

## Habitual Coffee Consumption and Risk of Heart Failure A Dose-Response Meta-Analysis

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**Background**—There have been discrepant findings on the association between coffee consumption and risk of incident heart failure.

**Methods and Results**—We conducted a systematic review and a dose-response meta-analysis of prospective studies that assessed the relationship between habitual coffee consumption and the risk of heart failure. We searched electronic databases (MEDLINE, Embase, and CINAHL) from January 1966 through December 2011, with the use of a standardized protocol. Eligible studies were prospective cohort studies that examined the association of coffee consumption with incident heart failure. Five independent prospective studies of coffee consumption and heart failure risk, including 6522 heart failure events and 140 220 participants, were included in the meta-analysis. We observed a statistically significant J-shaped relationship between coffee and heart failure. Compared with no consumption, the strongest inverse association was seen for 4 servings/day and a potentially higher risk at higher levels of consumption. There was no evidence that the relationship between coffee and heart failure risk varied by sex or by baseline history of myocardial infarction or diabetes.

**Conclusions**—Moderate coffee consumption is inversely associated with risk of heart failure, with the largest inverse association observed for consumption of 4 servings per day. (*Circ Heart Fail.* 2012;5:401-405.)

**Key Words:** dose-response meta-analysis ■ coffee ■ heart failure ■ epidemiology

There have been discrepant findings on the association between coffee consumption and incident heart failure. Wilhelmsen and colleagues<sup>1</sup> reported that, compared with no coffee consumption, the risk of hospitalization or death from heart failure was 17% higher (95% confidence interval, 1.05 to 1.30) among men who consumed 5 or more cups of coffee per day. This finding served as the basis for the suggestion in the most recent statement from the American Heart Association on heart failure prevention,<sup>2</sup> stating that coffee may increase heart failure risk; however, the Wilhelmsen analysis did not adjust for any potential confounders. Subsequent studies have shown that coffee may protect against heart failure incidence<sup>3</sup> or that no association exists.<sup>4,5</sup> One study<sup>6</sup> found an inverse association that was statistically significant among women but not men; however, most of these studies did not have sufficient power to detect modest results.

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Since the results have been inconsistent and the prior studies had limited power, we conducted a systematic review and a dose-response meta-analysis of prospective studies that assess the relation between habitual coffee consumption and the risk of heart failure.

### Methods

We followed the Meta-Analysis of Observational Studies in Epidemiology<sup>7</sup> protocol throughout the design, implementation, analysis, and reporting for this study.

### Literature Search Strategy

We performed a literature search of the MEDLINE, Embase, and CINAHL databases from January 1966 through December 2011, using the key words *coffee* and *heart failure* without restrictions. We also reviewed the reference lists of retrieved articles. We reviewed all articles with an abstract suggesting that it was relevant. Prospective cohort studies were included if they reported odds ratios or incidence rate ratios (IRR) with 95% confidence intervals (CI) of heart failure incidence or mortality.

### Data Extraction

The following details were recorded for each study: author, year of publication, cohort/study name, geographic location of study, study period, participants' sex, age range at baseline, health at baseline (no prior myocardial infarction [MI], prior MI, history of diabetes), and outcome (nonfatal or fatal; primary or secondary cause). For each study, we obtained information about the levels of coffee intake, the number of cases and the total population or person-time at risk at each exposure level, the adjusted estimates of the odds ratio or IRR compared with abstention for each exposure level, and the corresponding lower and upper 95% CIs of the adjusted odds ratios and IRRs.

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We extracted the relative risks for the models with the greatest degree of adjustment for potentially confounding variables, but if an additional model was reported that further adjusted for potential intermediates of the association between coffee and heart failure, we used the data from the model that did not include the intermediates. Data abstraction was conducted independently by 2 investigators (E.M. and M.S.R.), with disagreements adjudicated by a third reader (M.A.M.). For articles that did not include all of the necessary data for the meta-analysis, we contacted authors for additional information.

### Statistical Analysis

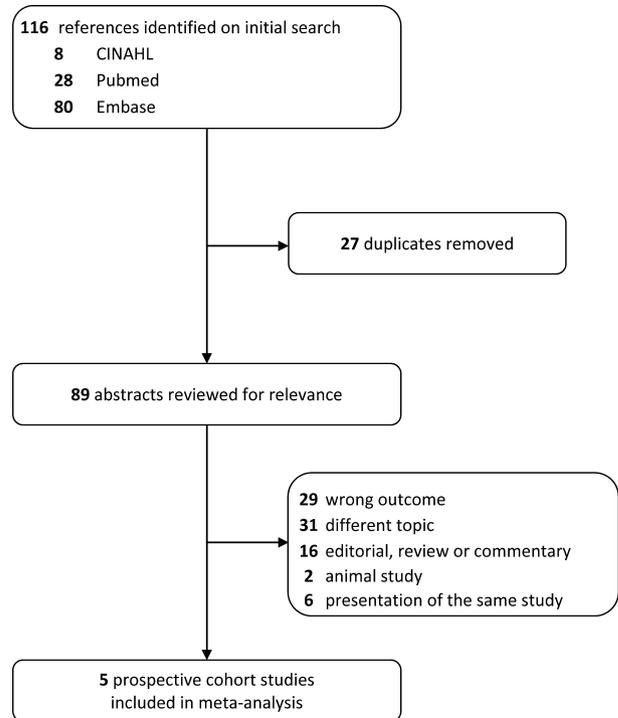
Since some studies used different categories of coffee consumption, we conducted a dose-response meta-analysis to assess the pooled dose-response relation between coffee consumption and risk of heart failure for studies that considered at least 3 levels of coffee consumption, including the reference category. For every study, the median or mean coffee intake for each category was assigned to each corresponding odds ratio or IRR. When the median or mean intake per category was not provided by the study authors, we assigned the midpoint of the upper and lower boundaries in each category as the average intake. If the lower or upper boundary for the lowest and highest category respectively was not reported, we assumed that the boundary had the same magnitude as the closest category.

We used the method described by Greenland and Longnecker<sup>8</sup> to compute study-specific ORs and IRRs and 95% CI from the natural logarithms of the relative risks and CIs across categories of coffee consumption. To examine a potential nonlinear relationship between coffee intake and heart failure risk, we performed a 2-stage, random-effects, dose-response meta-analysis, as summarized recently.<sup>9</sup> At the first stage, we constructed study-specific restricted cubic spline models, with 4 knots at fixed percentiles (5%; 35%; 65%; 95%) of the exposure distribution,<sup>10</sup> assuming the fixed effects model. At the second stage, we combined the study-specific estimates and the variance/covariance matrix that had been estimated within each study, using a random-effects model for meta-analysis.<sup>11</sup> We conducted a test for the overall significance of the curve by testing the joint impact of the spline transformations. We examined whether a nonlinear relationship exists by testing the null hypothesis that the regression coefficients of the spline transformations are all equal to zero. We assessed whether our results were different for men and women and for results based on people with versus without a prior MI or diabetes at baseline. We did not have sufficient statistical power to formally assess differences between these subgroups, so we conducted stratified analyses and reported a qualitative assessment of any differences. We carried out sensitivity analyses excluding 1 study at a time to explore whether the results were driven by a single large study.

Statistical heterogeneity among studies was assessed using the  $I^2$  statistic.<sup>12</sup> Possible publication bias was evaluated with Egger's regression asymmetry test.<sup>13</sup> All statistical analyses were conducted using SAS 9.2 (SAS Institute, Inc., 2003) and the `metadose` macro,<sup>9</sup> with 2-tailed  $\alpha$  set at  $P \leq 0.05$  for statistical significance.

### Results

The search identified 116 publications, and, after excluding 27 duplicates, an additional 84 articles were excluded following review of the title or abstract (Figure 1). The meta-analysis included 5<sup>1,3-6</sup> independent prospective studies of coffee consumption and heart failure risk published between 2001 and 2011 (Table). Combined, these studies included 6522 heart failure events among 140220 participants. Four of the studies were conducted in Sweden,<sup>1,3-5</sup> and 1 was conducted in Finland.<sup>6</sup> Three of the studies consisted of participants with no history of MI,<sup>1,5,6</sup> 1 consisted of participants with a history of MI,<sup>3</sup> and 1 included separate analyses for people with and without a history of diabetes or MI.<sup>4</sup> Two of the studies included men,<sup>1,4</sup> 1 included women,<sup>5</sup> and 2 included both men and women.<sup>3,6</sup>



**Figure 1.** Selection of studies published in 1996 to 2011 included in a meta-analysis of coffee consumption and risk of heart failure.

We found a nonlinear association between coffee consumption and heart failure risk ( $P$  for nonlinearity=0.02;  $P$  for overall significance of curve=0.02) (Figure 2A). Compared with no coffee consumption, the pooled relative risk for heart failure was 0.96 (95% CI, 0.90 to 0.99) for 1 to 2 servings/day, 0.93 (95% CI, 0.86 to 0.99) for 2 to 3 servings/day, 0.90 (95% CI, 0.82 to 0.99) for 3 to 4 servings/day, 0.89 (95% CI, 0.81 to 0.99) for 4 to 5 servings/day, 0.91 (95% CI, 0.83 to 1.01) for 5 to 6 servings/day, 0.93 (95% CI, 0.85 to 1.02) for 6 to 7 servings/day, 0.95 (95% CI, 0.87 to 1.05) for 7 to 8 servings/day, 0.97 (95% CI, 0.89 to 1.07) for 8 to 9 servings/day, 0.99 (95% CI, 0.90 to 1.10) for 9 to 10 servings/day, 1.01 (95% CI, 0.90 to 1.14) for 10 to 11 servings/day, and 1.03 (95% CI, 0.89 to 1.19) for 11 servings/day.

The relationship between coffee consumption and heart failure incidence did not vary by sex or by history of MI or diabetes. The results were not meaningfully altered in sensitivity analyses, excluding 1 study at a time. In a sensitivity analysis excluding the 1 study that did not adjust for potential confounders,<sup>1</sup> the curve is shifted slightly to the right, indicating that the inverse association exists for most levels of observed coffee consumption. There was moderate between-study heterogeneity among study-specific estimates ( $I^2=37.5%$ ). Egger regression test provided no evidence of substantial publication bias ( $P=0.17$ ), but since we had a small number of studies, formal assessment of publications bias may not be appropriate.

### Discussion

The results of this meta-analysis of 5 independent prospective studies indicate that there is a statistically significant J-shaped relationship between coffee and heart failure, with the strongest

**Table. Characteristics of Prospective Studies of Coffee Consumption and Incidence Rate of Heart Failure Included in the Meta-Analysis, 2001–2011**

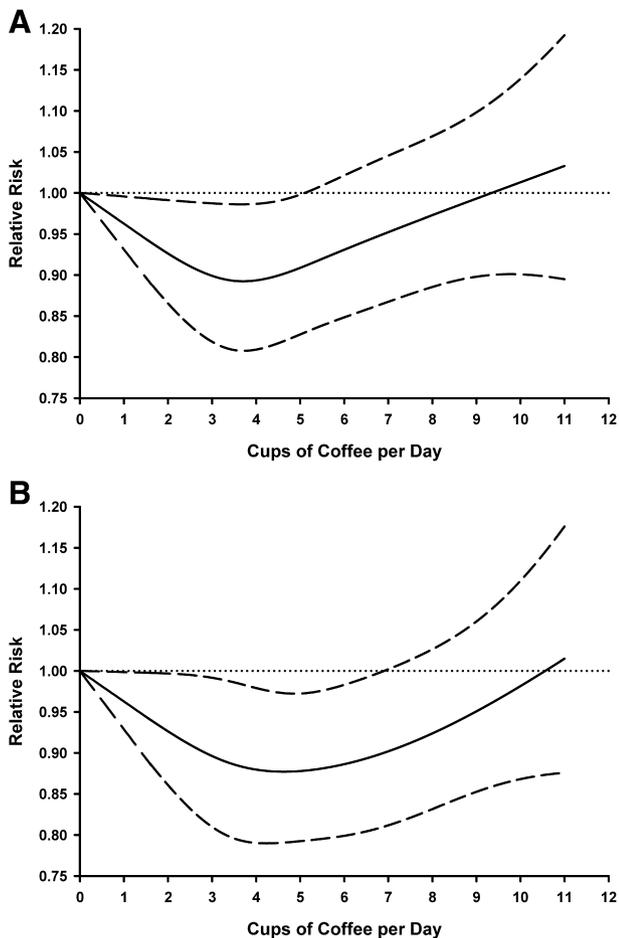
First Author, Year (Ref) Cohort	Country, Study Period	Pop	Age Range, yrs	Adjustment Variables	Coffee Consumption Categories	Sample Size	Cases	Multivariable Adjusted Estimates		
								Point Estimate	95% CI	
Wilhelmsen, 2001 <sup>1</sup> Multifactor Primary Prevention Study	Sweden 1970–1996	Men	47–55	None	0 cups/day	982	121	1.00 (ref)		
					1–4 cups/day	3506	410	0.94	0.76–1.17	
					≥5 cups/day	2886	390	1.11	0.89–1.38	
Ahmed, 2009 <sup>4</sup> Cohort of Swedish Men	Sweden 1998–2006	Men	45–79	Age, BMI, total activity, smoking, history of high cholesterol, family history of MI <60 y, education	≤1 cups/day	4262	108	1.00 (ref)		
					2 cups/day	7751	192	0.87	0.69–1.11	
					3 cups/day	8499	183	0.89	0.70–1.14	
					4 cups/day	6582	141	0.89	0.69–1.15	
					≥5 cups/day	10221	160	0.89	0.69–1.15	
					Men with history of DM or MI	≤1 cups/day	662	68	1.00 (ref)	
					2 cups/day	1206	111	0.82	0.70–0.97	
Mukamal, 2009 <sup>3</sup> Stockholm Heart Epidemiology Program	Sweden 1992–2001	Men and women with history of MI	45–70	Age, sex, diabetes, smoking, obesity, physical inactivity, intake of alcohol, tea, education, boiled coffee	0 to <1 cup/day	192	65	1.00 (ref)		
					1 to <3 cups/day	315	96	1.01	0.70–1.47	
					3 to <5 cups/day	405	114	1.04	0.71–1.52	
					5 to <7 cups/day	284	67	0.91	0.60–1.38	
					≥7 cups/day	173	30	0.71	0.42–1.18	
Levitán, 2011 <sup>5</sup> Swedish Mammography Cohort	Sweden 1998–2006	Women	48–83	Age, BMI, total activity, smoking, history of high cholesterol, family history of MI <60 y, education	≤1 cups/day	4378	98	1.00 (ref)		
					2 cups/day	9057	193	1.01	0.79–1.30	
					3 cups/day	8885	136	0.82	0.62–1.07	
					4 cups/day	6102	104	0.94	0.70–1.25	
					≥5 cups/day	6129	71	0.87	0.63–1.20	
Wang, 2011 <sup>6</sup> 7 Cross-sectional surveys	Finland 1972–2007	Men	25–74	Age, study year, education, cigarette smoking, alcohol, physical activity, BMI, SBP, total cholesterol, history of MI	0 cups/day	1887	113	1.00 (ref)		
					1–2 cups/day	3510	185	0.91	0.71–1.16	
					3–4 cups/day	7042	438	0.88	0.70–1.10	
					5–6 cups/day	8916	691	0.91	0.73–1.13	
					7–9 cups/day	4127	338	0.96	0.76–1.22	
		≥10 cups/day			3355	255	1.02	0.80–1.30		
		Women			0 cups/day	2015	84	1.00 (ref)		
					1–2 cups/day	4348	149	0.73	0.56–0.97	
					3–4 cups/day	9777	514	0.77	0.60–0.98	
					5–6 cups/day	9775	681	0.68	0.53–0.88	
7–9 cups/day	3287		257	0.80	0.61–1.04					
≥10 cups/day	1451	122	0.88	0.65–1.19						

Ref indicates reference; yrs, years; CI, confidence interval; BMI, body mass index; MI, myocardial infarction; DM, diabetes mellitus.

inverse association observed for 4 servings per day (11% lower risk) and returns to baseline beyond 10 cups of coffee per day. In stratified analyses, there was no evidence that the relationship varied by sex or by baseline history of MI or diabetes.

Although heart failure shares many risk factors with other cardiovascular diseases (such as hyperlipidemia, obesity, and increasing age), elevated blood pressure and diabetes mellitus are particularly strong risk factors for heart failure.<sup>2</sup> Experimental studies have consistently shown that coffee and caffeine are associated with acutely raised blood pressure,<sup>14,15</sup> circulating concentrations of (nor)epinephrine, increased arterial stiffness, and impaired endothelium-dependent vasodilation.<sup>16</sup> For instance, Noordzij<sup>15</sup> reported that, for every cup of coffee consumed, systolic pressure increased by 2.04 mm Hg (95% CI, 1.10 to 2.99) and diastolic pressure by 0.73 mm Hg

(95% CI, 0.14 to 1.31). Findings from studies of habitual consumption and heart disease have been inconsistent,<sup>16,17</sup> with reports from case-control studies showing increased risk and prospective studies showing either an increased risk, no association, or that coffee is protective against cardiovascular disease.<sup>18</sup> A recent meta-analysis reported that habitual light to moderate coffee consumption (1 to 3 cups/day) increased the risk of developing hypertension, but more frequent consumption (>3 cups/day) posed no increased risk.<sup>19</sup> These findings are concordant with trials showing that one develops a tolerance to the acute hemodynamic effects of caffeine in response to habitual moderate consumption.<sup>16</sup> There is also consistent evidence that frequent coffee consumption is associated with a lower risk of type 2 diabetes, with most studies showing greater reductions in diabetes risk with higher levels of coffee consumption.<sup>20,21</sup>



**Figure 2.** Relative risk (solid line) and 95% confidence interval (dashed lines) for the association between heart failure and cups of coffee per day compared with no consumption in a meta-analysis of studies published in 2001 to 2011. **A**, represents the primary analysis, including all 5 studies, and **B**, excludes the Wilhelmsen study. Coffee consumption was modeled with restricted cubic splines in a multivariable, random-effects, dose-response model. The dotted line indicates the value for no association.

Despite the small number of studies included in the meta-analyses, it consisted of high-quality prospective studies with large samples, many cases, and a long duration of follow-up. Our meta-analysis cannot address any confounding that may remain in the adjusted analyses of the original studies, though all but 1<sup>1</sup> of the studies included in our meta-analysis accounted for important confounders such as age, body mass index, alcohol consumption, and smoking status. The studies relied on self-reported coffee consumption, which may involve misclassification of coffee intake. This may impact the location of the nadir in our risk curve and make it difficult to detect statistically significant associations; however, since these studies were prospective, the misclassification of coffee consumption is unlikely to vary by the future incidence of heart failure. In all of the studies, coffee consumption was measured at a single time point, which does not allow for examination of the effect of changing consumption. Because there is a common belief that coffee is harmful, people with health conditions may lower their coffee consumption, but

most of the studies included in this analysis were restricted to people with no MI or diabetes at baseline, and, in a sensitivity analysis, the results were similar when we excluded the studies that enrolled people with a history of MI or diabetes.

The studies included in this meta-analysis may have involved consumption of different types of coffee (eg, caffeinated versus decaffeinated coffee); however, in Sweden<sup>22</sup> and Finland,<sup>23</sup> most of the coffee consumed is caffeinated. Although we cannot examine whether heart failure risk varies by coffee type, prior studies did not find differences in the risk of hypertension for caffeinated versus decaffeinated coffee,<sup>24,25</sup> and, since hypertension is a strong risk factor for heart failure, it is possible that protection against heart failure would not differ between caffeinated and decaffeinated coffee. The included studies may have involved different methods of coffee preparation (eg, filtered, boiled, espresso). The impact of boiled coffee, which contains the higher concentrations of cholesterol-raising oils,<sup>14</sup> should be examined in future research. All of the included studies involved participants from Nordic countries with high consumption of caffeinated coffee; future research in other countries and populations that drink decaffeinated coffee would help elucidate whether decaffeinated coffee impacts heart failure risk.

The findings are reported in terms of servings per day, but coffee intake is determined by the strength of the brew and the size of the coffee serving. Stronger brews may have higher levels of caffeine, antioxidants, and other compounds that, in turn, impact cardiovascular health. The brew is usually weaker in the United States than in Europe, but the size of a standard serving of coffee is larger in the United States (250 mL) than in Europe (125 to 150 mL).<sup>20</sup> In the Swedish nutrition database, a standard cup of coffee is 150 mL, and, in the Finnish study, a serving was defined as 100 mL. Therefore, our finding of a nadir of risk for 4 cups of coffee per day may seem like a large amount, but, based on the current US serving size, this is only slightly more than 2 cups of coffee at popular coffee chains, where a standard serving size varies from 295 to 590 mL, and this does not take into account the strength of the brew.

There is some suggestion that baseline history of hypertension may modify the impact of coffee on cardiovascular risk,<sup>26–28</sup> and there is substantial evidence that the CYP1A2 genotype modifies the association between coffee consumption and cardiovascular risk,<sup>29</sup> so it seems plausible that the relationship between coffee consumption and heart failure risk varies by genotype. Further research is necessary to examine these potential modifiers of the coffee-heart failure relationship. There are several aspects of the relationship between coffee and heart failure that we were not able to explore, such as the potential heart failure risk from different types of coffee and brewing methods, the associations in non-European populations, and the relationship between coffee consumption and heart failure prognosis.

In summary, the results of this meta-analysis indicate that there is a J-shaped relationship between coffee consumption and heart failure incidence, with a modest inverse association with moderate consumption. These results were robust to sensitivity analyses, excluding studies that may include participants with different baseline risks of heart failure. In light of these findings, the current heart failure prevention guidelines<sup>2</sup> suggesting

that coffee poses harmful effects may warrant revision to reflect the research showing that coffee may, in fact, provide moderate protection against heart failure incidence.

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### Disclosures

None.

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### CLINICAL PERSPECTIVE

The most recent statement on heart failure prevention from the American Heart Association states that coffee may increase heart failure risk, but the results from prior studies have yielded inconsistent results, and these studies did not have sufficient power to detect modest associations. Therefore, we conducted a systematic review and a dose-response meta-analysis of prospective studies that assessed the relationship between habitual coffee consumption and the risk of heart failure. The results of this meta-analysis indicate that there is a J-shaped relationship between coffee consumption and heart failure incidence, with a modest inverse association with moderate consumption. In light of these findings, the current heart failure prevention guidelines suggesting that coffee poses harmful effects may warrant revision to reflect the research showing that coffee may, in fact, provide moderate protection against heart failure incidence.