95% CI)</th>
<th>Outcome</th>
<th>Exposure/Outcome Assessment</th>
<th>Confounders Adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilhelmsen et al,26 1977, Europe</td>
<td>Men</td>
<td>12</td>
<td>60/834</td>
<td>Per cup increase of coffee consumption: 1.11 (0.83–1.51)</td>
<td>CHD</td>
<td>Nonspecific diet questionnaire (baseline)/hospital record</td>
<td>Smoking, cholesterol, SBP, dyspnea, registration by temperance board</td>
</tr>
<tr>
<td>Legrady et al,18a 1987, US</td>
<td>Men</td>
<td>19</td>
<td>220 CHD, 57 stroke/1910</td>
<td>Stroke mortality 0–1 cup/d 1.00 (1.00–1.00) &gt;1 cup/d 1.64 (0.80–3.38)</td>
<td>Stroke mortality</td>
<td>Nonspecific diet questionnaire (baseline)/death certificates</td>
<td>Age, diastolic blood pressure, serum cholesterol, and smoking status</td>
</tr>
<tr>
<td>Martin et al,19a 1988, US, hypertensive population</td>
<td>Both</td>
<td>4</td>
<td>336/10 064</td>
<td>Stroke mortality 0 cup/d 1.00 (1.00–1.00) 0.1 mg–2 cups/d 0.73 (0.37–1.46) 2–4 cups/d 0.61 (0.26–1.44) &gt;4 cups/d 1.30 (0.56–3.04) CHD mortality 0 cup/d 1.00 (1.00–1.00) 0.1–2 cups/d 0.93 (0.66–1.3) 2–4 cups/d 0.81 (0.53–1.23) &gt;4 cups/d 0.80 (0.46–1.39)</td>
<td>CVD</td>
<td>Nonspecific diet questionnaire (baseline)/death certificates</td>
<td>Age, sex, race, type of care, marital status, month of interview, body weight, initial diastolic blood pressure, fasting plasma blood glucose and serum cholesterol, initial end organ damage, and location of the study center</td>
</tr>
<tr>
<td>Grobbee et al,20a 1990, US</td>
<td>Men</td>
<td>2</td>
<td>411/45 589</td>
<td>Stroke mortality 0 cup/d 1.00 (1.00–1.00) 0–1 cup/d 0.70 (0.51–0.97) 2–3 cups/d 1.00 (0.79–1.26) &gt;4 cups/d 0.90 (0.67–1.22)</td>
<td>CVD</td>
<td>FFQ (baseline)/confirmed cases</td>
<td>Age; quintiles of Quetelet Index; smoking habits; history of diabetes mellitus; alcohol use; parental history of myocardial infarction; specific health profession; energy intake; cholesterol; and saturated, monounsaturated, and polyunsaturated fat</td>
</tr>
<tr>
<td>Klatsky et al,21a 1990, US, nested case-control study</td>
<td>Both</td>
<td>8 (median, 5)</td>
<td>1914/101 774</td>
<td>MI 0 cup/d 1.00 (1.00–1.00) &lt;1 cup/d 0.78 (0.56–1.07) 1–3 cups/d 1.16 (0.93–1.45) &gt;4 cups/d 1.42 (1.11–1.81) Other coronary cases 0 cup/d 1.00 (1.00–1.00) &lt;1 cup/d 0.90 (0.72–1.11) 1–3 cups/d 0.89 (0.76–1.04) &gt;4 cups/d 1.03 (0.85–1.24)</td>
<td>CHD</td>
<td>Nonspecific diet questionnaire (baseline)/hospitalization for coronary disease</td>
<td>Age, race, cigarette smoking, alcohol intake, education, baseline disease, and tea use</td>
</tr>
<tr>
<td>Tverdal et al,22a 1990, Europe</td>
<td>Both</td>
<td>6.4</td>
<td>184/38 564</td>
<td>no sugar in coffee &lt;1 cup/d 1.00 (1.00–1.00) ≥9 cups/d 4.10 (1.30–13.20) Sugar in coffee &lt;1 cup/d 1.00 (1.00–1.00) ≥9 cups/d 1.60 (0.60–4.30)</td>
<td>CHD</td>
<td>Nonspecific diet questionnaire (baseline)/confirmed cases</td>
<td>Age, HDL, total cholesterol, SBP, and No. of cigarettes/d</td>
</tr>
<tr>
<td>Rosengren et al,23a 1991, Europe</td>
<td>Men</td>
<td>7.1</td>
<td>399/67 65</td>
<td>0 cup/d 1.00 (1.00–1.00) ≥9 cups/d 1.40 (0.80–2.40)</td>
<td>CHD</td>
<td>Nonspecific diet questionnaire (baseline)/national registries</td>
<td>Age, SBP, BMI, diabetes mellitus, registration for alcohol abuse, family history of myocardial infarction, mental stress, physical activity, occupational class, and smoking</td>
</tr>
<tr>
<td>Lindsted et al,24a 1992, Europe</td>
<td>Men</td>
<td>15</td>
<td>NA/9484</td>
<td>&lt;1 cup/d 1.00 (1.00–1.00) 1–2 cups/d 1.38 (1.18–1.62) ≥3 cups/d 1.44 (1.18–1.76)</td>
<td>CVD</td>
<td>FFQ (baseline)/confirmed cases</td>
<td>BMI, stroke, heart disease, hypertension, race, exercise, sleep, marital status, education, smoking history, and dietary pattern</td>
</tr>
</tbody>
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Table. Continued

<table>
<thead>
<tr>
<th>Author, Year, Country, Special Annotation</th>
<th>Sex</th>
<th>Follow-Up, y</th>
<th>Age at Start of Follow-Up, y</th>
<th>Cases/Total Participants, n/N</th>
<th>Exposure (cup/d) Relative Risk (95% CI)</th>
<th>Outcome</th>
<th>Exposure/Outcome Assessment</th>
<th>Confounders Adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klag et al,23a 1994, US</td>
<td>Men</td>
<td>32</td>
<td>26</td>
<td>111/1040</td>
<td>0 cup/d 1.00 (1.00–1.00) 1–2 cups/d 1.70 (0.78–3.68) 3–4 cups/d 3.02 (1.37–6.65) ≥5 cups/d 2.94 (1.27–6.81)</td>
<td>CHD</td>
<td>Nonspecific diet questionnaire (baseline)/national registries</td>
<td>Age at graduation, baseline serum cholesterol, calendar time, time-dependent hypertension status, number of cigarettes, diabetes mellitus, and BMI</td>
</tr>
<tr>
<td>Gyllen et al,24a 1995, Europe</td>
<td>Men</td>
<td>6</td>
<td>53–74</td>
<td>184/2975</td>
<td>1–4 cups/d 1.00 (1.00–1.00) 5–8 cups/d 1.00 (0.70–1.40) ≥9 cups/d 0.60 (0.30–1.00)</td>
<td>CHD</td>
<td>Nonspecific diet questionnaire (baseline)/confirmed cases</td>
<td>Age, alcohol, blood pressure, serum selenium level, social class, and triglycerides</td>
</tr>
<tr>
<td>Hart et al,25a 1997, Europe</td>
<td>Men</td>
<td>21</td>
<td>35–64</td>
<td>625/5766</td>
<td>0 cup/d 1.00 (1.00–1.00) 0.5–1 cup/d 1.20 (0.87–1.64) 1.5–2 cup/d 1.17 (0.83–1.65) 2.5–4 cup/d 1.16 (0.81–1.66) ≥4.5 cup/d 1.49 (0.89–2.47)</td>
<td>CHD mortality</td>
<td>Nonspecific diet questionnaire (average)/national registries</td>
<td>Age, diastolic blood pressure, cholesterol, smoking, social class, age leaving full-time education, BMI, angina, and ECG ischemia</td>
</tr>
<tr>
<td>Hakim et al,26a 1998 US, hypertensive population</td>
<td>Men</td>
<td>25</td>
<td>55–68</td>
<td>76/499</td>
<td>0 cup/d 1.00 (1.00–1.00) ≥6 cups/d 2.1 (1.2–3.7)</td>
<td>Stroke</td>
<td>24-h diet recall (baseline)/confirmed cases</td>
<td>Age, SBP, total cholesterol, triglycerides, diabetes mellitus, alcohol use, and physical activity index as measured at the time of study enrollment</td>
</tr>
<tr>
<td>Woodward et al,27a 1999, Europe</td>
<td>Both</td>
<td>7.7</td>
<td>40–59</td>
<td>567/11000</td>
<td>Men 0 cup/d 1.00 (1.00–1.00) 1–2 cups/d 0.68 (0.42–1.10) 3–4 cups/d 0.39 (0.21–0.73) ≥5 cups/d 0.68 (0.37–1.24) women 0 cup/d 1.00 (1.00–1.00) 1–2 cups/d 0.54 (0.22–1.34) 3–4 cups/d 0.36 (0.20–1.56) ≥5 cups/d 0.55 (0.18–1.66)</td>
<td>CHD</td>
<td>Food consumption table (baseline)/confirmed cases</td>
<td>Age, housing tenure, activity at work, activity in leisure, cigarette smoking status, BMI, Bortner score, cotinine, SBP, fibrinogen, total cholesterol, HDL cholesterol, triglycerides, alcohol, vitamin C, and tea</td>
</tr>
<tr>
<td>Kleemola et al,28a 2000, Europe</td>
<td>Both</td>
<td>10</td>
<td>30–59</td>
<td>1645/20179</td>
<td>Men with nonfatal MI &lt;1 cup/d 1.09 (0.78–1.54) 1–3 cups/d 1.00 (1.00–1.00) 4–7 cups/d 0.95 (0.79–1.15) ≥7 cups/d 0.79 (0.64–0.98) Women with nonfatal MI &lt;1 cup/d 1.72 (1.01–2.92) 1–3 cups/d 1.00 (1.00–1.00) 4–7 cups/d 0.84 (0.62–1.13) ≥7 cups/d 0.93 (0.63–1.36) Men with CHD mortality &lt;1 cup/d 1.88 (1.20–2.95) 1–3 cups/d 1.00 (1.00–1.00) 4–7 cups/d 1.23 (0.93–1.62) ≥7 cups/d 1.22 (0.90–1.65) Women with CHD mortality &lt;1 cup/d 0.00 (0.00–0.00) 1–3 cups/d 1.00 (1.00–1.00) 4–7 cups/d 0.67 (0.41–1.07) ≥7 cups/d 0.57 (0.28–1.16)</td>
<td>CHD, CHD mortality</td>
<td>Nonspecific diet questionnaire (baseline)/national registries</td>
<td>Age, smoking status, serum cholesterol level, blood pressure, and history of MI</td>
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</table>

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<thead>
<tr>
<th>Author, Year, Country, Special Annotation</th>
<th>Sex Follow-Up, y</th>
<th>Age at Start of Follow-Up, y</th>
<th>Cases/Total Participants, n/N</th>
<th>Exposure (cup/d)/Relative Risk (95% CI)</th>
<th>Outcome</th>
<th>Exposure/Outcome Assessment</th>
<th>Confounders Adjusted for</th>
</tr>
</thead>
</table>
| Jazbec et al,29a 2003, Europe           | Both           | 10             | 35–59           | Men 0 cup/d 1.00 (1.00–1.00)  
<1 cups/d 0.70 (0.49–1.00)  
1–2 cups/d 0.82 (0.58–1.16)  
>2 cups/d 0.72 (0.44–1.18)  
Women 0 cup/d 1.00 (1.00–1.00)  
<1 cup/d 0.88 (0.56–1.39)  
1–2 cups/d 0.67 (0.43–1.05)  
>2 cups/d 0.62 (0.30–1.28) | CVD mortality | Nonspecific diet questionnaire (baseline)/confirmed cases | Age, number of cigarettes consumed per day, diastolic blood pressure, ulcer, feeling of well-being, and region |
| Happonen et al,30a 2004, Europe        | Men            | 14            | 42–60           | None 0.84 (0.41–1.72) Light 1.22 (0.90–1.64) Moderate 1.00 (1.00–1.00) Heavy 1.43 (1.06–1.94) | CHD mortality | Diet record (baseline)/national registries | Age, pack-years of smoking, ischemia in exercise test, diabetes mellitus, income, and serum insulin concentration; physical activity; family history of CHD; intake of alcohol, tea, saturated fat, total energy, and total water; serum glucose and plasma vitamin C concentration |
| Lopez-Garcia et al,31a 2006, US        | Both           | 20            | Men, 53  
Women, 46           | Women <0.033 cup/d 1.00 (1.00–1.00)  
0.033–0.57 cup 0.97 (0.83–1.14)  
0.57–1 cup/d 1.02 (0.90–1.17)  
2–3 cups/d 0.84 (0.74–0.97)  
4–5 cups/d 0.99 (0.83–1.17)  
≥6 cups/d 0.87 (0.68–1.11)  
Men <0.033 cup/d 1.00 (1.00–1.00)  
0.033–0.57 cup/d 1.04 (0.91–1.17)  
0.57–1 cup/d 1.02 (0.90–1.15)  
2–3 cups/d 0.97 (0.86–1.11)  
4–5 cups/d 1.07 (0.88–1.31)  
≥6 cups/d 0.72 (0.49–1.07) | CHD | FFQ (baseline)/national registries | Age, smoking status, serum cholesterol level, blood pressure, and history of MI |
| Andersen et al,32a 2006, US            | Women          | 15            | 55–69           | 0 cup/d 1.00 (1.00–1.00)  
<1 cup/d 0.85 (0.68–1.06)  
1–3 cups/d 0.76 (0.64–0.91)  
4–5 cups/d 0.81 (0.66–0.99)  
≥6 cups/d 0.87 (0.69–1.09) | CVD mortality | FFQ (baseline)/national registries | Age; smoking; intake of alcohol; 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 |
| Bidel et al,29 2006, Europe, type 2 diabetic population | Both           | 20.8          | 25–74           | 0–2 cups/d 1.00 (1.00–1.00)  
3–4 cups/d 0.79 (0.64–0.97)  
5–6 cups/d 0.70 (0.57–0.86)  
≥7 cups/d 0.71 (0.56–0.90) | CVD mortality | Nonspecific diet questionnaire (baseline)/national registries | Age, sex, study year, BMI, SBP, total cholesterol, education, alcohol and tea consumption, and smoking status |
| Greenberg et al,33 2007, US            | Both           | 8.8           | 32–86           | <65 y <0.5 cup/d 1.00 (1.00–1.00)  
0.5–2 cups/d 0.95 (0.38–2.35)  
2–4 cups/d 0.79 (0.34–1.85)  
≥4 cups/d 0.86 (0.38–1.06)  
≥65 y <0.5 cup/d 1.00 (1.00–1.00)  
0.5–2 cups/d 0.72 (0.52–0.99)  
2–4 cups/d 0.69 (0.52–0.92)  
≥4 cups/d 0.53 (0.38–0.75) | CVD mortality | FFQ (baseline)/confirmed cases | Age, smoking, BMI, sex, race, physical activity, alcohol consumption, per capita income, educational level, and American-style diet |

(Continued)
### Table. Continued

<table>
<thead>
<tr>
<th>Author, Year, Country, Special Annotation</th>
<th>Sex</th>
<th>Follow-Up, y</th>
<th>Age at Start of Follow-Up, y</th>
<th>Cases/Total Participants, n/N</th>
<th>Exposure (cup/d)/Relative Risk (95% CI)</th>
<th>Outcome</th>
<th>Exposure/Outcome Assessment</th>
<th>Confounders Adjusted for</th>
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<tbody>
<tr>
<td>Silletta et al, 2007, Europe, myocardial infarction population</td>
<td>Both</td>
<td>3.5</td>
<td>52–63</td>
<td>1167/11 231</td>
<td>0 cup/d 1.00 (1.00–1.00) &lt;2 cups/d 1.02 (0.87–1.20) 2–4 cups/d 0.91 (0.75–1.09) &gt;4 cups/d 0.88 (0.64–1.2)</td>
<td>CVD</td>
<td>FFQ (average)/confirmed cases</td>
<td>Age, sex, smoking, BMI, dietary habits, cardiovascular risk factors, history of MI before the index MI, time from the index MI to enrollment, post-MI complications, and pharmaceutical therapies, with inclusion of the allocation treatments</td>
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<tr>
<td>Greenberg et al, 2008, US</td>
<td>Both</td>
<td>10.1</td>
<td>65–97</td>
<td>523/1354</td>
<td>0 cup/d 1.00 (1.00–1.00) ≥1 cup/d 1.00 (0.84–1.20)</td>
<td>CVD events</td>
<td>FFQ (baseline)/confirmed cases</td>
<td>Age, sex, smoking, BMI, alcohol consumption, physical activity, marital status, blood pressure, history of CVD, and antihypertensive medication use</td>
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<tr>
<td>Happonen et al, 2008, Europe</td>
<td>Both</td>
<td>14.5</td>
<td>70–94</td>
<td>344/817</td>
<td>0 cups/d 0.80 (0.47–1.35) 1–2 cups/d 1.00 (1.00–1.00) 3–4 cups/d 0.96 (0.72–1.27) 5–6 cups/d 0.89 (0.64–1.24) ≥7 cups/d 0.84 (0.48–1.47)</td>
<td>CVD mortality</td>
<td>Nonspecific diet questionnaire (baseline)/national registries</td>
<td>Sex, current age, calendar period, marital status, educational level, previous occupational group, current smoking, BMI, history of MI, presence of diabetes mellitus, cognitive impairment, physical disability, and self-rated health</td>
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<tr>
<td>Larsson et al, 2008, Europe</td>
<td>Men</td>
<td>13.6</td>
<td>50–69</td>
<td>2702/26 556</td>
<td>&lt;2 cup/d 1.00 (1.00–1.00) 2–3 cups/d 0.91 (0.79–1.06) 4–5 cups/d 0.88 (0.77–1.02) 6–7 cups/d 0.77 (0.66–0.90) ≥8 cups/d 0.77 (0.66–0.90)</td>
<td>Stroke</td>
<td>FFQ (baseline)/national registries</td>
<td>Age, supplementation group, No. of cigarettes smoked daily, BMI, systolic and diastolic blood pressures, serum total cholesterol, serum HDL cholesterol, histories of diabetes mellitus and coronary heart disease, leisure-time physical activity, alcohol intake, and tea consumption</td>
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<tr>
<td>Mukamal et al, 2009, Europe, myocardial infarction population</td>
<td>Both</td>
<td>6.9–9.9</td>
<td>45–70</td>
<td>331 (MI), 135 (stroke)/1369</td>
<td>MI 0–1 cup/d 1.00 (1.00–1.00) 1–3 cups/d 0.97 (0.65–1.45) 3–5 cups/d 0.75 (0.50–1.13) 5–7 cups/d 0.94 (0.61–1.44) ≥7 cups/d 0.84 (0.51–1.40) Stroke 0–1 cup/d 1.00 (1.00–1.00) 1–3 cups/d 1.08 (0.57–2.02) 3–5 cups/d 0.94 (0.49–1.78) 5–7 cups/d 1.17 (0.59–2.29) ≥7 cups/d 0.74 (0.31–1.75)</td>
<td>CHD, stroke</td>
<td>FFQ (baseline)/national registries</td>
<td>Age, sex, diabetes mellitus, smoking, obesity, physical inactivity, alcohol consumption, tea consumption, education, and intake of boiled coffee</td>
</tr>
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Table. Continued

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<thead>
<tr>
<th>Author, Year, Country, Special Annotation</th>
<th>Sex</th>
<th>Follow-Up, y</th>
<th>Age at Start of Follow-Up, y</th>
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<th>Exposure (cup/d)/Relative Risk (95% CI)</th>
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<th>Exposure/Outcome Assessment</th>
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<tbody>
<tr>
<td>Sugiyama et al,17 2010, Japan</td>
<td>Both</td>
<td>10.3</td>
<td>40–64</td>
<td>426/37 742</td>
<td>Men CVD mortality 0 cup/d 1.00 (1.00–1.00) 0–1 cup/d 1.09 (0.79–1.51) 1–2 cups/d 0.85 (0.56–1.23) ≥3 cups/d 0.88 (0.56–1.39) Women CVD mortality 0 cup/d 1.00 (1.00–1.00) 0–1 cup/d 0.56 (0.36–0.86) 1–2 cups/d 0.48 (0.29–0.80) ≥3 cups/d 0.45 (0.20–1.03)</td>
<td>CVD mortality FFQ (baseline)/mortality certificates at the public health center</td>
<td>Age in years; sex; history of hypertension and diabetes mellitus; education level; BMI; walking time; cigarette smoking; consumption of alcohol, green tea, oolong tea, black tea; and intake of rice, miso soup, total meat, total dairy products, total fish, total vegetables, total fruits, and energy</td>
<td></td>
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<tr>
<td>Ahmed et al,38a 2009, Europe</td>
<td>Men</td>
<td>9</td>
<td>45–79</td>
<td>784/37 315</td>
<td>≤1 cup/d 1.00 (1.00–1.00) 2 cups/d 0.87 (0.69–1.11) 3 cups/d 0.89 (0.70–1.14) 4 cups/d 0.89 (0.69–1.15) ≥5 cups/d 0.89 (0.69–1.15)</td>
<td>Heart failure FFQ (baseline)/confirmed cases</td>
<td>Age, BMI, total activity score, smoking, history of high cholesterol, family history of MI before 60 y of age, education level, marital status, aspirin use, alcohol, tea, energy-adjusted fat intake, and energy-adjusted daily sodium intake</td>
<td></td>
</tr>
<tr>
<td>Lopez-Garcia et al,39a 2009, US</td>
<td>Women</td>
<td>24</td>
<td>56</td>
<td>2280/83 076</td>
<td>&lt;0.03 cup/d 1.00 (1.00–1.00) 0.03–0.57 cup/d 0.96 (0.82–1.13) 0.57–1 cup/d 0.88 (0.77–1.02) 2–3 cups/d 0.84 (0.72–0.98) ≥4 cups/d 0.85 (0.69–1.06)</td>
<td>Stroke FFQ (average)/confirmed cases</td>
<td>Age, smoking status, BMI, physical activity, alcohol intake, menopausal status and use of hormone replacement therapy, aspirin use; total caloric intake; quintiles of calcium, potassium, sodium, and folate intake; glycemic load; whole grain intake; and tertiles of fruits, vegetables, and fish consumption, high blood pressure, hypercholesterolemia, and type 2 diabetes mellitus</td>
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</table>
| Leurs et al,40 2010, Europe, case-cohort study | Both | 10           | 55–69                         | 1789 (IHD deaths), 708 (stroke deaths) /120 852 | Men with MI mortality 0–2 cups/d 1.00 (1.00–1.00) 2–4 cups/d 0.91 (0.71–1.16) 3–6 cups/d 1.02 (0.79–1.31) ≥6 cups/d 1.17 (0.86–1.59) Women with MI mortality 0–2 cups/d 1.00 (1.00–1.00) 2–4 cups/d 0.75 (0.58–0.97) 3–6 cups/d 0.62 (0.46–0.84) ≥6 cups/d 0.71 (0.45–1.12) Men with stroke mortality 0–2 cups/d 1.00 (1.00–1.00) 2–4 cups/d 0.84 (0.60–1.18) 3–6 cups/d 0.72 (0.50–1.04) ≥6 cups/d 1.15 (0.74–1.77) Women with stroke mortality 0–2 cups/d 1.00 (1.00–1.00) 2–4 cups/d 0.79 (0.57–1.09) 3–6 cups/d 0.70 (0.48–1.02) ≥6 cups/d 1.10 (0.63–1.90) | CHD mortality, stroke mortality FFQ (baseline)/national registries | Age, current smoking, number of cigarettes smoked, years of active smoking, and total energy intake | (Continued)
### Table.

<table>
<thead>
<tr>
<th>Author, Year, Country, Special Annotation</th>
<th>Sex</th>
<th>Follow-Up, y</th>
<th>Cases/Total Participants, n/N</th>
<th>Exposure (cup/d)/Relative Risk (95% CI)</th>
<th>Outcome Assessment</th>
<th>Confounders Adjusted for</th>
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<tr>
<td><strong>de Koning Gans et al,17 2010, Europe</strong></td>
<td>Both</td>
<td>13</td>
<td>20–69</td>
<td>CHD morbidity</td>
<td>CHD, CHD mortality, national stroke mortality</td>
<td>Sex; age; educational level; physical activity; smoking status; waist circumference; menopausal status; alcohol and tea intake; total energy and saturated fat, fiber, and vitamin C level</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1387 (CHD cases), 563 (stroke cases), 123 (CHD deaths), 70 (stroke deaths)/37 514</td>
<td>&lt;1 cup/d 1.00 (1.00–1.00), 1–2 cups/d 0.85 (0.70–1.04), 2–3 cups/d 0.79 (0.65–0.96), 3–4 cups/d 0.82 (0.68–0.98), 4–6 cups/d 0.86 (0.73–1.02), &gt;6 cups/d 0.91 (0.74–1.11)</td>
<td>FFQ (baseline)/national registries</td>
<td></td>
</tr>
<tr>
<td><strong>Larsson et al,19 2011, Europe</strong></td>
<td>Women</td>
<td>10.4</td>
<td>49–83</td>
<td>Stroke morbidity</td>
<td>Stroke FFQ (baseline)/national registries</td>
<td>Age; smoking status and pack-years of smoking; education; BMI; total physical activity; history of diabetes mellitus; history of hypertension; aspirin use; family history of myocardial infarction; and intakes of total energy, alcohol, red meat, fish, fruits, and vegetables</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1680/34 670</td>
<td>&lt;1 cup/d 1.00 (1.00–1.00), 1–2 cups/d 1.08 (0.79–1.47), 2–3 cups/d 1.15 (0.85–1.57), 3–4 cups/d 1.10 (0.82–1.46), 4–6 cups/d 1.11 (0.84–1.46), &gt;6 cups/d 1.22 (0.88–1.70)</td>
<td>FFQ (baseline)/national registries</td>
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<tr>
<td><strong>Mineharu et al,41a 2011, Japan</strong></td>
<td>Both</td>
<td>13.1</td>
<td>40–79</td>
<td>CHD mortality</td>
<td>BMI, history of hypertension, history of diabetes mellitus, 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</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2012/76 979</td>
<td>&lt;0.14 cup/d 1.00 (1.00–1.00), 0.14–1 cup/d 0.71 (0.53–0.96), 1–2 cups/d 0.84 (0.64–0.99), ≥3 cups/d 1.17 (0.77–1.76)</td>
<td>FFQ (baseline)/mortality certificates at the public health center</td>
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<tr>
<td><strong>Floegel et al,13 2012, Europe</strong></td>
<td>Both</td>
<td>8.9</td>
<td>35–65</td>
<td>CVD morbidity</td>
<td>CVD, confirmed self-reported</td>
<td>Age at recruitment, center, sex, smoking, alcohol intake, physical activity, education, employment, vitamin and mineral supplement use during past 4 wk, total energy intake, tea intake, decaffeinated coffee intake, BMI, waist-to-hip ratio, and prevalent hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>704/42 659</td>
<td>≥0.14 cup/d 1.00 (1.00–1.00), 1–2 cups/d 0.94 (0.64–1.36), 2–3 cups/d 1.07 (0.81–1.42), 3–4 cups/d 1.02 (0.75–1.38), &gt;4 cups/d 1.10 (0.84–1.44)</td>
<td>FFQ (baseline)/confirmed self-reported</td>
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<th>Exposure (cup/d)/Relative Risk (95% CI)</th>
<th>Outcome</th>
<th>Exposure/Outcome Assessment</th>
<th>Confounders Adjusted for</th>
</tr>
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<tr>
<td>Rautiainen et al,42a 2012, Europe</td>
<td>Women</td>
<td>9.9</td>
<td>49–83</td>
<td>1114/329561</td>
<td>≤2 cups/d 1.00 (1.00–1.00)</td>
<td>CHD</td>
<td>FFQ (baseline)/national registries</td>
<td>Age, education, smoking, BMI, physical activity, hypertension, hypercholesterolemia, family history of myocardial infarction, aspirin use, hormone replacement therapy use, dietary supplement use, and intakes of total energy and alcohol intake; consuming fruit, vegetables, red meat, and saturated fat; use or nonuse of vitamin supplements; and use or nonuse of postmenopausal hormone therapy</td>
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<tr>
<td>Freedman et al,11 2012, US</td>
<td>Both</td>
<td>14</td>
<td>50–71</td>
<td>11828 (CHD deaths), 2293 (stroke deaths)/402 260</td>
<td>Men CHD mortality ≤1 cup/d 0.93 (0.85–1.02)</td>
<td>CHD mortality, FFQ (baseline)/stroke mortality</td>
<td>national registries</td>
<td>Age; BMI; race or ethnic group; level of education; alcohol consumption; number of cigarettes smoked per day, use or nonuse of pipes or cigars, and time of smoking cessation; health status; diabetes mellitus; marital status; physical activity; total energy intake; consumption of fruits, vegetables, red meat, white meat, and saturated fat; use or nonuse of vitamin supplements; and use or nonuse of postmenopausal hormone therapy</td>
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<tr>
<td>Kokubo et al,12 2013, Japan</td>
<td>Both</td>
<td>13</td>
<td>45–74</td>
<td>4335/82369</td>
<td>Total CVD ≤2 cups/week 1.00 (1.00–1.00)</td>
<td>CVD, CHD stroke, FFQ (baseline)/confirmed cases</td>
<td>confirmed cases</td>
<td>Age; sex; smoking; alcohol; BMI; history of diabetes mellitus; medication of antihypercholesterolemia and antihypertension; sports; dietary intake of fruits, vegetables, fish, and energy; public health centers; and green tea consumption</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; FFQ, food frequency questionnaire; HDL, high-density lipoprotein; MI, myocardial infarction; and SBP, systolic blood pressure.
For the risk of CHD, compared with the lowest category of coffee consumption, the RRs of CHD were 0.89 (95% CI, 0.85–0.94; \( P \) for heterogeneity=0.83; \( F=0.0% \)) for the third highest category, 0.90 (95% CI, 0.84–0.97; \( P \) for heterogeneity=0.02; \( F=40.3% \)) for the second highest category, and 0.93 (95% CI, 0.84–1.02; \( P \) for heterogeneity <0.001; \( F=52.8% \)) for the highest category of coffee consumption. The corresponding RRs of stroke were 0.89 (95% CI, 0.84–0.94; \( P \) for heterogeneity=0.58; \( F=0.0% \)) for the third highest category, 0.80 (95% CI, 0.75–0.86; \( P \) for heterogeneity=0.37; \( F=6.5% \)) for the second category, and 0.95 (95% CI, 0.84–1.07; \( P \) for heterogeneity=0.001; \( F=54.5% \)) for the highest category.

**Dose–Response Analysis of Coffee Consumption With Risk of CVD**

In our dose–response analysis, we observed a nonlinear association between coffee consumption and risk of CVD (\( P \) for nonlinearity <0.001) with a significant trend (\( P \) for trend <0.001) and limited heterogeneity in study results (\( P \) for heterogeneity=0.09) (Figure 4A). Compared with those with no coffee consumption, the RR estimated directly from the cubic spline model was 0.95 (95% CI, 0.93–0.97) for 1 cup per day, 0.92 (95% CI, 0.88–0.95) for 2 cups per day, 0.89 (95% CI, 0.85–0.93) for 3 cups per day, 0.88 (95% CI, 0.83–0.93) for 4 cups per day, 0.89 (95% CI, 0.83–0.95) for 5 cups per day, 0.91 (95% CI, 0.84–0.99) for 6 cups per day, and 0.93 (95% CI, 0.85–1.03) for 7 cups per day.

Nonlinear (\( P \) for nonlinearity <0.001) associations between coffee consumption and disease risk with significant trends (\( P \) for trend <0.001) were found for both CHD and stroke (Figure 4B and 4C). There was stronger evidence for heterogeneity in study results for the association of coffee consumption with CHD risk (\( P \) for heterogeneity=0.001) than for the association with stroke risk (\( P \) for heterogeneity=0.07).
We further explored the reason for the heterogeneity between coffee consumption and CHD risk by stratifying the studies by publication year (2000 or before or after 2000). We found that in studies published in 2000 or earlier, coffee consumption was not significantly associated with CHD risk (n=13; $P$ for heterogeneity=0.20), whereas in later studies, coffee consumption was nonlinearly associated with CHD risk (n=18; $P$ for heterogeneity=0.08). We did not perform a similar analysis for stroke because very few studies on stroke were published before 2000.

Sensitivity Analysis

We tested the robustness of our results in sensitivity analyses. Because the RRs of stroke and CHD from the same cohort were correlated and a total of 6 studies included both CHD and stroke results, we conducted a sensitivity analysis by including only 1 outcome at a time. Our results remained largely unchanged, and nonlinear curves were found with including either CHD or stroke as the outcome (Figure IA and IB in the online-only Data Supplement).

One study with coffee consumption modeled as a continuous variable was excluded from the main analysis.\textsuperscript{26} We added the RR from this study to the dose–response analysis by a 2-stage method, and the results did not substantially change.

To test whether the association between coffee consumption and risk of CVD was different for unadjusted and multivariable adjusted models, we performed a dose–response meta-analysis of the only age-adjusted data including 34 comparisons (Figure II in the online-only Data Supplement). Multivariate adjustment strengthened the inverse association between moderate consumption and CVD risk, most likely as a result of the adjustment for smoking.

Publication Bias

The Egger test did not suggest publication bias for associations for any category of coffee consumption and risk of CVD (Figure III and Table II in the online-only Data Supplement).

Discussion

The findings from this systematic review and meta-analysis, based on \approx=1283685 study participants and 47779 CVD cases, including \approx=28347 CHD cases, 12030 stroke cases, and 7402 other CVD cases, demonstrate a nonlinear association
between coffee consumption and risk of CVD. Moderate coffee consumption (3–5 cups per day) was associated with lower CVD risk, and heavy coffee consumption (≥ 6 cups per day) was neither associated with a higher nor a lower risk of CVD.

In contrast to our results, a previous meta-analysis summarizing 21 prospective cohort studies found no association between moderate coffee consumption and CHD risk in the overall population. One possible reason is that the previous meta-analysis included 7 studies without adjustment for confounders, which might have biased the RRs upward because of confounding by factors such as smoking.

A recent cohort study by Liu et al found that 4 cups per day of coffee consumption was associated with increased mortality, but the association was only significant for participants <55 years of age. The results from this study contradict those from this meta-analysis and the majority of studies in the literature. Possible reasons for this discrepancy include a relatively small size, lack of updated dietary assessment, and subgroup analysis. In our meta-analysis, stratified analysis by age revealed no significant differences in the association across age groups.

The debate about the relation between coffee consumption and CVD risk stemmed mainly from inconsistent results according to different study designs. Case-control studies, which are prone to recall bias and selection bias, tended to show a positive association, whereas cohort studies generally showed a null association. Still, findings from prospective cohort studies on coffee consumption and CVD risk have remained inconsistent. Differences among studies in sample sizes, the characteristics of the study populations, the assessment methods for coffee consumption, and statistical adjustments may have contributed to divergent results. Because the true association between coffee consumption and CVD risk is likely to be modest and nonlinear, the differences in coffee assessments and covariate adjustments may result in changes the magnitude and even the direction of the associations and thus lead to different conclusions.

The U-shaped association between coffee consumption and CVD risk observed in this meta-analysis needs to be considered from both methodological and biological points of view. First, individuals with hypertension or other conditions related to CVD risk might have changed their coffee consumption before baseline. Thus, baseline disease, especially hypertension, as a confounder could result in reverse causation. However, we observed no significant difference in the association between coffee consumption and CVD risk between cohorts with hypertensive and myocardial infarction patients and the general population cohorts. Second, smoking is likely to be an important confounder for the association between coffee consumption and CVD risk and...
could bias the RRs upward. Heavy coffee consumption was associated with higher risk of CVD in age-adjusted analyses, but this is likely due to confounding by smoking. After adjustment for smoking and other covariates, heavy coffee consumption was not significantly associated with CVD, and the inverse association between moderate consumption and CVD became stronger.

The nonlinear U-shaped relationship between coffee consumption and CVD risk might also be true on the basis of plausible biological mechanisms. Coffee is a complex chemical mixture with hundreds of compounds, including the phenolic compound chlorogenic acid, caffeine, minerals such as potassium and magnesium, niacin and its precursor trigonelline, and lignans. Coffee consumption has been associated with higher insulin sensitivity, a lower risk of type 2 diabetes mellitus, and lower concentrations of inflammatory markers such as C-reactive protein and E-selectin. However, short-term metabolic studies have shown that caffeine can acutely increase blood pressure by antagonizing the adenosine A1 and A2A receptors and could acutely affect arterial stiffness and endothelium-dependent vasodilation adversely. Long-term heavy coffee consumption has been associated with a slightly elevated risk of hypertension and a higher level of plasma homocysteine. In addition, cafestol in unfiltered coffee increases serum total cholesterol concentrations. The nonlinear U-shaped relationship between coffee consumption and risk of CVD might be due to a combination of beneficial and detrimental effects: For moderate coffee consumption, beneficial effects may be greater than adverse effects, whereas for heavy consumption, detrimental effects may counterbalance beneficial effects. Results from case-crossover studies suggest that coffee consumption transiently increases risk of nonfatal myocardial infarction, ischemic stroke onset, and sudden cardiac death. However, we could not differentiate short-term effects from long-term effects of habitual coffee consumption in this study.

No significant association between decaffeinated coffee consumption with CVD risk was observed in this meta-analysis. There were several potential explanations. First, the consumption of decaffeinated coffee was much lower than caffeinated coffee, diminishing the power to detect any association. Second, the null association might be due to a reverse causation problem in that individuals with hypertension or other CVD-related conditions might switch from regular coffee to decaffeinated coffee. This reverse causation may mitigate an inverse association between decaffeinated coffee consumption and CVD risk.

We did not observe a significant association between coffee consumption and CHD risk for earlier publications (2000 or earlier). There are 2 potential reasons for this finding. First, coffee brewing methods have changed over time, and nowadays the filter method is more popular, effectively replacing unfiltered forms of coffee such as boiled coffee that were more widely consumed by participants in earlier studies. It has been shown that drinking boiled coffee increases serum cholesterol, an important risk factor for CVD. Second, in earlier studies, the sample size was typically small, the measurement of baseline characteristics was typically crude, statistical control of confounders such as diet was inadequate, and the average NOS study quality

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**Figure 3.** Stratified analysis of the association between coffee consumption and risk of cardiovascular disease (CVD). The included studies for the stratified analysis were the same as for the dose-response analysis. CI indicates confidence interval; NOS score, score using the Newcastle-Ottawa scale; and specific dietary assessment method, diet that was assessed by 24-hour diet recall, diet record, or food frequency questionnaire.
score was lower. Our stratified analysis showed that coffee consumption was not associated with CVD risk in subgroups with a lower NOS score.

A study by Cornelis et al47 showed that the CYP1A2 genotype was an effect modifier between coffee consumption and risk of myocardial infarction: Coffee consumption was related to higher risk of myocardial infarction for the slow caffeine metabolizer and was not related to myocardial infarction for the fast caffeine metabolizer. However, this analysis was based on a case-control study conducted in Costa Rica, and the results have not yet been replicated in prospective cohort studies.

Recently, a genome-wide association study found a highly significant association between a variant of CYP1A2 and coffee intake.48 However, this variant explains only a very small population variance. Because the vast majority of our participants were whites, the allele frequency was expected to be consistent across various cohorts. Ideally, the meta-analyses should be done according to different genotypes of CYP1A2. However, none of the included cohorts assessed the genotypes; thus, we were unable to conduct such a stratified analysis.

Our meta-analysis has several strengthens. First, our meta-analysis included 35 cohort studies and 1,283,685 participants, which provided sufficient power to detect modest associations. Second, because of the prospective design of all included studies, differential misclassification of coffee consumption as a result of recall bias was minimized, and the likelihood of selection bias is reduced. Third, we used both semiparametric and parametric methods, and both analyses indicated a U-shaped relationship between coffee consumption and CVD risk. Finally, we conducted stratified analyses according to disease end points, geographic locations of the studies, type of coffee, and baseline characteristics of the study populations. The subgroup results are highly consistent and robust.

Our study also has several limitations. Given the observational nature of the studies, the possibility of residual confounding cannot be excluded. However, because higher coffee consumption was generally associated with a less healthy lifestyle such as a higher prevalence of cigarette smoking, less physical activity, and a less healthy diet, the observed association between moderate coffee consumption and a lower CVD risk is unlikely to be explained by these confounders. In addition, residual confounding by smoking may have biased the association for heavy coffee consumption upward, which may explain our finding that adjustment for smoking and other covariates actually strengthened the inverse association. Nonetheless, because of the observational nature of the included studies, a causal relationship cannot be established with these data alone. In addition, coffee brewing methods were not assessed in the included studies. However, given coffee consumption habits in the studied populations, most consumed coffee is likely to have been filtered coffee. As a result, our results may not apply to unfiltered coffee (eg, French press, Scandinavian boiled, or Turkish/Greek coffee).

**Conclusion**

Our meta-analysis suggests a nonlinear relationship between coffee consumption and CVD risk. Moderate coffee consumption was associated with lower CVD risk, with the lowest CVD risk at 3 to 5 cups per day of coffee consumption, and heavy coffee consumption was not associated with CVD risk. This nonlinear association with coffee consumption was observed for the risks of both CHD and stroke.

**Sources of Funding**

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Disclosures

Dr van Dam received a research grant from the Nestec Co. The other authors report no conflicts.

References


Coffee is one of the most widely consumed beverages around the world, and its association with cardiovascular disease has been investigated in numerous epidemiological studies. However, a key issue that remains to be resolved is the dose–response relationship of long-term coffee consumption with cardiovascular disease (CVD) risk, including incidence of coronary heart disease, stroke, and heart failure, and CVD mortality. In the current meta-analysis, we summarized results from 36 prospective cohort studies on coffee consumption and CVD risk with 1,279,804 study participants and 36,352 CVD cases. We found a nonlinear relationship of coffee consumption with CVD risk: Moderate coffee consumption was associated with lower risk of CVD, with the lowest CVD risk at 3 to 5 cups per day, and heavy coffee consumption was not associated with risk of CVD. Looking at outcomes separately, we also found nonlinear relationships of coffee consumption with coronary heart disease and stroke risks. The present study provides strong evidence that long-term heavy consumption of coffee is not associated with CVD risk and provides insight into the potential mechanism of the nonlinear relationship between coffee consumption and CVD risk. We believe that this report will be of significant interest to clinicians involved in the prevention and treatment of CVD.
Long-Term Coffee Consumption and Risk of Cardiovascular Disease: A Systematic Review and a Dose–Response Meta-Analysis of Prospective Cohort Studies
Ming Ding, Shilpa N. Bhupathiraju, Ambika Satija, Rob M. van Dam and Frank B. Hu

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### SUPPLEMENTAL MATERIAL

**Supplemental table 1: the quality assessment of included studies using the Newcastle–Ottawa scale**

<table>
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<th>Author</th>
<th>Year</th>
<th>Represen tatives s of Exposed Cohort</th>
<th>Selection of Non - Exposed Cohort</th>
<th>Ascertainment of Exposure</th>
<th>Demonstration That Outcome of Interest Was Not Present at Start of Study</th>
<th>Comparability</th>
<th>Outcome</th>
<th>Assessment of outcome</th>
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The quality of included studies was assessed by the Newcastle Ottawa scale. A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories and a maximum of two stars for Comparability.

**Selection:** 1) Representativeness of exposed cohort: 1, study population truly or somewhat representative of a community/population based study; 0, study population was sampled from a special population, i.e. population from a company, hospital patients, data from the health insurance company or health examination organization, nurses, Adventist group.
2) Selection of non-exposed cohort: 1, drawn from the same community as the exposed cohort.

3)Ascertainment of exposure: 1, specific dietary assessment method of coffee consumption (FFQ/diet record/24h diet recall) with validation; 0, no specific dietary assessment method or specific dietary assessment method without validation

4) Demonstration that outcome was not present at start of study: 1, exclusion of participants with a history of CVD at the beginning of the study.

Comparability: 1) 1, whether a study adjusted for smoking deliberately (not only adjust for the smoking status, but also the number of cigarettes or duration of smoking); 1, whether a study adjusted for baseline hypertension.

Outcome: 1) Assessment of outcome: 1, CVD cases were confirmed by medical records or record linkage; 0, self-reported.

2) Was follow-up long enough for outcomes to occur: 1, duration of follow-up >= 5 year; 0, if duration of follow-up < 5 year.

3) Loss to follow-up rate: 1, complete follow-up or loss to follow up rate <=20 %; 0, follow-up rate < 80% or no description of those lost.
**Supplemental table 2: Egger’s test for the publication bias on coffee consumption and risk of type 2 diabetes**

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Supplemental figures

Supplemental figure 1: Dose response relationship of coffee consumption with cardiovascular disease risk choosing only one outcome for correlated outcomes within the same study. n was the number of comparisons.

a. Coffee consumption and risk of CVD choosing CHD for correlated outcomes (n=36)  
b. Coffee consumption and risk of CVD choosing stroke for correlated outcomes (n=37)
Supplemental figure 2. Dose response relationship of coffee consumption with cardiovascular disease risk from models adjusted for different confounders. Red curve: included studies only adjusted for age; Black curve: included studies with multivariate adjusted models.
Supplemental figure 3: Egger’s test for publication bias for the association between coffee consumption and risk of CVD

a. The third highest category of coffee consumption

b. The second highest category of coffee consumption

c. The highest category of coffee consumption
The study selection process:

Of the 53 initially included studies, we excluded 14 studies due to duplicate publication\(^1\)\(^-\)\(^14\), one study with point estimate without standard error\(^15\), and one nested case control study with a retrospective design\(^16\). Thirty-six studies were remained in the meta-analysis\(^17\)\(^-\)\(^52\).

**Reference**


33. Andersen LF, Jacobs DR, Jr., Carlsen MH, Blomhoff R. Consumption of coffee is associated with reduced risk of death attributed to inflammatory and cardiovascular diseases in the iowa women's health study. The American journal of clinical nutrition. 2006;83:1039-1046


