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STATE-OF-THE-ART PAPER

# Effects of Habitual Coffee Consumption on Cardiometabolic Disease, Cardiovascular Health, and All-Cause Mortality

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**Coffee, after water, is the most widely consumed beverage in the United States, and is the principal source of caffeine intake among adults. The biological effects of coffee may be substantial and are not limited to the actions of caffeine. Coffee is a complex beverage containing hundreds of biologically active compounds, and the health effects of chronic coffee intake are wide ranging. From a cardiovascular (CV) standpoint, coffee consumption may reduce the risk of type 2 diabetes mellitus and hypertension, as well as other conditions associated with CV risk such as obesity and depression; but it may adversely affect lipid profiles depending on how the beverage is prepared. Regardless, a growing body of data suggests that habitual coffee consumption is neutral to beneficial regarding the risks of a variety of adverse CV outcomes including coronary heart disease, congestive heart failure, arrhythmias, and stroke. Moreover, large epidemiological studies suggest that regular coffee drinkers have reduced risks of mortality, both CV and all-cause. The potential benefits also include protection against neurodegenerative diseases, improved asthma control, and lower risk of select gastrointestinal diseases. A daily intake of ~2 to 3 cups of coffee appears to be safe and is associated with neutral to beneficial effects for most of the studied health outcomes. However, most of the data on coffee's health effects are based on observational data, with very few randomized, controlled studies, and association does not prove causation. Additionally, the possible advantages of regular coffee consumption have to be weighed against potential risks (which are mostly related to its high caffeine content) including anxiety, insomnia, tremulousness, and palpitations, as well as bone loss and possibly increased risk of fractures.** (J Am Coll Cardiol 2013;62:1043–51) © 2013 by the American College of Cardiology Foundation

Coffee is second only to water as the most widely consumed beverage in the United States. U.S. coffee consumption has been increasing for the past 2 decades, and today about two thirds of American adults drink coffee on a daily basis (1). Each day Americans drink >400 million cups of coffee, and the United States consumes more coffee than any other nation (1). Even potentially small health benefits or risks associated with coffee intake may have important public health implications given its widespread popularity. Many misconceptions persist regarding the health-related effects of coffee. The purpose of this article is to review existing data regarding the effects of long-term coffee consumption, with a focus on cardiovascular (CV) health.

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## Biologically Active Constituents of Coffee

Coffee is a complex beverage containing >1,000 compounds. Among the many with known biological activity are caffeine (a potent stimulant and bronchodilator), diterpene alcohols (which can increase serum cholesterol), and chlorogenic acid (one of many types of antioxidant and anti-inflammatory compounds found in coffee). Caffeine is by far the most studied compound in coffee, and this agent largely accounts for the inherently habit-forming nature of the beverage. Coffee accounts for 71% of caffeine intake among American adults (soft drinks are the primary source of caffeine for children and adolescents) (2). The caffeine content of coffee is highly variable, even when the coffee beverage is obtained from the same outlet (3). A standard 8-oz cup of brewed coffee can contain anywhere from ~95 to 200 mg of caffeine. However, coffee is increasingly served in containers that are considerably larger (e.g., 12 to 16 oz), typically delivering 180 to 300 mg of caffeine per serving (4). Brewed decaffeinated coffee still contains caffeine, albeit at much lower doses that usually range from 5 to 15 mg per 8 oz.

Given the focus on *caffeine* for much of the research around *coffee*, the terms caffeine and coffee are often conflated in both

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**Abbreviations and Acronyms**

AF = atrial fibrillation
BP = blood pressure
CHD = coronary heart disease
CHF = congestive heart failure
CI = confidence interval
CV = cardiovascular
HTN = hypertension
LDL = low-density lipoprotein
MI = myocardial infarction
RCT = randomized, controlled trial
RR = relative risk
T2DM = type 2 diabetes mellitus

the biomedical literature and public perception. However, the terms are not synonymous, and the biological effects of coffee cannot be reduced to the isolated effects of the caffeine that it contains. Here we discuss the evidence of coffee's effects on cardiometabolic risk factors (i.e., hypertension [HTN], insulin resistance, dyslipidemia), CV disease (i.e., coronary heart disease [CHD], congestive heart failure [CHF], arrhythmias, and stroke), and mortality (CV and all-cause). We also discuss other potential health benefits and health risks of coffee consumption, distinguishing between data specifically on caffeine and data on coffee.

## Coffee and Blood Pressure

Hypertension is a strong independent risk factor for stroke and CHD. Coffee consumption has been associated with acute increases in blood pressure (BP) in caffeine-naive people but exerts negligible effects on the long-term levels of BP in habitual coffee drinkers (5). The acute effects of coffee are transient, and, with regular intake, tolerance develops to the hemodynamic and humoral effects of caffeine (6). A recent meta-analysis of 10 randomized, controlled trials (RCTs) and 5 cohort studies assessed BP and the incidence of HTN in coffee consumers. Nonsignificant mean changes in systolic BP of −0.55 mm Hg (95% confidence interval [CI]: 2.46 to 1.36) and diastolic BP −0.45 mm Hg (95% CI: −1.52 to 0.61) were noted in coffee drinkers compared with the control group. Evidence analyzed from this large study showed no clinically important effects of long-term coffee consumption on BP or risk of HTN (7). Studies and reviews done previously have also come to similar conclusions (8). The Nurses' Health Study, with 1.4 million person-years of follow-up, demonstrated that daily intake of up to 6 cups of coffee was not associated with an increased risk of HTN (9).

Caffeine is the major acute BP-increasing compound found in coffee, but other compounds present in coffee may counteract these acute pressor effects. A study of 15 volunteers, including 6 habitual and 9 nonhabitual coffee drinkers, demonstrated that intravenous caffeine infusion induced similar increases in muscle sympathetic activity and BP in the 2 groups. In contrast, coffee drinking increased BP in nonhabitual drinkers but not in the habitual coffee drinkers, despite comparable increases of muscle sympathetic activity and plasma caffeine levels in the 2 groups after coffee ingestion. The authors concluded that caffeine is not solely responsible for the CV effects associated with short- and long-term coffee consumption (10).

## Coffee and Insulin Sensitivity

Antioxidants in coffee, such as chlorogenic acid, have been recognized to improve glucose metabolism and insulin sensitivity (11). A recently published randomized study found that consumption of 5 cups of coffee per day increased adiponectin levels and decreased insulin resistance (12). Caffeine acutely activates 5′-adenosine monophosphate–activated protein kinase and insulin-independent glucose transport in skeletal muscle (13). Studies in rat models confirmed that it upregulates insulin-like growth factor 1 signaling, which in turn enhances insulin sensitivity as well as insulin secretion (14).

A systematic review of 9 cohort studies compared minimal to low coffee consumption (<2 cups/day) with that of heavy coffee consumption (≥6 cups/day) for the risk of the development of type 2 diabetes mellitus (T2DM). These researchers concluded that the risk of the development of T2DM was lowest in subjects who drank >6 cups daily (relative risk [RR]: 0.65; 95% CI: 0.54 to 0.78) and also was significantly reduced for subjects who consumed 4 to 6 cups daily (RR: 0.72; 95% CI: 0.62 to 0.83) (Fig. 1) (15). A prospective study of >88,000 women 26 to 46 years of age established a linear relationship of coffee consumption with the reduction in T2DM, whereby even small amounts of coffee on a daily basis conferred benefit (16). Associations were similar for noncaffeinated and caffeinated coffee.

## Coffee and Serum Lipids

Coffee contains cholesterol-increasing compounds classified as diterpenes, including cafestol and kahweol (17). Importantly, the concentration of these compounds depends on how coffee is prepared. Boiled coffee has higher concentrations because diterpenes are extracted from the coffee beans by prolonged contact with hot water. By comparison, brewed/filtered coffee, because of the much shorter contact with hot water and retention of diterpenes by filter paper, has a much lower concentration of cafestol and kahweol.

The effect of coffee on serum lipid levels was studied in 107 young adults with normal cholesterol levels followed for 12 weeks. Coffee was brewed by 2 common methods, filtering and boiling, and the participants were assigned to 1 of 3 groups: drinking 4 to 6 cups of boiled coffee per day, 4 to 6 cups of filtered coffee per day, or no coffee, for a period of 9 weeks. A significant increase in total cholesterol and a nonsignificant increase in low-density lipoprotein (LDL) cholesterol were observed in participants consuming boiled coffee. On the other hand, there was no significant difference in the change in serum total or LDL cholesterol levels between the filtered-coffee group and the group who drank no coffee (18). These results were replicated in a meta-analysis of 14 RCTs in which the consumption of boiled coffee dose-dependently increased serum total and LDL cholesterol concentrations, whereas the consumption of filtered coffee resulted in very little change in serum cholesterol (19). A large cohort of 132,000 men and women

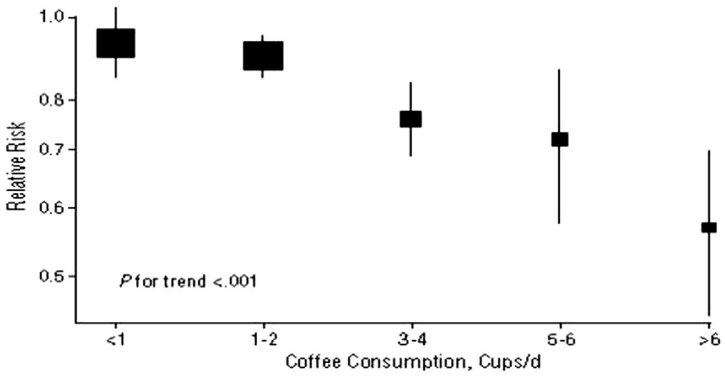


**Figure 1** **The Relationship Between Coffee Consumption and Subsequent Type 2 Diabetes Mellitus in Different Categories of Coffee Consumption**

The center of each black square is placed at the summary point estimate; the area of the square is proportional to the population size; and each vertical line shows the 95% confidence interval about the summary estimate. Reprinted with permission from Husley et al. (15).

from Health Professionals Follow-up Study and the Nurses' Health Study without history of CV disease and cancer also found no impact of filtered coffee on total cholesterol, LDL and high-density lipoprotein levels (20).

Conversely, tea, however, shares many of the health effects of coffee and has a favorable effect on the lipid profiles, especially the LDL/high-density lipoprotein ratio, which is in contrast to the lipid effects of unfiltered coffee consumption (21).

## Coffee and CHD

Decades-old studies suggested coffee consumption might cause adverse CV effects including an increased risk of myocardial infarction (MI) (22,23). However, unmeasured confounding probably flawed those early studies; in subsequent analyses when other important health-related variables (such as smoking, alcohol use, saturated fat consumption, physical activity, and body mass index) were adjusted for, the risk of mortality, both all-cause and CV related, appeared to be lower in regular coffee drinkers (Figs. 2A and 2B) (24,25).

Many epidemiological studies have evaluated the potential effects of coffee on CHD, and these individual studies have generally shown neutral effects. However, a meta-analysis of 21 independent prospective cohort studies from January 1966 to January 2008 suggested that moderate coffee consumption may decrease the long-term risk of CHD (26). In this study, 15,599 CHD cases developed in 407,806 participants. Compared with the light-to-absent coffee consumption (<1 cup/day in the United States or ≤2 cups/day in Europe), moderate coffee consumption (>1 or 2 cups daily, respectively) was associated with significantly lower rates of CHD in the entire group of men and women with an RR of 0.87 ($p = 0.001$).

Several studies have suggested that it is safe for patients with established CHD to continue their habitual coffee consumption. An RCT involving 103 patients with acute ST-segment elevation MI evaluated the effect of acute ingestion (immediate effects) of coffee on autonomic function and CV health. Coffee ingestion was associated with an increase in parasympathetic tone, and coffee did not increase cardiac arrhythmia. The authors concluded that coffee ingestion is safe and not associated with adverse CV outcomes in post-MI patients (27). A more recent study showed that acute caffeine ingestion significantly decreased high-sensitivity C-reactive protein levels in 2 groups of patients with and without CHD compared with placebo (28).

## Coffee and CHF

A recent large meta-analysis reported a U-shaped relationship between coffee consumption and the incidence of CHF. Five independent prospective studies evaluating coffee consumption and CHF risk, from January 1966 through December 2011, were included in the meta-analysis. A total 6,522 heart failure events were recorded among the 140,220 participants during follow-up. A statistically significant association between coffee and CHF was observed, with the strongest inverse association noted for 4 servings per day with increased CHF risks for both higher and lower levels of coffee consumption (Fig. 3). There was no evidence that the relationship between coffee and risk of heart failure varied by sex or by baseline history of MI or diabetes (29).

## Coffee and Arrhythmias

Data linking coffee consumption to increased risk of arrhythmias are inconsistent. Early animal studies indicated that coffee appeared to cause arrhythmias in a canine model (30). Yet, more recent studies have suggested that coffee appears not to increase arrhythmias; to the contrary, long-term coffee drinking might actually reduce the risk of abnormal cardiac rhythms. In a Kaiser Permanente study of 130,054 adults living in California, an inverse relationship between habitual coffee

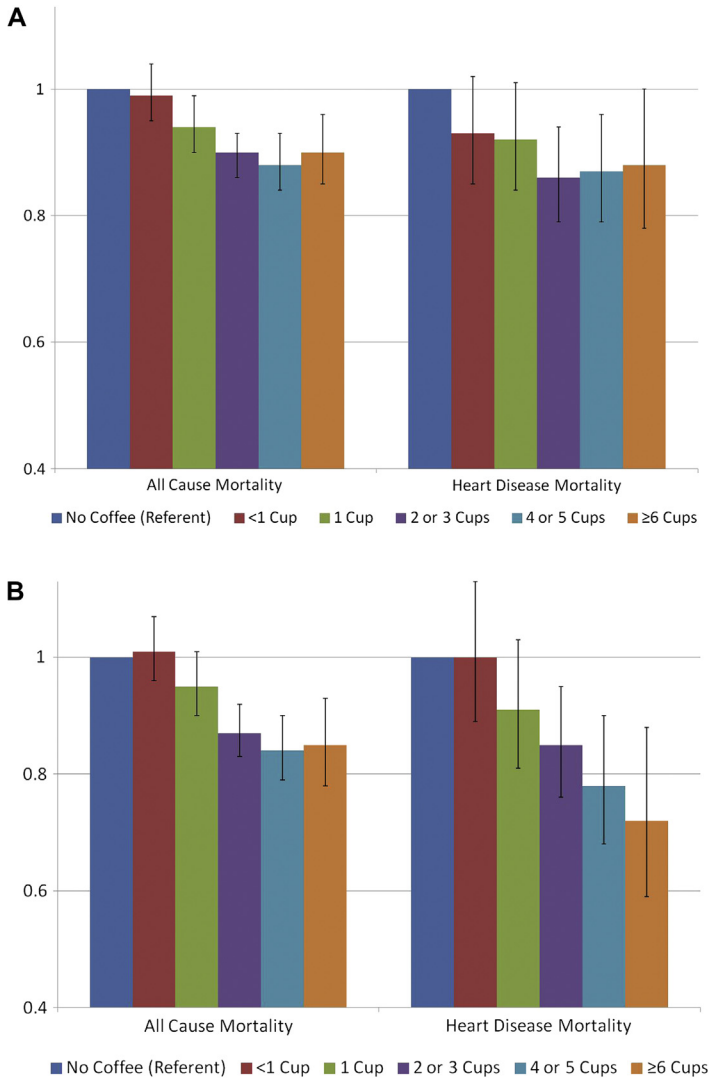


**Figure 2** **Adjusted Hazard Ratios for Risk of Death as a Function of Coffee Consumption**

Association of daily coffee consumption with total and heart disease mortality among men **(A)** and women **(B)**. Error bars indicate 95% confidence interval. Adapted from Freedman et al. (25).

consumption and risk of hospitalization for arrhythmia was observed during long-term follow-up. A total of 3,137 persons were hospitalized over a mean follow-up period of 17.6 years. Coffee intake correlated inversely with cardiac arrhythmia (Fig. 4). The relationship was consistent in men, women, whites, blacks, and persons younger than or older than 60 years of age. The authors concluded that people who drank 4 cups of coffee per day tended to have fewer cardiac arrhythmias, including less atrial fibrillation (AF) (31).

Considering the effects of caffeine in isolation, controlled interventional studies show that in normal adults, even high-dose caffeine does not affect prevailing cardiac rhythm and rate, and, moreover, does not cause clinically significant ventricular or supraventricular arrhythmias (32). In 5 placebo-controlled trials, caffeine in doses as high as 500 mg/day (equivalent to 4 or 5 cups of coffee) did not increase the frequency or severity of ventricular arrhythmias (33). In a prospective interventional electrophysiological study, ingestion of 275 mg of caffeine did not significantly alter inducibility or severity of arrhythmias (34).

The mechanisms conferring potential protection against arrhythmias are still largely unknown, but according to 1 hypothesis, caffeine inhibits adenosine in the heart, as it does in the brain. Endogenously secreted adenosine affects cardiac electrical conduction and cardiomyocyte repolarization and may cause shortening of the atrial and ventricular refractory periods, thereby predisposing to arrhythmias. Caffeinated coffee intake could theoretically confer cardioprotection by attenuating these negative effects of endogenous adenosine (31).

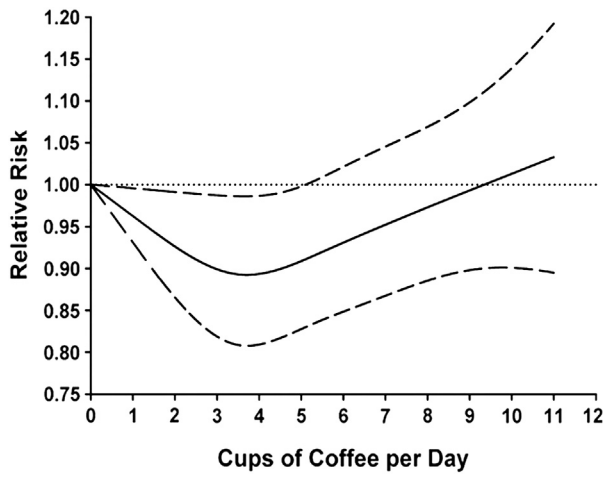


**Figure 3** Coffee and Risk of Heart Failure

Association between heart failure and cups of coffee per day compared with no consumption. Relative risk **(solid line)** and 95% CI **(dashed lines)**. Adapted with permission from Freedman et al. (25) and Mostofsky et al. (29).

On the other hand, caffeine acting as an adenosine receptor blocker might reduce the efficacy of exogenously administered adenosine for the treatment of paroxysmal supraventricular tachycardia. One case-control study found that ingestion of caffeine within 4 h before a 6-mg adenosine bolus significantly reduced its effectiveness for the conversion of supraventricular tachycardia to normal sinus rhythm (35). A large prospective, observational study found that drinking coffee, even ≥6 cups/day, was not associated with any QT interval abnormalities that might predispose to serious arrhythmias (36).

In the Women's Health Study, 33,638 women older than 45 years of age and free of CV disease and AF at baseline were prospectively followed for incident AF from 1993 through 2009. During a median follow-up of 14.4 years in this large cohort of initially healthy women, caffeine consumption was not associated with an increased risk of incident AF (37). In the Danish Diet, Cancer, and Health study, 47,949 participants 50 to 64 years of age were followed for a mean of 5.7 years. Caffeine consumption in the form of coffee, tea, and cola was not associated with the risk of the development of AF or flutter (38). These results were replicated in the Framingham Heart Study cohort of 4,526 participants; during a prospective follow-up of 4 years, no significant association between coffee consumption and AF risk was noted (39).

## Coffee and Stroke

Coffee may reduce the risk of ischemic stroke. A recent meta-analysis of 7 prospective studies with 442,098 participants, 6,962 stroke events, and follow-up of 2 to 24 years demonstrated that 1 to 3 cups of coffee were associated with a decreased risk of stroke (RR: 0.82, 95% CI: 0.74 to 0.90, $p < 0.001$). The evaluation of the risk of stroke in the general population consuming 3 to 6 cups of coffee per day showed a significant reduction (RR: 0.79, 95% CI: 0.68 to 0.92, $p = 0.003$). By contrast, habitual consumption of >6 cups of coffee per day was not associated with any effect on stroke risk (RR: 1.00, 95% CI: 0.76 to 1.32, $p = 0.97$). The authors concluded that coffee consumption is not associated with a higher risk of stroke and that habitual moderate consumption may exert a protective effect (40).

In the Swedish Mammography Cohort, 34,670 women without a history of CV disease or cancer were followed for a mean of 10.4 years. The multivariable RRs of total stroke across categories of coffee consumption (<1 cup/day, 1 to 2 cups/day, 3 to 4 cups/day, and ≥5 cups/day) were 1.00, 0.78 (95% CI: 0.66 to 0.91), 0.75 (95% CI: 0.64 to 0.88), and 0.77 (95% CI: 0.63 to 0.92), respectively (p for trend = 0.02). The findings suggested that coffee consumption was associated with a statistically significant lower risk of stroke (41). This inverse association of coffee consumption and mortality from stroke was also observed in a diabetic population (Fig. 5) (42). An analysis of a prospective group of >83,000 women from the Nurses' Health Study who were free of CV disease and cancer at baseline found that coffee consumption was associated with a modest but statistically significant reduction in the risk of stroke during the 24-year follow-up period (43). Exactly how coffee lowers the risk of stroke is unknown, but postulated mechanisms include coffee's anti-inflammatory and insulin-sensitizing effects (44–46).

## Coffee Consumption and Mortality

In the National Health and Nutrition Examination Survey I, 6,594 participants 32 to 86 years of age with no history of CV disease at baseline were prospectively followed for 8.8 years. Coffee intake of participants who were 65 years of age or older exhibited a dose-response protective effect whereby increasing habitual consumption of coffee was associated with lower RRs of adverse CV events and heart disease mortality (Fig. 6) (47).

In another study, 41,736 men and 86,214 women with no history of CV disease or cancer at baseline were followed for 18 years (men) and 24 years (women) to assess the association between coffee consumption and CV mortality, cancer, and all-cause mortality. An inverse association between coffee consumption and all-cause mortality was seen mainly due to a moderately reduced risk of CV disease mortality and was independent of caffeine intake; decaffeinated coffee was also associated with a small reduction in all-cause and CV disease mortality (48).

In the recent National Institutes of Health-AARP Diet and Health Study, 229,119 men and 173,141 women were followed from 1995 through 2008 to examine the association of coffee drinking with subsequent total and cause-specific mortality. Participants were 50 to 71 years of age at baseline and were excluded if they had a personal history of cancer,

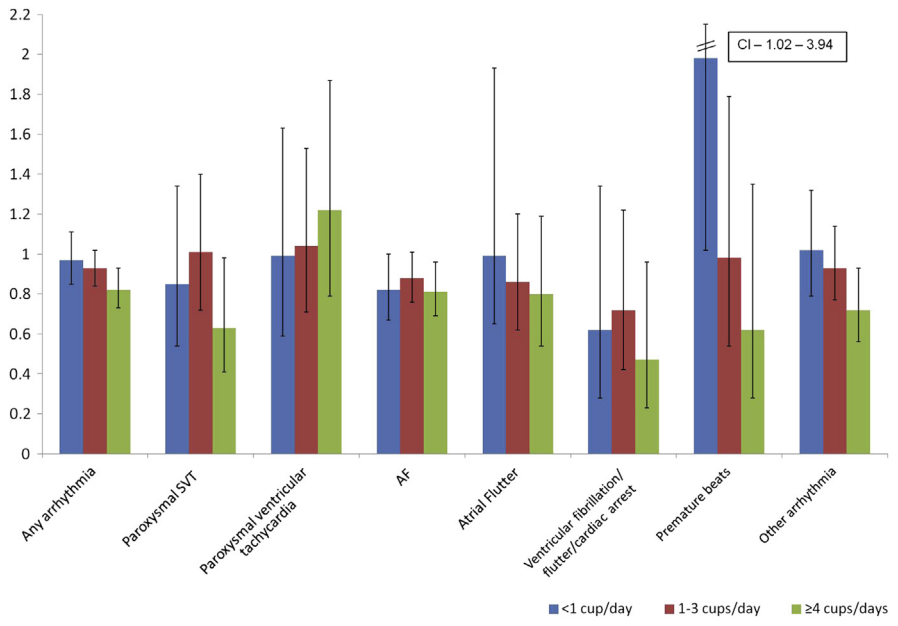


**Figure 4** Coffee Consumption and Risk of Arrhythmias

Adjusted hazard ratio (no coffee take is referent = 1) of arrhythmia diagnoses by coffee intake. **Error bars** indicate 95% confidence interval (CI). Adapted from Klatsky et al. (31). AF = atrial fibrillation; SVT = supraventricular tachycardia.

heart disease, or stroke. Although the unadjusted risk of death was increased in coffee drinkers, coffee drinkers were also more likely to smoke. After adjustment for tobacco smoking and other potential confounders, men who drank ≥6 cups of coffee per day had a 10% lower risk of death and women had a 15% lower risk, irrespective of whether they drank caffeinated or decaffeinated coffee. Inverse associations were observed for deaths due to heart disease, respiratory disease, stroke, injuries and accidents, diabetes, and infections, but not for deaths due to cancer (25).

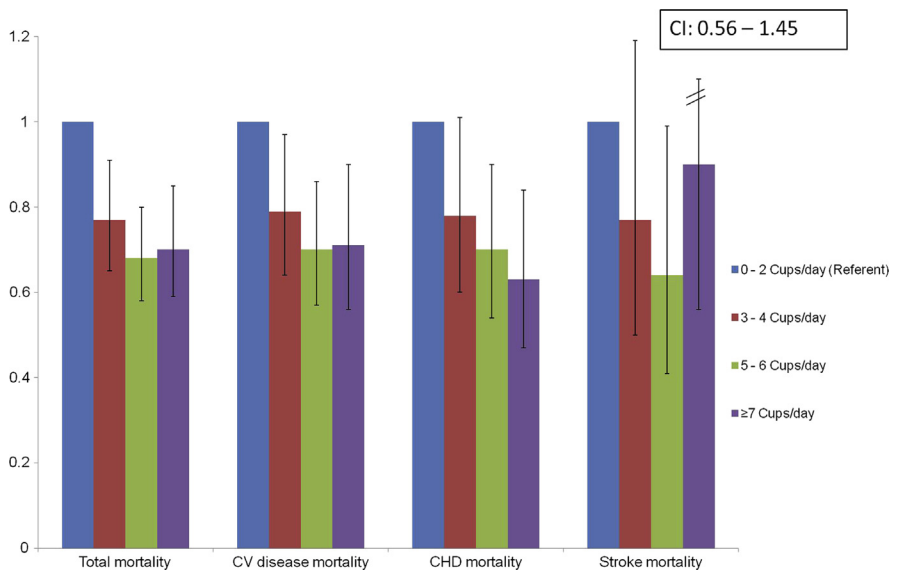


**Figure 5** Coffee Intake in Diabetic Subjects

Adjusted hazard ratios of total, cardiovascular (CV) disease, coronary heart disease (CHD), and stroke mortality by volume of coffee consumption among subjects with type 2 diabetes mellitus. **Error bars** indicate 95% confidence interval (CI). Adapted from Bidel et al. (42).

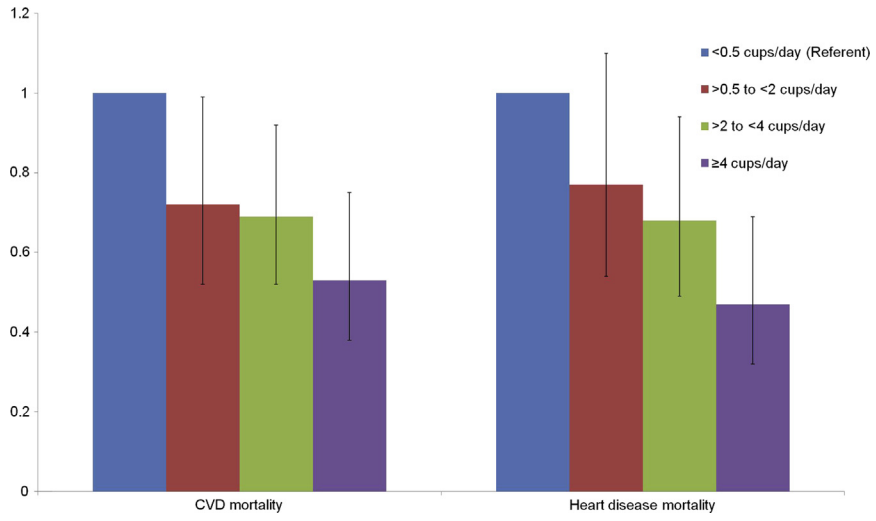


**Figure 6** Coffee Over Age 65

Relative risk of cardiovascular disease (CVD) and heart disease mortality by level of caffeinated beverage intake in individuals 65 years of age and older. **Error bars** indicate 95% confidence interval (CI). Adapted from Greenberg et al. (47).

## Coffee and Other Health Effects

Coffee consumption is also associated with various other health effects. For instance, coffee may reduce the risk of depression, a known risk factor for the development of CV disease, as well as an independent predictor of poor prognosis (49). In a recent longitudinal study of 50,739 women, ingesting ≥4 cups of coffee daily significantly decreased the RR of depression (Fig. 7). The effect may be due largely to the caffeine content because women consuming decaffeinated coffee did not show a reduced risk (50). Coffee consumption may also benefit efforts at weight control, increasing the thermic effect of food and fat oxidation in normal-weight subjects (51).

Other beneficial health effects of coffee may include reduced risks of Alzheimer's dementia (52,53) and other diseases of the central nervous system including Parkinson's disease (54–56). Additionally, coffee may improve asthma symptoms, probably through caffeine, which is a methylxanthine bronchodilator, and enhance performance in sustained high-intensity exercise (57,58). Coffee may prevent symptomatic gallstones (59) and be associated with protection against some infectious and malignant diseases, particularly of the liver (60–62).

All of this is not to say that coffee is without its own risks. Many individuals experience palpitations, anxiety, tremulousness, and trouble sleeping after drinking coffee, particularly when it contains higher doses of caffeine (63). The polycyclic aromatic hydrocarbon-inducible cytochrome P450 1A2 participates in the metabolism of caffeine and a number of drugs, including certain selective serotonin reuptake inhibitors (particularly fluvoxamine), antiarrhythmics (mexiletine), antipsychotics (clozapine), psoralens, idrocilamide and phenylpropanolamine, bronchodilators (furafylline and theophylline), and quinolones (enoxacin), can aggravate the unwanted secondary effects of coffee by inhibiting this isoenzyme (64). Decaffeinated coffee may be a good option, particularly because many of coffee's potential benefits likely derive from sources other than its caffeine. Moreover, high levels of caffeine (>750 mg/day) may increase urine output and urinary calcium and magnesium excretion, which has implications for bone health (65). Caffeinated coffee increases the risk of bone loss (66,67) and

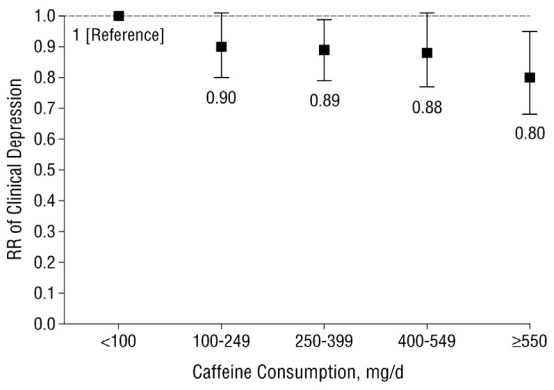


**Figure 7** Coffee and Depression

Multivariate-adjusted relative risk (RR) of clinical depression according to caffeine consumption (p for trend = 0.02). **Error bars** indicate 95% confidence interval. Reproduced with permission from Lucas et al. (50).

fractures (68). Still, it has been estimated that the amount of calcium lost from consuming 1 cup of coffee can be offset by mixing in just 2 tablespoons of milk (66). Moreover, a daily glass of milk might offset the calcium loss and reductions in bone mineral density due to coffee consumption (67). Additionally, the human body develops tolerance to caffeine usually after 3 to 5 days of regular use and kidneys ensure that proper homeostatic conditions are maintained, which attenuate the already limited diuretic effects of kidney (69).

## Coffee and Clinical Considerations

People who consume coffee typically do so on a daily basis, often due to caffeine dependence. Caffeine is a central nervous system stimulant, and its regular use typically causes mild physical dependence as evidenced by the development of tolerance, withdrawal symptoms (headaches, irritability, fatigue, depressed mood, anxiety, and difficulty concentrating), and cravings with abstinence (70,71). Notwithstanding, daily caffeine use generally does not threaten one's physical health and emotional/social well-being the way that many addictive drugs like alcohol, opiates, cocaine, and methamphetamines do; thus, substance abuse experts generally do not consider caffeine dependence a serious addiction (70). Indeed the tendency for coffee to promote habitual daily consumption may ultimately turn out to be advantageous if its myriad potential health benefits are confirmed.

Caffeine, in moderate daily doses of ~300 mg, or ~3 cups of coffee, appears to be safe and harmless for healthy adults. Conversely, ingesting 10 times that amount of caffeine in a short period could be lethal (72). Moderation, tending toward 2 or 3 to as much as 4 cups a day if tolerated, seems a reasonable suggestion.

## Conclusions

The currently available evidence on CV effects related to habitual coffee consumption is largely reassuring. Coffee can be included as part of a healthy diet for the general public and also for those with increased CV risk or CV disease. Those with dyslipidemia may consider brewed and filtered coffee as opposed to preparations made from boiling beans without filtering. While many of coffee's benefits probably derive from its caffeine content, decaffeinated coffee seems to offer some health benefits too and may be a reasonable option for those who experience uncomfortable effects from caffeine stimulation. Drinkers of caffeinated coffee in particular might be advised to ensure adequate calcium consumption from dietary sources to guard against potential adverse outcomes related to bone health. Finally, it is possible that individuals who consume coffee differ in other important dietary and sociological aspects from the nonconsumers. Therefore, the possibility that coffee consumption may be acting as a surrogate marker of some other dietary or lifestyle risk factor cannot be fully excluded.

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**Key Words:** caffeine ■ cardiometabolic disease ■ coffee ■ coronary heart disease ■ hypertension.