

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

Mostofsky et al: Meta-Analysis of Coffee and Heart Failure

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Abstract

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 6,522 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 to 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 MI 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.

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 colleagues¹ reported that compared to no coffee consumption, the risk of hospitalization or death from heart failure was 17% higher (95% confidence interval 1.05-1.30) 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,² 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 incidence³ or that no association exists.^{4,5} One study⁶ 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.

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 Epidemiology⁷ protocol throughout the design, implementation, analysis, and reporting for this study.

Literature Search Strategy

We performed a literature search of the CINAHL, Embase and PubMed 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 (ORs) or incidence rate ratios (IRRs) 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 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 incidence rate ratio compared with abstention for each exposure level, and the corresponding lower and upper 95% confidence intervals (95% CI) of the adjusted IRRs.



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 two investigators (EM, MSR), with disagreements adjudicated by a third reader (MAM). 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 three 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 incidence rate ratio. 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 Longnecker⁸ to compute study-specific odds ratios or incidence rate ratios and 95% confidence intervals (CI) from the natural logarithms of the relative risks and confidence intervals 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.⁹ 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 distribution¹⁰ 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.¹¹ 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 myocardial infarction 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 one 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.¹² Possible publication bias was evaluated with Egger's regression asymmetry test.¹³ All statistical analyses were conducted using SAS 9.2 (SAS Institute, Inc., 2003) and the metadose macro⁹ with 2-tailed α 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 after review of the title or abstract (Figure 1). The meta-analysis included five^{1, 3-6} independent prospective studies of coffee consumption and heart failure risk published between 2001 and 2011 (Table). Combined, these studies included 6,522 heart failure events among 140,220 participants. Four of the studies were conducted in Sweden^{1, 3-5} and one was conducted in Finland.⁶ Three of the studies consisted of participants with no history of myocardial infarction (MI),^{1, 5, 6} one consisted of participants with a history of MI,³ and one included separate analyses for people with and without a history of diabetes or MI.⁴ Two of the studies included men,^{1, 4} one included women⁵ and two included both men and women.^{3, 6}

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 -0.99) for 1-2 servings/day, 0.93 (95% CI 0.86 to 0.99) for 2-3 servings/day, 0.90 (95% CI 0.82-0.99) for 3-4 servings/day, 0.89 (95% CI 0.81-0.99) for 4-5 servings/day, 0.91 (95% CI 0.83-1.01) for 5-6 servings/day, 0.93 (95% CI 0.85-1.02) for 6-7 servings/day, 0.95 (95% CI 0.87-1.05) for 7-8 servings/day, 0.97 (95% CI 0.89-1.07) for 8-9 servings per day, 0.99 (95% CI 0.90-1.10) for 9-10 servings/day, 1.01 (95% CI 0.90-1.14) for 10-11 servings/day and 1.03 (95% CI 0.89-1.19) for 11 servings/day.



The relationship between coffee consumption and heart failure incidence did not vary by sex or by history of myocardial infarction or diabetes. The results were not meaningfully altered in sensitivity analyses excluding one study at a time. In a sensitivity analysis excluding the one study that did not adjust for potential confounders,¹ 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's 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 five independent prospective studies indicate that there is a statistically significant J-shaped relationship between coffee and heart failure, with the strongest

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.

While 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.² Experimental studies have consistently shown that coffee and caffeine are associated with acutely raised blood pressure,^{14, 15} circulating concentrations of (nor)epinephrine, increased arterial stiffness and impaired endothelium dependent vasodilation.¹⁶ For instance, Noordzij¹⁵ reported that for every cup of coffee consumed, systolic pressure increased by 2.04 mmHg (95% CI 1.10 to 2.99) and diastolic pressure by 0.73 mmHg (95% CI, 0.14 to 1.31). Findings from studies of habitual consumption and heart disease have been inconsistent^{16, 17} 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.¹⁸ 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.¹⁹ 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.¹⁶ 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.^{20, 21}

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 one¹ 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 (e.g., caffeinated vs. decaffeinated coffee). However, in Sweden²² and Finland,²³ 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^{24, 25}, 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 (e.g., filtered, boiled, espresso). The impact of boiled coffee, which contains the higher concentrations of cholesterol-raising oils,¹⁴ 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 US than in Europe, but the size of a standard serving of coffee is larger in the US (250 mL) than in Europe (125-150 mL).²⁰ 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 two 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 risk²⁶⁻²⁸ and there is substantial evidence that the CYP1A2 genotype modifies the association between coffee consumption and cardiovascular risk,²⁹ 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 which 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 risk of heart failure. In light of these findings, the current heart failure prevention guidelines² 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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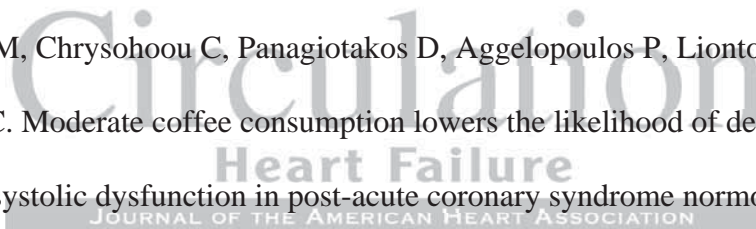


Table. Characteristics of Prospective Studies of Coffee Consumption and Incidence Rate of Heart Failure Included in the Meta-Analysis, 2001–2011



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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 ¹	Sweden		47-55		0 cups/day	982	121	1.00 (ref)	
Multifactor Primary Prevention Study	1970-1996	Men		None	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 ⁴	Sweden		45-79		≤1 cups/day	4262	108	1.00 (ref)	
Cohort of Swedish Men	1998-2006	Men		age, BMI, total activity, smoking, history of high cholesterol, family history of MI<60 yrs, education	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
					≤1 cups/day	662	68	1.00 (ref)	
					2 cups/day	1206	111	0.82	0.70-0.97
					3 cups/day	1131	98	0.83	0.70-0.98
					4 cups/day	882	67	0.88	0.74-1.05
Men with Hx of DM or MI				≥5 cups/day	1100	94	0.92	0.77-1.09	



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
Mukamal, 2009 ³	Sweden	Men and women with Hx of MI	45-70	age, sex, diabetes,	0 to <1 cup/day	192	65	1.00 (ref)	
Stockholm Heart Epidemiology Program	1992-2001		smoking, obesity,	1 to <3 cups/day	315	96	1.01 0.70-1.47		
			physical inactivity,	3 to <5 cups/day	405	114	1.04 0.71-1.52		
			intake of alcohol, tea, education, boiled coffee	5 to <7 cups/day	284	67	0.91 0.60-1.38		
				≥ 7 cups/day	173	30	0.71 0.42-1.18		
Levitan, 2011 ⁵	Sweden	Women	48-83	Age, BMI, total	≤ 1 cups/day	4378	98	1.00 (ref)	
Swedish Mammography Cohort	1998-2006		activity, smoking,	2 cups/day	9057	193	1.01 .79-1.30		
			history of high	3 cups/day	8885	136	0.82 0.62-1.07		
			cholesterol, family	4 cups/day	6102	104	0.94 0.70-1.25		
			history of MI <60 yrs, education	≥ 5 cups/day	6129	71	0.87 0.63-1.20		
Wang, 2011 ⁶	Finland	Men	25-74	age, study year,	0 cups/day	1887	113	1.00 (ref)	
7 cross-sectional surveys	1972-2007			education, cigarette	1-2 cups/day	3510	185	0.91 0.71-1.16	
				smoking, alcohol,	3-4 cups/day	7042	438	0.88 0.70-1.10	

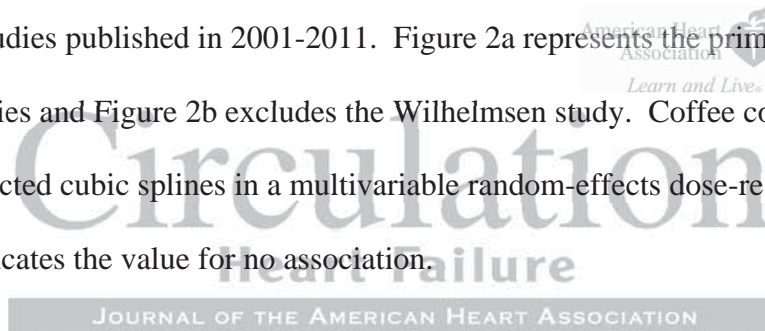
First Author, Year (Ref) Cohort	Country, Study Period	Pop	Age Range, yrs	Adjustment variables	Coffee Consumption Categories	Sample Size	Cases	Multivariable Adjusted Estimates	
								Point Estimate	95% CI
				physical activity, BMI,	5-6 cups/day	8916	691	0.91	0.73-1.13
				SBP, total cholesterol,	7-9 cups/day	4127	338	0.96	0.76-1.22
				history of MI	≥10 cups/day	3355	255	1.02	0.80-1.30
					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
		Women			5-6 cups/day	9775	681	0.68	0.53-0.88
					7-9 cups/day	3287	257	0.8	0.61-1.04
					≥10 cups/day	1451	122	0.88	0.65-1.19



Figure Legends

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

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 to no consumption in a meta-analysis of studies published in 2001-2011. Figure 2a represents the primary analysis including all 5 studies and Figure 2b 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.



116 references identified on initial search

8 CINAHL
28 Pubmed
80 Embase

27 duplicates removed

89 abstracts reviewed for relevance

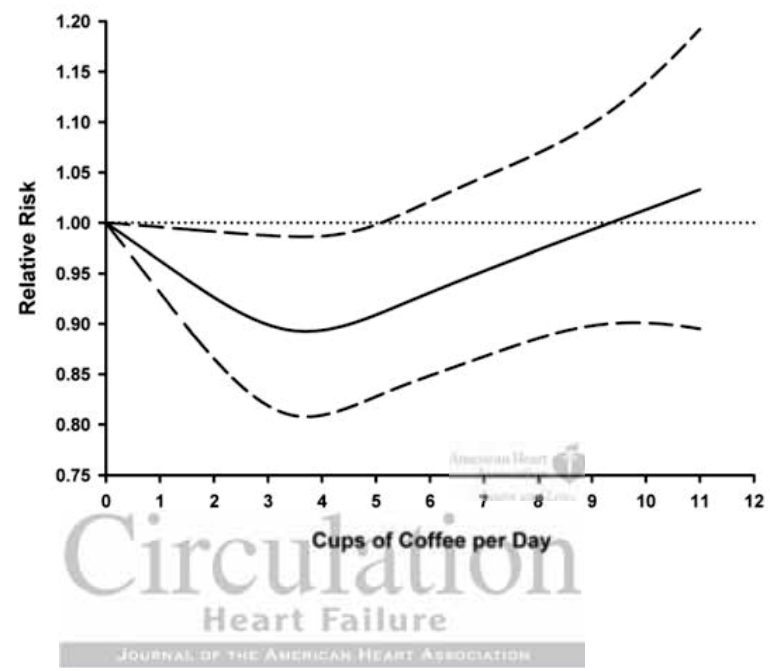
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2 animal study
6 presentation of the same study

5 prospective cohort studies
included in meta-analysis

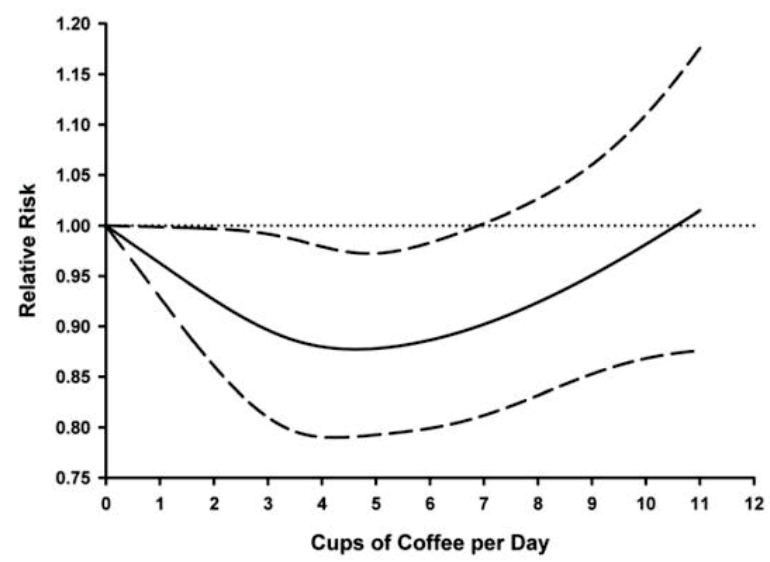


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