

## Coffee Consumption and Cardiovascular Risk: An Updated Overview

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Received: November 11, 2014

Revised: December 1, 2014

Accepted: December 7, 2014

Published online: December 10, 2014

stroke; moreover, large epidemiological studies suggest that regular coffee consumption reduces risks of both cardiovascular and all-cause mortality. A daily intake of ~2-3 cups of coffee appears to be safe and is associated with neutral to beneficial effects for most of the studied health outcomes. Nevertheless, evidences on coffee's health effects are largely based on observational data, with very few randomized, controlled studies, and association does not prove causation. Additionally, the possible advantages of regular coffee consumption must be weighed against potential risks, mostly related to its caffeine content, such as anxiety, insomnia, tremulousness, palpitations, bone loss and fractures.

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**Key words:** Cardiovascular risk; Coffee; Caffeine

Lombardi M, Cruciani G, Mazza A, Luzi L, Leggio M. Coffee Consumption and Cardiovascular Risk: An Updated Overview. *Journal of Cardiology and Therapy* 2014; 1(9): 200-205 Available from: URL: <http://www.ghrnet.org/index.php/jct/article/view/913>

### ABSTRACT

Coffee is one of the most widely consumed beverages worldwide. Since coffee contains caffeine, a stimulant, coffee drinking is not generally considered to be part of a healthy lifestyle. However, coffee is a rich source of antioxidants and other bioactive compounds, and many misconceptions persist regarding the health-related effects of coffee. Because of coffee is a complex beverage containing many bioactive compounds, its biological effects may be substantial and are not limited to the actions of caffeine; consequently, the health effects of chronic coffee intake are wide ranging. Coffee consumption may reduce the risk of type 2 diabetes mellitus, hypertension, obesity and depression, but it may adversely affect lipid profiles depending on how the beverage is prepared. A growing body of evidences suggests that habitual coffee consumption is neutral to beneficial regarding the risks of a variety of adverse cardiovascular outcomes including coronary heart disease, congestive heart failure, arrhythmias, and

### INTRODUCTION

Coffee is one of the most widely consumed beverages, both in the United States and worldwide<sup>[1]</sup>. In the United States coffee is second only to water as the most widely consumed beverage, 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<sup>[2]</sup>. Each day Americans drink >400 million cups of coffee, and the United States consumes more coffee than any other nation<sup>[2]</sup>.

Since coffee contains caffeine, a stimulant, coffee drinking is not generally considered to be part of a healthy lifestyle. However, coffee is a rich source of antioxidants<sup>[3]</sup> and other bioactive compounds, and studies have shown inverse associations between coffee consumption and serum biomarkers of inflammation<sup>[4]</sup> and insulin resistance<sup>[5,6]</sup>. Even potentially small health benefits or risks associated with coffee intake may have important public health implications given its

widespread popularity, and many misconceptions persist regarding the health-related effects of coffee<sup>[2]</sup>.

Considerable attention has been focused on the possibility that coffee may increase the risk of heart disease<sup>[7,8]</sup>, particularly since drinking coffee has been associated with increased low-density lipoprotein cholesterol levels<sup>[9]</sup> and short-term increases in blood pressure<sup>[10]</sup>.

The relationship between coffee consumption and risk of coronary heart disease (CHD) was first studied in the 1960s, given that the prevalences of both coffee drinking and CHD were high in Western countries<sup>[11]</sup>. Short-term metabolic studies found that caffeine ingestion acutely induces cardiac arrhythmias and increases plasma renin activity, catecholamine concentrations, and blood pressure<sup>[12,13]</sup>. In the 1980s, cross-sectional studies found a positive association between coffee consumption and serum total cholesterol concentrations, which might be related to the coffee brewing method (ie, boiled or unfiltered coffee)<sup>[14]</sup>. A later randomized trial showed that boiled coffee consumption increased serum cholesterol<sup>[15]</sup>. From the 1980s to the 2000s, many case-control studies, which are prone to recall and selection bias, showed a positive association between coffee consumption and CHD risk<sup>[7,8,16]</sup>. In contrast, meta-analyses of prospective cohort studies tended to find no association, although results varied substantially across studies<sup>[17-19]</sup>.

Since 2000, the associations between coffee consumption and other cardiovascular disease (CVD) outcomes such as stroke, heart failure, and total CVD mortality have also been more frequently studied<sup>[1,20,21]</sup>. Meta-analyses have been published to summarize the association between coffee and risk of CHD<sup>[22]</sup>, stroke<sup>[23]</sup>, and heart failure<sup>[24]</sup>, and these meta-analyses did not support an association between coffee consumption and a higher CVD risk.

Additional studies have been published since the publication of these meta-analyses<sup>[1,20,21,25-27]</sup>, and another recent meta-analysis showed that heavy coffee consumption was not associated with risk of CVD mortality<sup>[25]</sup>. Therefore, the association between coffee consumption and CVD risk remains unclear.

## 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<sup>[2]</sup>.

Coffee accounts for 71% of caffeine intake among American adults (soft drinks are the primary source of caffeine for children and adolescents)<sup>[29]</sup>. The caffeine content of coffee is highly variable, even when the coffee beverage is obtained from the same outlet<sup>[30]</sup>. 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<sup>[31]</sup>. Brewed decaffeinated coffee still contains caffeine, albeit at much lower doses that usually range from 5 to 15 mg per 8 oz.

## COFFEE AND BLOOD PRESSURE

Coffee consumption has been associated with acute increases in blood pressure (BP) in caffeine-naïve people but exerts negligible

effects on the long-term levels of BP in habitual coffee drinkers<sup>[32]</sup>. The acute effects of coffee are transient, and, with regular intake, tolerance develops to the hemodynamic and humoral effects of caffeine<sup>[33]</sup>.

A recent meta-analysis showed no clinically important effects of long-term coffee consumption on BP or risk of hypertension (HTN)<sup>[34]</sup>, and the Nurses' Health Study also demonstrated that daily intake of up to 6 cups of coffee was not associated with an increased risk of HTN<sup>[35]</sup>.

Furthermore, caffeine is the major acute BP-increasing compound found in coffee but other compounds present in coffee may counteract these acute pressor effects: in consequence, caffeine is not solely responsible for the cardiovascular effects associated with short and long-term coffee consumption<sup>[36]</sup>.

## COFFEE AND CARDIOMETABOLIC DISEASE

Antioxidants in coffee, such as chlorogenic acid, have been recognized to improve glucose metabolism and insulin sensitivity<sup>[37]</sup>. A recently published randomized study found that consumption of 5 cups of coffee per day increased adiponectin levels and decreased insulin resistance<sup>[38]</sup>. Caffeine acutely activates 50-adenosine monophosphate-activated protein kinase and insulin-independent glucose transport in skeletal muscle<sup>[39]</sup>. A systematic review with meta-analysis showed that the risk of the development of type 2 diabetes mellitus (T2DM) was lowest in subjects who drank >6 cups daily and also was significantly reduced for subjects who consumed 4 to 6 cups Daily<sup>[40]</sup>. Furthermore, a prospective study established a linear relationship of coffee consumption with the reduction in T2DM, whereby even small amounts of coffee on a daily basis conferred benefit<sup>[41]</sup>. Associations were similar for decaffeinated and caffeinated coffee.

Coffee contains cholesterol-increasing compounds classified as diterpenes, including cafestol and kahweol<sup>[42]</sup>. 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. In a study of 107 young adults with normal cholesterol levels followed for 12 weeks a significant increase in total cholesterol and a nonsignificant increase in low-density lipoprotein (LDL) cholesterol were observed in participants consuming boiled coffee, whereas 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<sup>[43]</sup>, and these results were replicated in a meta-analysis and in a large cohort study<sup>[44,45]</sup>.

## COFFEE AND CARDIOVASCULAR DISEASE

Although some early studies<sup>[7,8]</sup>, probably flawed by unmeasured confounding<sup>[1,46]</sup>, suggested coffee consumption might cause adverse cardiovascular effects, many epidemiological studies have evaluated the potential effects of coffee on CHD generally showing neutral effects. In particular, the meta-analysis performed by Wu *et al.*<sup>[19]</sup> including 21 independent prospective cohort studies from January 1966 to January 2008 suggested that moderate coffee consumption may decrease the long-term risk of CHD: 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.

Furthermore, several studies have suggested that it is safe for patients with established CHD to continue their habitual coffee consumption<sup>[47,48]</sup>: coffee ingestion was associated with an increase in parasympathetic tone<sup>[47]</sup> and a decrease in high-sensitivity C-reactive protein levels<sup>[48]</sup>.

In regard to congestive heart failure (CHF), a recent large meta-analysis performed by Mostofsky *et al.*<sup>[24]</sup> reported a J-shaped relationship between coffee consumption and the incidence of CHF: 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, with no evidence that the relationship varied by sex or by baseline history of myocardial infarction or diabetes.

Data linking coffee consumption to increased risk of arrhythmias are inconsistent. 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 recent Kaiser Permanente study of adults living in California, an inverse relationship between habitual coffee consumption and risk of hospitalization for arrhythmia was observed during long-term follow-up, and the authors concluded that people who drank 4 cups of coffee per day tended to have fewer cardiac arrhythmias, including less atrial fibrillation (AF)<sup>[49]</sup>. Moreover, controlled interventional studies and placebo-controlled trials show that in normal adults even high-dose caffeine in isolation does not affect prevailing cardiac rhythm and rate and also does not cause and/or worsen clinically significant ventricular or supraventricular arrhythmias<sup>[50-52]</sup>. In the Women's Health Study, In the Danish Diet, Cancer, and Health study, and in the Framingham Heart Study caffeine consumption was not associated with the risk of the development of AF or flutter<sup>[53-55]</sup>.

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<sup>[49]</sup>.

## COFFEE AND STROKE

Coffee may reduce the risk of ischemic stroke. A recent meta-analysis performed by D'Elia *et al.*<sup>[53]</sup> demonstrated that 1 to 3 and 3 to 6 cups of coffee per day were associated with a decreased risk of stroke, whereas habitual consumption of >6 cups of coffee per day was not associated with any effect on stroke risk, and 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<sup>[56]</sup>. In the Swedish Mammography Cohort<sup>[57]</sup> the findings also suggested that coffee consumption was associated with a statistically significant lower risk of stroke, and the inverse association of coffee consumption and mortality from stroke was also observed in a diabetic population<sup>[58]</sup> and in the Nurses' Health Study<sup>[59]</sup>. Exactly how coffee lowers the risk of stroke is unknown, but postulated mechanisms include coffee's anti-inflammatory and insulin-sensitizing effects<sup>[60-62]</sup>.

## COFFEE AND MORTALITY

In the National Health and Nutrition Examination Survey I<sup>[63]</sup>, 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 risk of adverse cardiovascular events and heart disease mortality.

In another study performed by Lopez-García *et al.*<sup>[64]</sup> an inverse association between coffee consumption and all-cause mortality was seen mainly due to a moderately reduced risk of CVD mortality and was independent of caffeine intake; decaffeinated coffee was also associated with a small reduction in all-cause and CVD mortality.

Furthermore, in the recent National Institutes of Health-AARP Diet and Health Study<sup>[11]</sup>, after adjustment for tobacco smoking and other potential confounders, men who drank  $\geq 6$  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.

## COFFEE AND THE "U-SHAPED" ASSOCIATION

A very recent meta-analysis performed by Ding *et al.*<sup>[65]</sup> demonstrated a nonlinear association between coffee consumption and risk of CVD (CHD and stroke): moderate coffee consumption (3-5 cups per day) was associated with lower CVD risk, and heavy coffee consumption ( $\geq 6$  cups per day) was neither associated with a higher nor a lower risk of CVD.

The authors suggest that this kind of relationship might be due to a combination of beneficial and detrimental effects: for moderate coffee consumption, beneficial effects may be greater than adverse effects, whereas for heavy consumption detrimental effects may counterbalance beneficial effects.

Furthermore, no significant association between decaffeinated coffee consumption and CVD risk was observed: nevertheless, the consumption of decaffeinated coffee was much lower than caffeinated coffee and individuals with hypertension or other CVD-related conditions might switch from regular coffee to decaffeinated coffee.

## COFFEE AND OTHER HEALTH EFFECTS

Coffee may reduce the risk of depression, a known risk factor for the development of CVD, as well as an independent predictor of poor prognosis<sup>[66]</sup>: the effect may be due largely to the caffeine content because women consuming decaffeinated coffee did not show a reduced risk<sup>[67]</sup>.

Coffee consumption may also benefit efforts at weight control, increasing the thermic effect of food and fat oxidation in normal-weight subjects<sup>[68]</sup>.

Other beneficial health effects may include reduced risks of Alzheimer's dementia<sup>[69,70]</sup> and other diseases of the central nervous system including Parkinson's disease<sup>[71-73]</sup>. Additionally, coffee may improve asthma symptoms<sup>[74]</sup>, enhance performance in sustained high-intensity exercise<sup>[75]</sup>, prevent symptomatic gallstones<sup>[76]</sup> and be associated with protection against some infectious and malignant diseases, particularly of the liver<sup>[77-79]</sup>.

In contrast, many individuals experience palpitations, anxiety, tremulousness, and trouble sleeping after drinking coffee, particularly when it contains higher doses of caffeine<sup>[80]</sup>. Moreover, caffeinated coffee increases the risk of bone loss and fractures, even if 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 and also that a daily glass of milk might offset the calcium loss and reductions in bone mineral density due to coffee consumption<sup>[81-83]</sup>.

Furthermore, 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<sup>[84,85]</sup>.

## CONCLUSION

According to the existing literature, the currently available evidence on cardiovascular 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 cardiovascular risk or CVD. Those with dyslipidemia may consider brewed and filtered coffee as opposed to preparations made from boiling beans without filtering. A daily intake of ~2-3 cups of coffee appears to be safe and is associated with neutral to beneficial effects for most of the studied health outcomes.

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. On the other hand, Decaffeinated coffee may be a good option, particularly because many of coffee's potential benefits likely derive from sources other than its caffeine.

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.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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