Association of Caffeine Use on Mortality in Survivors of Stroke and Myocardial Infarction. An analysis of Third National Health and Nutrition Examination Survey Mortality Follow-up Study

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Dedication

Dedicated to my parents, Muhammad Akram Khan and Sadiqa Bano who were overjoyed with my Masters completion; my wife Aqsa Nadeem, who provided continuous support; and my children Safaa, Safiullah and Manha, whose smiles were always refreshing.

Abstract

To study if there is any association of caffeine with mortality secondary to cardiovascular disease in survivors of myocardial infarction (MI) and stroke, we used the Third National Health and Nutrition Examination Survey and the Linked Mortality File. Out of 1083 survivors of stroke or MI, 51 died of stroke, 117 of MI and 305 of ischemic heart disease, during a mean follow-up of 9.0 ± 5.2 years. Using Cox-proportional hazard model adjusted for vascular risk factors, among survivors of cardiovascular disease relative risk (RR) for fatal stroke (RR=0.3), fatal cardiovascular disease (RR=0.5) and all-cause mortality (RR=0.7) was significantly lower among those with caffeine consumption of 3+ cups per day (vs no caffeine). Similarly, among survivors of stroke, RR for stroke related mortality was lower in those with 3+ cups of caffeine consumption per day. In conclusion, caffeine consumption may be associated with lower risk of cardiovascular death.

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INTRODUCTION

Each year an estimated 1,255,000 Americans suffer from myocardial infarction (MI) and 795,000 from stroke.[1] Out of these, 470,000 (37%) MIs and 185,000 (23%) strokes are recurrent events.[1] Cardiovascular diseases, with age-adjusted death rates of 251 per 100,000, are the most common cause of mortality in United States.[1,2] With such a large burden of morbidity and mortality associated with cardiovascular disease it is important to explore any potential modifiable risk factors.

Caffeine and cardiovascular disease. Coffee is one of the most commonly consumed beverages in the world. Caffeine is one of the main biologically active compounds in coffee. Its effects on cardiovascular system have been controversial. It has been noted to be associated with an acute[3-5] and chronic[6] increase in blood pressure, and increase in peripheral vascular resistance.[7] On other hand, it has been shown to improve the endothelium-dependent vasodilation[8,9] and increase nitric oxide production[8]. Homocysteine,[10] which promotes atherosclerosis, and adiponectin,[9] which has antidiabetic and antiatherogenic properties, are also increased by caffeine. C-reactive protein, an independent predictor of cardiovascular disease, may also be effected by caffeine intake.[9,11]

In addition to the biological effects of caffeine, the association of coffee consumption with cardiovascular disease has also been controversial. Whereas many studies have demonstrated association of coffee consumption with an increased risk of cardiovascular disease,[12-23] other studies have identified no such association.[24-33] Some studies have even identified a protective effect of coffee intake on cardiovascular disease.[34-41] Although multiple studies have examined the association of coffee consumption and cardiovascular disease, this association remains unstudied in patients who have already suffered a cardiovascular event. Since coffee is an extensively consumed nutrient worldwide, it is important to determine if it has any association with recurrent events of cardiovascular disease.

Purpose of Study

The objective of this study is to determine if there is any association of caffeine consumption with heart attack and stroke in patients who have suffered a cardiovascular event in the past (heart attack or stroke).

Specific Aim. To determine if caffeine intake noted by a dietary recall of last 24 hours is associated with cardiovascular mortality in subjects with previous history of cardiovascular disease

Hypothesis. Caffeine intake is associated with a lower risk of cardiovascular death in subjects with history or cardiovascular disease.

METHODS

Study population. We used the Third National Health and Nutrition Examination Survey (NHANES-III) and the Linked Mortality File for this project. NHANES-III is a nationally representative sample of 20,049 adults aged 17-90 years. The baseline data was acquired from 1988-94 and included extensive interview, examination and laboratory testing. NHANES-III Linked Mortality File was generated using National Death Index (NDI) death certificate records. The file used for this project links the NDI mortality data through December 31, 2006.

Inclusion criteria:

1. Physician diagnosis of MI or stroke at baseline, as reported by the participant during interview
2. Participants included in the dietary survey

Exclusion criteria: Information about caffeine intake could not be collected because of refusal, language barrier, unreliability or similar reasons.

Caffeine intake (predictor variable). Dietary interviews were administered to all participants by trained dietary interviewers. All nutrients consumed as food or beverages during last 24-hours were included for estimation of caffeine intake. Caffeine intake included all food and beverages including caffeinated sodas, but did not include nutrients obtained from nutritional supplements or medications. For data analysis caffeine intake was divided into equivalent of 150-mg of coffee cups. Caffeine consumption in last 24-hours was then categorized as 0-cups (0-mg), 1-2 cups (>0 to 300-mg), and 3 or more cups (>300mg).

Coffee and tea intake (predictor variables). In addition to 24-hour caffeine intake, the respondents were also asked how often, over the past month, they have consumed caffeinated coffee and caffeinated tea. The portion sizes were not defined. The amount was reported as number of cups per day, per week, per month,

or never. Frequency of consumption was standardized as “cups per month” using the conversion factor of 4.3 weeks/month and 30.4 days/month. For our analysis we calculated average daily consumption by dividing this value by 30.4. Since the coffee and tea consumption intake information was not as rigorously collected as caffeine intake, this information was only used for secondary analysis.

Race/Ethnicity. This variable was derived from self-reported race and ethnicity, and was categorized into non-Hispanic white, non-Hispanic black, Mexican American and other.

Medical insurance. Subjects were questioned about insurance coverage during the last 1 month. A subject was considered to have medical insurance if during the last month there is coverage by Medicare, Medicaid, CHAMPUS, CHAPVA, VA, military health care, or any other health insurance plan obtained privately or through an employer or union.

Socioeconomic status. NHANES III includes calculated poverty index. This is a calculated variable that is based on family income and family size, and uses tables published each year by Census Bureau. Based on the classification suggested in NHANES-III documentation,[42] we defined low, middle and high socioeconomic groups as poverty index 0 to 1.3, 1.301 – 3.5 and 3.501 and above respectively.

Education. Education was categorized into 3 categories --- less than 12 grades or never attended, 12 grades, or more than 12 grades.

Alcohol consumption. Binge alcohol consumption was identified as 9 drinks at least 7 days per year or 5 drinks at least 14 days per year.

Smoking status. Subjects who have smoked 100+ cigarettes in life were classified as smokers. Smokers who are not currently smoking were classified as past smokers.

Body mass index. Height and weight for all participants was recorded using standard methodology during NHANES III examination. Body mass index was calculated from these measurements and was categorized as obese (> 30 kg/m), over-weight (25 to 30 kg/m), and normal or underweight (<25 kg/m).

Baseline clinical conditions. Baseline history of stroke, MI, diabetes mellitus and hyperlipidemia were defined if the subjects were ever told by a physician to have the medical condition. Hypertension was defined if physician told on more than one visit that subject has high blood pressure.

Baseline disability. To adjust the analysis for baseline clinical condition, we used the following clinical disability questions asked to the participants at baseline.

Response graded as no difficulty, some difficulty, much difficulty and unable to do

1. Difficulty walking a quarter of a mile (that is about 2 or 3 blocks)
2. Difficulty walking 10 steps without rest
3. Difficulty stooping, crouching, kneeling
4. Difficulty lifting or carrying 10 pounds (like a sack of potatoes or rice)
5. Difficulty doing chores around the house (like vacuuming, sweeping, dusting, or straightening up)
6. Difficulty preparing own meals
7. Difficulty managing your money (such as keeping track of your expenses or paying bills)
8. Difficulty walking room to room, on same level
9. Difficulty standing from armless chair
10. Difficulty getting in or out of bed
11. Difficulty eating, like holding a fork, cutting food or drinking from a glass
12. Difficulty dressing yourself, including tying shoes, working zippers, and doing buttons

Response graded as yes/no

1. Because of any impairment or health problem, do you need the help of other persons with personal care needs such as eating, bathing, dressing or getting around this home
2. Because of any impairment or health problem, do you need the help of other persons in handling routine needs, such as everyday household chores, doing necessary business, shopping or getting around for other purposes
3. Do you usually use any device to help you get a round such as a cane, wheelchair, crutches or walker

4. Do you use any special eating utensils
5. Do you usually use any aids or devices to help you dress (such as button hooks, zipper pulls, long handled shoe horn, etc.)

Outcome variables. NHANES III mortality linked file includes cause of death collected from "medical certification" portion of the U.S. standard certificate of death. The underlying cause of death is provided as a recoded variable (UCOD_113) with 113 categorizes of cause of death. We used the following definitions for our outcomes

Outcome	**UCOD_113**	**ICD-9 categories**	**ICD-10 categories**
Stroke	70 (cerebrovascular disease)	430-434, 436-438	I60-I69
MI	59 (Acute MI)	410	I21-22
Cardiovascular disease (stroke or ischemic heart disease)	58-63,70 (acute or chronic ischemic heart disease, atherosclerotic cardiovascular disease, cerebrovascular disease)	410-414, 429.2, 430-434, 436-438	I20-25

Statistical analysis. Univariate analysis was done to identify potential confounders. Variables tested in univariate analysis included age at baseline, sex, race/ethnicity, history of hypertension, history of hyperlipidemia, history of diabetes mellitus, cigarette smoking status, body mass index, and binge drinking. Cox-proportional hazard model adjusted for duration from examination to the time of death was then used for multivariate analysis. Tests for trends across categories were conducted by modeling coffee consumption as a continuous variable using median value of each category. All analysis was performed in SAS version 9.2 (SAS Institute Inc., Research Triangle Park, NC)

RESULTS

A total of 344 survivors with stroke, 624 survivors with MI and 115 with both stroke and MI were included in the analysis. Out of 785 deaths reported during a mean follow-up of 9.0±5.2 years, deaths attributed to stroke, MI and ischemic heart disease were 51, 117 and 305, respectively.

Baseline characteristics of participants by categories of caffeine consumption are presented in Table 1. As compared with subjects who consume caffeine equivalent to 2 or less cups of coffee per day, those with caffeine consumption equivalent to 3 or more cups per day were more likely to be 45-64 years old (vs younger or older), men, white and smokers; and less likely to be diabetic. Subjects who consumed caffeine were more likely to have high socioeconomic status (PI > 3.5) when compared to subjects with no caffeine consumption. There was no significant difference in education level, insurance status, alcohol consumption, body mass index, difficulty with eating, history of hypertension or history of hyperlipidemia among different strata of caffeine consumption.

To determine independent association of caffeine consumption with cardiovascular diseases, multivariate adjusted Cox- proportional hazard analysis was performed. Among survivors of any cardiovascular disease (stroke or MI, table 2), relative risk (RR) for fatal stroke, fatal cardiovascular disease or all-cause mortality was significantly lower in subjects with caffeine consumption of 3 or more cups per day compared with those with no caffeine consumption.

Among survivors of stroke (table 3), risk of fatal stroke was significantly lower in subjects with caffeine consumption of 3 or more cups per day compared with subjects with no caffeine consumption. In subjects with baseline history of MI (table 4) the risk of fatal cardiovascular disease and all-cause mortality was significantly lower in subjects with 3 or more cups of caffeine per day compared with those with no caffeine consumption. There was no association of caffeine consumption with risk of fatal MI.

Additional similar multivariable analysis to determine association of average daily caffeinated coffee and tea consumption (either categorical or continuous) with risk of fatal cardiovascular event was negative for any association.

To investigate if the subjects who were more affected by physical illness at baseline may be consuming less coffee (‘reverse causation’), we assessed correlation between baseline disabilities with caffeine consumption. There was only weak correlation between difficulty preparing meals and difficulty

dressing with caffeine consumption (tables 5). There was no correlation between caffeine consumption and other measures of disability. To estimate the overall disability, we calculated a simple arithmetic sum of all disability scores and noted no correlation with caffeine consumption (r=-0.11). There was no change in the magnitude of association between caffeine consumption and risk of mortality after adjusting for each baseline disability measures (Table 6).

DISCUSSION

To our knowledge, this is the first study to determine the effect of caffeine consumption in survivors of MI and stroke. In this cohort of patients with history of stroke and MI, caffeine consumption was associated with reduced risk of all-cause mortality, fatal cardiovascular disease and fatal stroke, but not with fatal MI (Figure 1).

Coffee vs Caffeine. Coffee is composed of hundreds of chemicals.[43] Many of these compounds are considered to be associated with human disease.[43] Although caffeine is not the prime constituent of coffee, but it is the main biologically active compound in coffee. Since coffee is the major source (71%) of coffee consumption,[44] it is possible that the protective effect noted with caffeine consumption in our study is secondary to other constituents of coffee consumption. However we noted only a weak correlation between the 24-hour caffeine consumption and average daily coffee (r=0.54) or tea (r=0.08) consumption. Although lack of this correlation could be because of poor 30-day recall.

Caffeine and cardiovascular disease. Studies assessing the association of caffeine with cardiovascular disease are scanty. Groebbee et al reported no association of caffeine intake with risk of MI or stroke in 45,589 men enrolled in Health Professionals Follow-up Study.[45] Conen et al prospectively assessed the relation between caffeine intake and incident atrial fibrillation in 33,638 participants of Women's Health Study and identified no such association.[46]

Studies identifying harmful effect of coffee consumption. Whereas there is limited literature about association of caffeine with cardiovascular disease, many studies have assessed the effect of coffee consumption on cardiovascular disease. Some of these studies have suggested a detrimental effect of coffee

intake on cardiovascular disease. One of the earliest studies to support the notion of association of coffee consumption with MI were done in 1970s. Jick et al performed a case-control study in 12,759 hospitalized patients, including 440 with acute MI. There was a 60 percent increase in risk in those consuming one to 5 cups, and 120 percent increase in risk in those consuming 6+ cups of coffee per day when compared to those who were not drinking any coffee. A case-control analysis from Boston Collaborative Drug Surveillance Program of 276 patients with acute MI and 1104 matched control patients noted coffee consumption was more common in patients with myocardial infaction.[12] In 1977, a Swedish study noted a significant association between coffee consumption and MI in a pooled analysis of 230 patients with MI and a population sample of 834 men.[13]

In 1980's and 1990's multiple cohorts supported association of coffee consumption with cardiovascular disease. La Croix et al conducted a prospective investigation of 1130 male medical students and noted men drinking five or more cups of coffee per day have RR of 2.5 for coronary disease compared to those drinking none.[14] LeGrady et al noted a RR of 1.7 for death secondary to coronary heart disease in white males who were drinking 6+ cups of coffee per day compared to those drinking less.[15] Gramenzi et al noticed a positive association of coffee consumption and acute MI in a case-control study in women admitted to coronary care units in northern Italy.[16] Klatsky et al studied association of coffee intake with hospitalization for coronary disease in 101,774 persons in Kaiser Permanente Medical Care Program, and noted a RR of 1.4 for those drinking 4+ cups of coffee compared to non-drinkers.[17] Tverdal et al studied association of coffee consumption with mortality from coronary heart disease in 38,564 participants of National Health Screening Service in Norway and noticed a RR of 2.2 for those drinking 9+ cups of coffee compared to those drinking less than one cup.[18] Lindsted et al reported a weak association of coffee consumption with cardiovascular death in 9,484 males enrolled in Adventist Mortality Study.[19] D'Avanzo et al[20] studied the association of coffee consumption with acute MI in participants of GISSI-2 trial. In this case-control analysis of 801 men with acute MI and 792 control subjects, there was a weak association of 2+ cups of coffee consumption compared to no consumption. Moreover, there was a statistically significant trend for increased risk with increased dose of coffee consumption. Hakim et al[21] studied association of

coffee intake with incident stroke in 499 hypertensive and non-smoker men in Honolulu Heart Program. The RR for stroke was doubled for men who consumed 3+ cups of coffee per day compared to nondrinkers.

The results of these studies are contrary to our findings. Our cut-off for coffee consumption (3+ cups/day) was much smaller than what was reported in some of these studies.[14,15,18] We did not have enough power to identify any relationship with a cut-off higher than 3+ cups per day. Also all of these studies, except the Honolulu Heart Program study analysis (which was limited to hypertensive and non-smokers subjects), used MI as the outcome. It is possible that we could not identify a weak association with MI because of lack of power.

Studies identifying no association of coffee consumption with cardiovascular disease**.** Whereas the evidence supporting harmful effect of coffee towards cardiovascular disease was overwhelming from 1970s to 1990s, during the same period there were other studies that failed to find any such association.[22,24-30] More recently some large studies have failed to demonstrate any association of coffee consumption with cardiovascular disease. Lopez-Garcia et al, in a large pooled data of 128,493 participants of Health Professionals Follow-up Study and Nurses Health Study, noted no association of MI or fatal coronary heart disease with coffee consumption.[31] Zhang et al noted no association of caffeinated or decaffeinated coffee consumption with either all-cause mortality or cardiovascular disease in a cohort of 7,170 diabetic women.[32] Floegel et al noted no association of caffeinated or decaffeinated coffee consumption with cardiovascular disease in a European cohort of 42,659 participants.[33] Two of these studies also reported RR for stroke.[32,33] Neither of these studies identified an association of coffee consumption with stroke. Study sample limited to diabetic women in the cohort reported by Zhang et al could be the reason for lack of an association. Our sample size was not large enough to perform similar subgroup analysis.

Studies suggesting protective effect of coffee consumption with cardiovascular disease**.** Recently some large prospective studies are suggesting beneficial effect of coffee consumption with cardiovascular disease. Woodward et al in a large Scottish cohort noted increasing coffee consumption was associated with a beneficial effect for all-cause and coronary disease related mortality.[34] Happonen et al studied this association of caffeinated coffee consumption and incidence of MI or coronary death in a cohort of 1971

men.[35] They noted a U-shaped association with minimum risk of coronary events in those consuming 400-800 ml of coffee per day. de Koning Gans, in a large cohort of 37,514 participants, noted a non-significant trend towards beneficial effect of coffee consumption on CHD.[36] Larsson et al studied the association of coffee consumption with stroke and stroke-subtypes in a Swedish cohort of 34,670 women.[37] Those drinking 1+ cups of coffee per day were at significantly lower risk (RR < 0.8) for stroke, and there was a significant trend towards lower risk with increasing dose of coffee. Freedman et al noted, in a large cohort, that coffee consumption of 4+ cups compared with no coffee consumption was associated with reduced risk of stroke (RR 0.65) and heart disease (RR 0.87) related mortality.[38] Kokubo et al studied a cohort of 82,369 Japanese and noted an inverse association between coffee consumption and risk of cardiovascular disease and stroke.[39]

Overall, the review of the literature interestingly suggests a shift in paradigm, with initial studies suggesting harmful effect of coffee consumption and more recent studies suggesting either a U-shaped or a dose dependent protective effect. Only a few studies reported coffee consumption association with stroke, and the beneficial effect noted in these studies is more in concordance with the strong beneficial effect noted in our study. Our study is different from previous studies because 1) our cohort comprised only of subjects with previous history of cardiovascular disease, and 2) we used the total caffeine intake rather than coffee consumption. However, our results are concordant with the recent studies. Contrary to some of the previous studies, we did not note any association of coffee consumption and fatal MI. This is likely because of lack of enough power in our study to identify a small effect size.

Beneficial effect of caffeine intake on cardiovascular disease. Multiple biological effects of caffeine can attribute to the beneficial effect noted on secondary stroke prevention in our study. Caffeine has been shown to promote nitric oxide synthesis in endothelium.[47] Nitric oxide is considered a cardio-protective agent, partly because of its vasodilatation properties, and caffeine has also been shown to induce vasodilatation in vitro and in healthy subjects.[8,47] In addition to causing vasodilatation, nitric oxide also protects the vessel wall against development of atherosclerosis.[48]

Chronic intake of caffeine also reduces platelet aggregability due to upregulation of adenosine A_{2A} receptors.[49] However, another study noted inhibition in platelet aggregation not from caffeine, but from other compounds in coffee.[50]

There is growing evidence to support reduced risk of diabetes with coffee consumption.[51] van Dam et al reviewed 16 prospective cohort studies and all but 3 have suggested a substantial risk reduction of type 2 diabetes with frequent coffee consumption.[51] More recently, Ding et al performed a meta-analysis of 28 prospective studies with 45,335 cases of diabetes and noted inverse association of risk of type 2 diabetes with both caffeinated and decafffeintated coffee.[52] Relative risk of diabetes for 1 cup/day increase in caffeinated coffee consumption was 0.91, and for decaffeinated coffee consumption was 0.94.

Shechter et al, administered caffeine 200mg in 40 patients with coronary artery disease and 40 healthy subjects in a randomized cross-over study. Increase in serum caffeine levels was associated with a decrease in high-sensitivity C-reactive protein and increase in serum adiponectin – a chemical with antidiabetic and antiatherogenic properties.[9] C-reactive protein is believed to be a marker of extent of atherosclerosis and vulnerability of atherosclerotic plaques.[53]

It is also possible that the beneficial effect of caffeine ingestion noted in our study is not because of caffeine but because of other compounds in coffee. Although caffeine ingestion amount used in our study was calculated from all nutrients, including caffeinated sodas, since coffee is the primary source of caffeine, the association noted in our study may be because of other compounds in coffee. Coffee contains multiple compounds with antioxidant activities,[54] and it is possible that the beneficial effect is the cumulative effect of these compounds. Phenolic acids in coffee have been shown to have antithrombotic effects.[50,55] Studies have demonstrated beneficial effect of decaffeinated coffee, like improved endothelial function[56] or positive insulin sensitivity.[57]

There was no follow-up data about recurrent non-fatal cardiovascular events. It is possible that subjects more affected by physical illness at baseline, who are more likely to die, may be consuming less coffee. However, we did not identify any strong correlation between caffeine consumption and baseline

disability. Moreover, the association of caffeine consumption remained unchanged in magnitude after adjustment for disability measures.

Limitations. This study has several limitations. Information about amount of coffee consumption was only collected at baseline and may not reflect changes in dose during the follow-up period. Cause of death information was collected from death certificates and was not adjudicated. Although we reported association with caffeine consumption, considering that coffee is the main source of caffeine, it is possible that the beneficial effect noted in our study is basically a reflection of coffee consumption. We were unable to test the association at higher levels of caffeine consumption because of small sample size.

CONCLUSION

In this cohort of patients with history of heart attack and stroke, there was no suggestion of increased cardiovascular mortality associated with caffeine consumption. This study supports allowance of caffeinated drinks to the survivors of cardiovascular disease. This study also suggested that, in these patients, caffeine consumption may be associated with lower risk of cardiovascular death. Further prospective studies are needed to better understand this protective role of caffeine.

Table 1. Univariate association of different strata of caffeine consumption with baseline characteristics of the study population

	Number (%)	**Caffeine consumption**			**p-value***
		No	**Low (1-2 cups/day)**	**High (3+ cups/day)**	
		(n=129)	(n=751)	(n=203)	
Age (years)					
Mean ± SD	69 ± 17	67.2 ± 14.6	69.9 ± 13.2	65.4 ± 12.8	<0.0001
18-44	64 (6%)	14 (11%)	38 (5%)	12 (6%)	0.0005
45-64	290 (27%)	30 (23%)	185 (25%)	**75 (37%)**	
65+	729 (67%)	85 (66%)	528 (70%)	116 (57%)	
Gender					
Women	443 (59%)	60 (47%)	326 (43%)	57 (28%)	0.0002
Men	640 (41%)	69 (53%)	425 (57%)	**146 (72%)**	
Race/Ethnicity					
White	639 (59%)	49 (38%)	439 (58%)	**151 (74%)**	<0.0001
Black	248 (23%)	59 (46%)	171 (23%)	18 (9%)	
Hispanic	166 (15%)	17 (13%)	119 (16%)	30 15%)	
Other	30 (3%)	4 (3%)	22 (3%)	4 (2%)	
Education level					
< 12 grades	623 (58%)	85 (66%)	425 (56%)	112 (55%)	0.25
12 grade	258 (24%)	26 (20%)	185 (25%)	47 (23%)	
> 12 grades	202 (19%)	18 (14%)	140 (19%)	44 (22%)	
Socioeconomic status					
Missing	113 (10%)	15 (12%)	79 (11%)	19 (9%)	0.004
PI < 1.3	372 (34%)	63 (49%)	251 (33%)	58 (29%)	
PI 1.3 – 3.5	445 (41%)	42 (33%)	**309 (41%)**	**94 (46%)**	
PI > 3.5	153 (14%)	9 (7%)	**112 (15%)**	**32 (16%)**	

	Number (%)	**Caffeine consumption**			**p-value***
		No	**Low (1-2 cups/day)**	**High (3+ cups/day)**	
		(n=129)	(n=751)	(n=203)	
Insurance status (insured)	1011 (93%)	121 (94%)	708 (94%)	182 (90%)	0.06
Alcohol consumption (≥ 9 drinks 7 times or ≥ 5 drinks 5 times in a year)	57 (5%)	6 (5%)	34 (5%)	17 (8%)	0.08
Smoking status					
Current	204 (19%)	21 (16%)	108 (14%)	**75 (37%)**	<0.0001
Past	466 (43%)	52 (40%)	329 (44%)	85 (42%)	
Never	413 (38%)	56 (43%)	314 (42%)	43 (21%)	
Body mass index (kg/m^2)					
Mean ± SD	27.7 ± 5.8	28.6 ± 6.4	27.6 ± 5.7	27.5 ± 5.6	0.17
< 25	360 (33%)	36 (28%)	252 (34%)	72 (35%)	0.4
25 to < 30	425 (39%)	49 (38%)	295 (39%)	81 (40%)	
≥ 30	298 (28%)	44 (34%)	204 (27%)	50 (25%)	
Eating difficulty	216 (20%)	34 (26%)	138 (18%)	44 (22%)	0.09
Medical conditions					
Hypertension	593 (55%)	84 (65%)	56 (56%)	91 (45%)	0.14
Diabetes mellitus	245 (23%)	34 (26%)	175 (23%)	**36 (18%)**	0.001
Hyperlipidemia	372 (34%)	39 (30%)	262 (35%)	71 (35%)	0.6

Abbreviations used. PI= Poverty index, SD = standard deviation

* p-value using chi-square for categorical and ANOVA for continuous variables

Table 2. Relative risk of fatal cardiovascular event by caffeine consumption in all cardiovascular disease survivors (n=1083).

		Number of events, RR of stroke (95% confidence interval)			P for trend
		No caffeine	1-2 cups	3+ cups	
	Total patients	129	751	203	
	Person-years	1042	6605	2097	
Fatal stroke					
	Cases, no.	9(7%)	43(6%)	6(3%)	
	Age-adjusted	Ref	0.6 (0.2-1.2)	0.3 (0.1-0.9)	0.07
	Age and smoking	Ref	0.6 (0.3-1.2)	0.3 (0.1-0.8)	0.03
	Multivariable*	Ref	0.6 (0.3 – 1.3)	**0.3 (0.1 – 0.8)**	0.07
Fatal acute myocardial infarction					
	Cases, no.	8(6%)	87(12%)	22(11%)	
	Age-adjusted	Ref	1.5 (0.7-3.0)	1.4 (0.6-3.0)	1.0
	Age and smoking	Ref	1.4 (0.7-3.0)	1.3 (0.6 – 2.8)	0.8
	Multivariable*	Ref	1.2 (0.6 – 2.5)	0.9 (0.4 – 2.2)	0.3
Fatal stroke or ischemic heart disease					
	Cases, no.	41(32%)	266(35%)	56(28%)	
	Age-adjusted	Ref	0.8(0.6-1.2)	0.7(0.5-1.0)	0.9
	Age and smoking	Ref	0.8 (0.6 – 1.1)	0.6 (0.4 – 0.9)	0.01
	Multivariable*	Ref	0.8 (0.6 – 1.1)	**0.5 (0.4 – 0.8)**	0.01
All-cause mortality					
	Cases, no.	97(75%)	551(73%)	137(67%)	
	Age-adjusted	Ref	0.7(0.6-0.9)	0.7(0.5-0.9)	0.1
	Age and smoking	Ref	0.7(0.6-0.9)	0.6(0.5-0.8)	0.0
	Multivariable model*	Ref	0.8 (0.6 -0.99)	**0.7 (0.5 – 0.9)**	0.04

*Adjusted for age, sex, race/ethnicity (white, African American, Hispanic, other), socioeconomic status group (poverty index < 1.3, 1.3 to 3.5, >3.5), smoking status (current, past [>100 cigarettes in life], never), alcohol (more than 5 drinks 14 or more times or more than 9 drinks 7 or more times per year), history of diabetes mellitus, history of hyperlipidemia, history of hypertension, and type of qualifying event (myocardial infarction, stroke or both)

Table 3. Relative risk of fatal cardiovascular event by caffeine consumption in stroke survivors (n=459)

		Number of events, RR of stroke (95% confidence interval)			P for trend
		No caffeine	1-2 cups	3+ cups	
	Total patients	65	314	80	
	Person-years	513	2574	757	
Fatal stroke					
	Cases, no.	5(8%)	23(7%)	3(4%)	
	Age-adjusted	Ref	0.7(0.3-1.9)	0.4(0.1-1.5)	0.2
	Age and smoking	Ref	0.6(0.2-1.7)	0.2(0.06-1.1)	0.08
	Multivariable*	Ref	0.6(0.2-1.8)	**0.2(0.04-0.95)**	0.047
Fatal acute myocardial infarction					
	Cases, no.	3(5%)	33(11%)	7(9%)	
	Age-adjusted	Ref	1.8(0.6-6.0)	1.5(0.4-5.7)	0.9
	Age and smoking	Ref	1.8(0.5-5.9)	1.2(0.3-4.7)	0.5
	Multivariable*	Ref	1.4(0.4-4.8)	0.8(0.2-3.2)	0.2
Fatal stroke or ischemic heart disease					
	Cases, no.	18(28%)	115(37%)	21(26%)	
	Age-adjusted	Ref	1.0(0.6-1.7)	0.8(0.4-1.4)	0.2
	Age and smoking	Ref	1.0(0.6-1.6)	0.6(0.3-1.1)	0.02
	Multivariable*	Ref	1.0(0.6-1.7)	0.6(0.3-1.1)	0.02
All-cause mortality					
	Cases, no.	50(77%)	245(78%)	59(74%)	
	Age-adjusted	Ref	0.8(0.6-1.1)	0.8(0.5-1.1)	0.4
	Age and smoking	Ref	0.8(0.6-1.0)	0.6(0.4-0.9)	0.046
	Multivariable model*	Ref	0.9(0.6-1.2)	0.7(0.5-1.1)	0.2

* Adjusted for age, sex, race/ethnicity (white, African American, Hispanic, other), socioeconomic status group (poverty index < 1.3, 1.3 to 3.5, >3.5), smoking status (current, past [>100 cigarettes in life], never), alcohol (more than 5 drinks 14 or more times or more than 9 drinks 7 or more times per year), history of diabetes mellitus, history of hyperlipidemia, history of hypertension.

Table 4. Relative risk of fatal cardiovascular event by caffeine consumption in myocardial infarction survivors (n=739)

		Number of events, RR of stroke (95% confidence interval)			P for trend
		No caffeine	1-2 cups	3+ cups	
	Total patients	83	514	142	
	Person-years	657	4593	1460	
Fatal stroke					
	Cases, no.	5(6%)	27(5%)	3(2%)	
	Age-adjusted	Ref	0.6(0.2-1.5)	0.3(0.06-1.1)	0.1
	Age and smoking	Ref	0.5(0.2-1.4)	0.2(0.05-0.96)	0.09
	Multivariable*	Ref	0.6(0.2-1.6)	0.3(0.06-1.1)	0.1
Fatal acute myocardial infarction					
	Cases, no.	5(6%)	68(13%)	16(11%)	
	Age-adjusted	Ref	1.6(0.7-4.1)	1.5(0.5-4.0)	1.0
	Age and smoking	Ref	1.7(0.7-4.2)	1.5(0.5-4.1)	0.9
	Multivariable*	Ref	1.3(0.5-3.4)	1.0(0.4-2.9)	0.5
Fatal stroke or ischemic heart disease					
	Cases, no.	29 (35%)	193 (38%)	39 (27%)	
	Age-adjusted	Ref	0.8(0.5-1.2)	0.6(0.4-0.98)	0.07
	Age and smoking	Ref	0.8(0.5-1.1)	0.5(0.3-0.9)	0.02
	Multivariable*	Ref	0.7(0.5-1.0)	**0.5(0.3-0.8)**	0.01
All-cause mortality					
	Cases, no.	62(75%)	370(72%)	96(68%)	
	Age-adjusted	Ref	0.7(0.5-0.9)	0.7(0.5-0.97)	0.4
	Age and smoking	Ref	0.7(0.5-0.9)	0.6(0.5-0.9)	0.1
	Multivariable model*	Ref	0.7(0.5-0.9)	**0.7(0.5-0.9)**	0.2

* Adjusted for age, sex, race/ethnicity (white, African American, Hispanic, other), socioeconomic status group (poverty index < 1.3, 1.3 to 3.5, >3.5), smoking status (current, past [>100 cigarettes in life], never), alcohol (more than 5 drinks 14 or more times or more than 9 drinks 7 or more times per year), history of diabetes mellitus, history of hyperlipidemia, history of hypertension

Table 5. Correlation of caffeine consumption with disability measures

Disability measure	**with caffeine consumption as continuous variable**	**With caffeine consumption categorized as 0,1-2, 3+ cups of coffee**
1. Difficulty walking a quarter of a mile	-0.10 [a]	-0.16 [c]
2. Difficulty walking 10 steps without rest	-0.12 [a]	-0.22 [c]
3. Difficulty stooping, crouching, kneeling	-0.07 [a]	-0.08 [c]
4. Difficulty lifting or carrying 10 pounds	-0.11 [a]	-0.15 [c]
5. Difficulty doing chores around the house	-0.14 [a]	-0.18 [c]
6. Difficulty preparing own meals	-0.09 [a]	-0.27 [c]
7. Difficulty managing your money	-0.01 [a]	-0.12 [c]
8. Difficulty walking room to room, on same level	-0.08 [a]	-0.19 [c]
9. Difficulty standing from armless chair	-0.03 [a]	-0.08 [c]
10. Difficulty getting in or out of bed	-0.02 [a]	-0.04 [c]
11. Difficulty Eating	-0.08 [a]	-0.03 [c]
12. Difficulty dressing yourself	-0.10 [a]	-0.3 [c]
13. Need help of other persons with personal care needs	0.08 [b]	0.08 [d]
14. Need help of other persons in handling routine needs	0.07 [b]	0.07 [d]
15. Use any device to help you get a round	0.07 [b]	0.08 [d]
16. Use any special eating utensils	0 [b]	0.05 [d]
17. Use any aids or devices to help you dress	0 [b]	0.03 [d]

[a.] Spearman rho (continuous-ordinal), [b] Point-biserial (continuous-binomial), [c] Gamma statistic (ordinal-ordinal), [d] Cramer's V (ordinal-binomial)

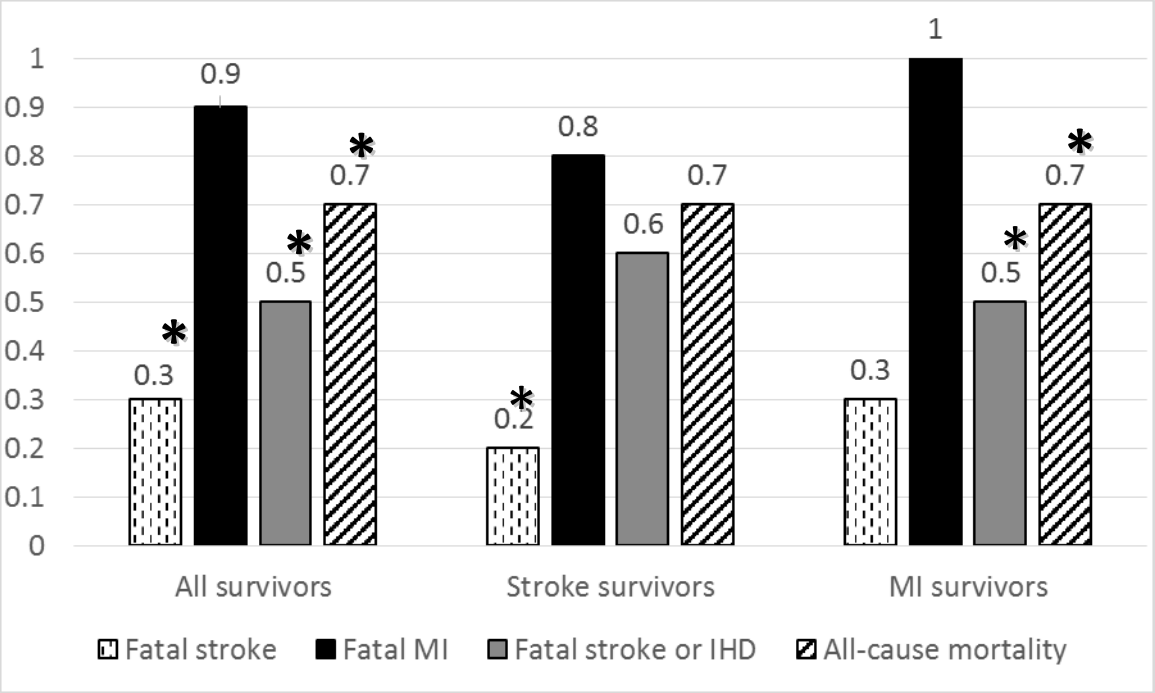
Table 6. Relative risk of fatal cardiovascular event by 3+ cups of caffeine consumption compared to no caffeine consumption in all cardiovascular disease survivors after adjustment for baseline disability

Disability measure adjusted-for in the model	N [a]	RR of stroke (95% confidence interval) [b]
Unadjusted for any disability measure	1082	0.3 (0.1-0.8)
1. Difficulty walking a quarter of a mile	928	0.2 (0.05 – 0.6)
2. Difficulty walking 10 steps without rest	917	0.2 (0.06-0.85)
3. Difficulty stooping, crouching, kneeling	945	0.2 (0.06-0.6)
4. Difficulty lifting or carrying 10 pounds	993	0.2 (0.06-0.7)
5. Difficulty doing chores around the house	882	0.3 (0.1-1.06)
6. Difficulty preparing own meals	882	0.35 (0.1-1.3)
7. Difficulty managing your money	919	0.2 (0.06-0.6)
8. Difficulty walking room to room, on same level	958	0.2 (0.05 – 0.6)
9. Difficulty standing from armless chair	959	0.2 (0.06 – 0.6)
10. Difficulty getting in or out of bed	961	0.2 (0.06 – 0.6)
11. Difficulty Eating	961	0.2 (0.06-0.6)
12. Difficulty dressing yourself	959	0.2 (0.06 – 0.6)
13. Need help of other persons with personal care needs	959	0.2 (0.06-0.6)
14. Need help of other persons in handling routine needs	836	0.2 (0.06-0.7)
15. Use any device to help you get a round	960	0.2 (0.06-0.6)
16. Use any special eating utensils	961	0.2 (0.06-0.6)
17. Use any aids or devices to help you dress	961	0.2 (0.06-0..6)
Total disability score (continuous variable)	764	0.33 (0.1-1.4)

[a.] Sample size for model – smaller for models with missing information

[b.] In addition to the disability question, also adjusted for age, sex, race/ethnicity (white, African American, Hispanic, other), socioeconomic status group (poverty index < 1.3, 1.3 to 3.5, >3.5), smoking status (current, past [>100 cigarettes in life], never), alcohol (more than 5 drinks 14 or more times or more than 9 drinks 7 or more times per year), history of diabetes mellitus, history of hyperlipidemia, history of hypertension

Figure 1. Relative risk of fatal cardiovascular event by 3+ cups of caffeine consumption vs no caffeine consumption in survivors of cardiovascular disease



* 95% confidence interval excludes 1 (statistically significant difference)

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