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AHA SCIENTIFIC STATEMENT

Caffeine and Cardiovascular Disease: A Scientific Statement From the American Heart Association

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ABSTRACT: Caffeine is one of the most commonly consumed drugs in the world. It is found in various naturally occurring substances and can be ingested in a synthetically derived pure form. The majority of human subject–based research is observational and has focused on beverages and foods that contain caffeine. The relationships between caffeine and cardiovascular risk factors and diseases are complex, exhibiting heterogeneity depending on the nature of the caffeine consumed and individual-level propensities. Acute versus chronic caffeine-associated cardiovascular effects are often different. Most studies suggest an inverse J-shaped relationship between consumption of naturally occurring caffeinated products and blood pressure. Data on relationships between caffeine and diabetes are not consistent, but habitual coffee consumption has been associated with a lower risk of incident type 2 diabetes. Whereas no clear relationship between caffeine and blood lipids is evident, unfiltered coffee raises low-density lipoprotein cholesterol. Caffeine, studied primarily in the context of coffee, has been shown either to have no relationship or to be associated with a lower risk of coronary artery disease and heart failure. Randomized controlled trial data among regular caffeinated coffee drinkers showed that caffeinated coffee decreases the risk of atrial fibrillation occurrence but increases the frequency of premature ventricular contractions. Data are fairly consistent that moderate caffeine consumption, again studied primarily in the setting of coffee consumption, was associated with a lower risk of stroke. Data on high doses of caffeine such as that found in energy drinks are limited and generally suggest cardiovascular harm.

Key Words: AHA Scientific Statements ■ arrhythmias, cardiac ■ caffeine ■ cardiology ■ coffee ■ heart failure ■ hypertension ■ myocardial infarction

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Caffeine is one of the most commonly consumed drugs in the world. The science evaluating the effects of caffeine on human health must be considered in the context of several complicating factors. First, although caffeine is available by prescription in a pure form, it is most commonly consumed within foods or beverages, often making distinguishing effects inherent to caffeine from those of the constituents in which it travels difficult if not impossible. Indeed, because much of the related literature focuses on coffee (the most commonly consumed beverage in the United States[1]), much of this scientific statement is dedicated to describing literature pertinent to cardiovascular health that can be attributed to coffee rather than caffeine per se. Second, caffeine affects multiple organs and, even within the cardiovascular system, has myriad effects. Third, individuals can metabolize caffeine at different rates, depending on both inherited genetic variants and prior patterns of exposure. Last, investigators have used various study designs to understand its health effects, each with their own pros and cons worthy of careful consideration. The majority of studies have used observational study designs prone to unmeasured and residual confounding, with a few but growing number of randomized controlled trials to provide more definitive evidence.

MECHANISMS AND PHARMACOLOGY

With use dating as far back as 2737 BC, caffeine is the world's most popular stimulant and psychoactive substance. Today, >60 different plant species, including cacao beans and tea leaves, naturally contain caffeine in varying

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degrees; however, caffeine can also be found in many over-the-counter, prescription, and other commercially available food products (Table 1).[2] Caffeine is a methylxanthine derivative with alkaloid properties that can be administered orally, intravenously, topically, or rectally. As a result of its 100% oral bioavailability and high hydrophilicity, caffeine rapidly undergoes dissolution and is absorbed on consumption, reaching peak concentrations in 1 hour (Table 2).[3,4] Because of its minimal first-pass metabolism, caffeine exhibits a linear pharmacokinetic profile, meaning increasing doses result in proportionate increases in caffeine blood levels. In addition, caffeine is lipophilic enough to cross all biological membranes, including the blood-brain and placental barriers. Although caffeine does not accumulate in tissues or organs, high concentrations of caffeine (up to 80%) can be found in the brain.[3]

As shown in Figure 1, caffeine is extensively metabolized by hepatic cytochrome P450 (CYP) isoenzymes CYP1A2 and CYP2C9, leading to oxidative N-demethylation and resulting in paraxanthine (80%), theobromine (11%), and theophylline (4%), each of which has biological activity similar to that of caffeine. The primary route of elimination for caffeine and its metabolites is by the kidneys through urine excretion. Only a small percentage (<3%) of caffeine is excreted unchanged from the body; most of the caffeine molecules are reabsorbed back into the bloodstream by the renal tubules. Moreover, caffeine elimination is dose dependent and follows the Michaelis-Menten kinetics, meaning that at low to moderate caffeine concentrations, caffeine exhibits first-order kinetics, but at higher concentrations, it follows zero-order kinetics. Hence, at higher concentrations, the decline of caffeine concentrations occurs over longer periods of time. Ultimately, caffeine and its metabolites are excreted primarily in the urine as uric acid and minimally through sweat and feces.[3,5,6]

Food consumption, particularly meals high in fat or fiber, can delay the onset of caffeine and reduce the peak concentration in the blood by slowing gastric emptying. In addition, different types and volumes of food consumed and the composition of the caffeine delivery matrix (eg, infused coffees or teas, energy bars or gels, and sodas or energy drinks) can affect the rate of caffeine absorption and bioaccessibility. For example, compared with tea and coffee, caffeine absorption from soft drinks occurs at a slower rate.[3] The composition of energy drinks such as through the presence of ingredients such as taurine increases the solubility, absorption, and onset of action of caffeine.[7]

Caffeine has different biochemical targets and several mechanisms through which it exerts its effects: (1) antagonism of adenosine receptors, (2) inhibition of the phosphodiesterase enzyme, (3) calcium release from intracellular stores, and (4) antagonism of $GABA_A$ receptors. Table 3 summarizes the pharmacological effects based on its target tissues.[3,5,6]

Table 1. Concentrations of Caffeine in Commercial Food Products, Over-the-Counter/Supplement Medications, and Prescription Medications

Example	Caffeine content
Commercial food products	
Coffee, caffeinated	
Regular, brewed, nonspecialty	9.4–20.6 mg/fluid oz
Specialty coffees, all	7.9–15.8 mg/fluid oz
Cappuccino	9.3–15.8 mg/fluid oz
Café au lait or latte	9.3–11.9 mg/fluid oz
Mocha or other flavored syrup	10.6 mg/fluid oz
Ready to drink, bottles or cans	4.1–9.5 mg/fluid oz
Coffee, decaffeinated	
All types, including regular, brewed, specialty, brand or brand not specified, ready to drink, bottles, or cans	0.25 mg/fluid oz
Colas/soft drinks	
All types, caffeinated, regular or diet, including flavors	3.0–5.8 mg/fluid oz
Citrus, all types, caffeinated	4.6–5.9 mg/fluid oz
Other, all types, regular or diet	1.9–6.9 mg/fluid oz
Tea	
Black, all types, brewed, caffeinated, brand or no brand specific	5.9 mg/fluid oz
Green, all types, brewed, caffeinated, brand or no brand specified	3.1 mg/fluid oz
White, all types, brewed, caffeinated, brand or no brand specified	1.9 mg/fluid oz
Energy drinks	
Drinks, all types, bottles or cans, diet or regular	3.4–20.5 mg/fluid oz
Shots, all types	40.0–69.0 mg/fluid oz
Chocolate	
Chocolate milk, prepared from powered mix	0.3–1.5 mg/fluid oz
Cocoa, restaurant/coffee house/homemade	0.8–1.6 mg/fluid oz
Over-the-counter/supplements	
Alka-Seltzer Hangover Relief	130 mg/2 tablets
Bayer Back and Body	70 mg/2 capsules
Excedrin Migraine	130 mg/2 gel–tabs
Excedrin Tension Headache	130 mg/2 capsules
Midol Complete	120 mg/2 capsules
Hydroxycut Hardcore	265 mg/2 capsules
NoDoz	200 mg/1 capsules
Vivarin	200 mg/1 tablet
Prescription medications	
Butalbital/aspirin/caffeine	40 mg/capsule
Orphenadrine citrate/aspirin/caffeine	30 mg/capsule (standard tablets) 60 mg/capsule (forte or extra strength)

Although much of the evidence on caffeine derives from studies of coffee consumption, coffee contains numerous bioactive compounds beyond caffeine, including chlorogenic acids, diterpenes, trigonelline, and

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Table 2. Summary of the Pharmacokinetics of Caffeine

Pharmacokinetic properties	Comments
Absorption	
Oral	20% through stomach, 80% through GI tract (99%–100% bioavailability)
Rectal	Highly variable; topical caffeine has high skin permeability because of its small molecule size
Topical	Absorption rate of 2.24 $\mu g \cdot cm^{-1} \cdot h^{-1}$ in which hair follicles shunt into bloodstream within 5 min
Onset	After 30–45 min, passes into bloodstream; after 1–2 h with topical formulations Peak concentrations reached in 1 h (which can be delayed by food)
Distribution	
Protein binding	10%–30% bound to plasma proteins (eg, albumin)
Volume of distribution	0.7 L/kg
Tissue distribution	Crosses blood-brain barrier and the placental barrier Actively passes into the brain (80%), breastmilk, and placenta
Metabolism	
Hepatic metabolism	Metabolized extensively by CYP1A2 and CYP2C9 through demethylation into active metabolites: theobromine, theophylline, and paraxanthine
Half-life	2–12 h (4–5 h in healthy adults)
Factors affecting metabolism	Smoking cigarettes induces CYP1A2 through polycyclic aromatic hydrocarbons and thus increases metabolism while decreasing the half-life of caffeine; pregnancy reduces CYP1A2, leading to slower metabolism and a longer half-life
Elimination	
Kidney	Primary route of elimination is through urine; 98% of caffeine and metabolites are reabsorbed in the renal tubules and affected by renal blood flow and urine output
Feces, sweat, saliva	These modes of elimination are not significant forms or effective because only a small percentage is eliminated

CYP indicates cytochrome P450 isoenzyme; and GI, gastrointestinal.

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melanoidins. In large cohort studies, inverse associations between coffee intake and risk of type 2 diabetes and cardiovascular disease have also been observed for decaffeinated coffee, supporting a role for noncaffeine components.[8,9] Experimental studies conducted in animals and humans suggest that the bioactive compounds in coffee have antioxidant and anti-inflammatory properties and may improve insulin sensitivity, endothelial function, and glucose metabolism, partly through effects on the gut microbiota.[10]

GENETICS

The estimated heritability of caffeine consumption and symptoms of caffeine tolerance, toxicity, and withdrawal ranges from 30% to >50%.[11,12] Genetics also underlie the wide interindividual variation in the activity of CYP1A2, itself responsible for >95% of caffeine metabolism.[13–15] The most successful approach to identify specific genetic factors has been population-based genome-wide association studies of dietary caffeine (coffee, tea, total caffeine) consumption and plasma levels of caffeine metabolites. The strongest and most replicated single-nucleotide polymorphisms map to the biologically plausible genes *CYP1A2* and *AHR*.[16–22] Those with genetic variants associated with lower plasma caffeine metabolites also generally consume more caffeine, attributed to the fact that individuals with these variants would need more caffeine for the same psychostimulant effects.[15,19,23] These and multiple other single-nucleotide polymorphisms in various genetic regions have been associated with other behavioral patterns related to caffeine consumption, including preferences for black coffee (without added creamers) and decaffeinated coffee. Specific single-nucleotide polymorphisms and their relative contribution to caffeine behaviors and metabolism vary by populations because of differences in allele frequencies, as well as social or cultural factors and concomitant behaviors or medications affecting these traits.[11]

RELATIONSHIPS WITH CARDIOVASCULAR RISK FACTORS

Blood Pressure

Relationships between caffeine and blood pressure are complex, and the chronicity of use may result in divergent effects. For example, men with hypertension experienced a >1.5-fold increase in both systolic and diastolic blood pressures after the consumption of 250 mg caffeine compared with individuals with optimal blood pressure.[24] In contrast, a mendelian randomization analysis using data derived from the UK Biobank, the International Consortium for Blood Pressure Research, and the UK Blood Pressure Study revealed significantly lower systolic and diastolic blood pressures among those with genetic

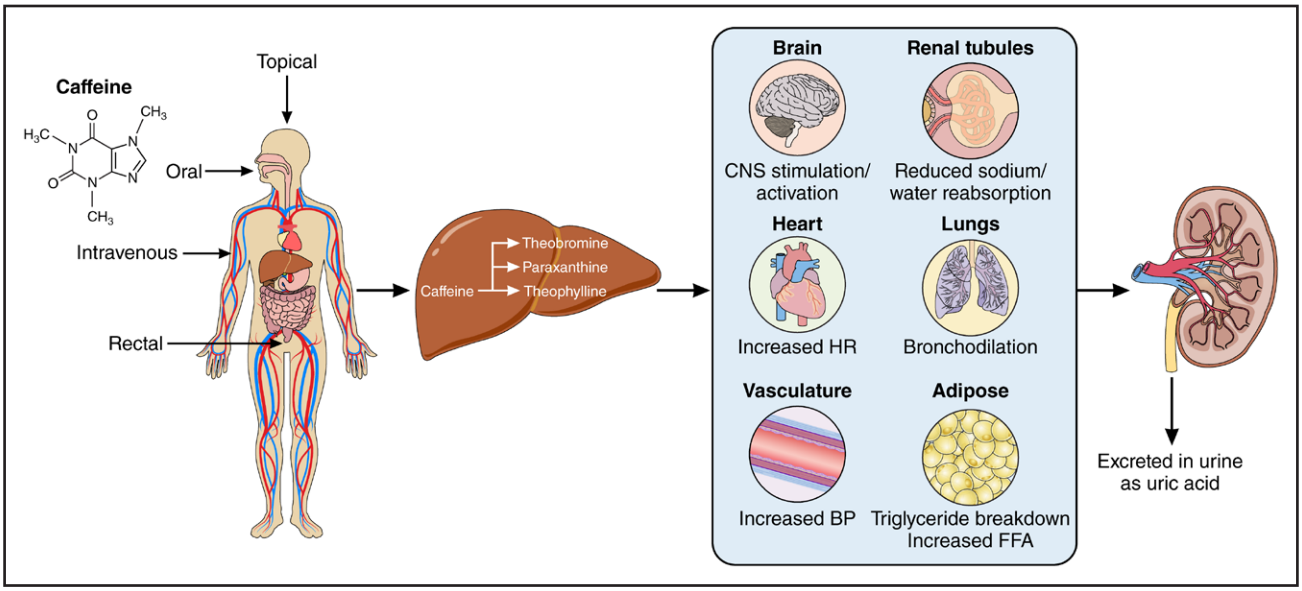


Figure 1. Summary of the metabolism of caffeine and its immediate effects on tissues.
BP indicates blood pressure; CNS, central nervous system; FFA, free fatty acids; and HR, heart rate.

variants expected to correspond to regular caffeine intake.[25] Indeed, prospective cohort studies with long-term follow-up have revealed an inverse J-shaped association of habitual coffee consumption with the risk of hypertension, demonstrating an increased risk with intake of 1 to 3 cups/d but a trend toward a decreased risk with higher consumption.[26] The long-term effects of habitual caffeine consumption on blood pressure remain unclear and are likely minimal, although the risk may increase with high intake, particularly among individuals with severe hypertension or heightened sensitivity, because regular use can lead to tolerance.[27]

Consumption of energy drinks containing high concentrations of caffeine has been shown to result in significant increases in both systolic and diastolic blood pressures in healthy adults.[28] In contrast, green coffee bean extract has been shown to decrease both systolic and diastolic blood pressures in adults, particularly among individuals with elevated baseline levels.[29] These contrasting outcomes may be attributed to differences in caffeine concentration and the presence of other bioactive compounds such as taurine in energy drinks and chlorogenic acid in coffee with opposing effects on blood pressure.[28,29]

Consuming energy drinks before exercise has been shown to elevate submaximal systolic blood pressure in healthy individuals, and this effect may pose a greater risk for those with hypertension.[30] Furthermore, findings from a recent double-blind, randomized, placebo-controlled trial indicated that habitual pre-exercise consumption of a moderate daily doses (1.9±0.34 mg/kg) of a caffeine-based supplement attenuated exercise-induced reductions in blood pressure in young women.[31]

Diabetes

Although mechanistic studies suggest that caffeine may reduce insulin sensitivity in the short term, the majority of studies examining caffeine and diabetes risk have focused on coffee consumption and reveal predominantly salutary effects. Habitual coffee consumption has been consistently associated with a lower risk of type 2 diabetes in observational cohort studies, revealing significant dose-dependent reductions in disease risk. A review of 28 prospective cohort studies noted a 20% and 30% decreased risk of type 2 diabetes among people who, on average, consumed 3.5 and 5 cups/d, respectively.[8] The European Prospective Investigation Into Cancer and Nutrition demonstrated a 27% lower risk of type 2 diabetes among 69 532 women who consumed ≥3 cups of coffee compared with those who did not consume coffee.[32] In another large cohort consisting of both sexes, associations were in a similar direction for higher total coffee consumption and for caffeine intakes of 126 to 400 mg/d.[33] It is important to note that these findings may be more specific to coffee than to caffeine: In the Health Professionals and Nurses' Health Study of more than 100 000 women, coffee consumption was associated with reduced incidence of type 2 diabetes, regardless of caffeine content.[34]

Although observational cohort studies consistently report strong inverse associations with type 2 diabetes, data from (predominantly acute) clinical trials are inconsistent.[8,35] In a review including 8 clinical trials (n=247), results were analyzed 1 to 3 hours after coffee intake and over 2 to 16 weeks.[35] Although improvements in blood glucose was observed for the long term, there

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 Circulation. 2026;154:e00–e00. DOI: 10.1161/CIR.0000000000001454

Table 3. Summary of the Pharmacology of Caffeine by Mechanism of Action

Mechanism of action	Comment
Antagonism of adenosine receptors	Blocks adenosine A1 and $A2_A$ receptors nonselectively, thus antagonizes and inhibits adenosine stimulation of the receptors
	Observed with typical levels of caffeine consumption
	Binding of adenosine to the receptors in the central nervous systems will promote drowsiness
Inhibition of phosphodiesterase	Minimal at normal levels of consumption but is more commonly observed at higher doses
	At higher doses, caffeine will inhibit phosphodiesterase activity, preventing the breakdown of cAMP and leading to accumulation and increased duration and effects of cAMP action
	High cAMP levels activate the hormone-sensitive lipase in the adipose tissue, which is required for lipolysis, thus promoting lipolysis, which causes the release of fatty acids and glycerol
Calcium release	Occurs at very high, nonphysiological concentrations (beyond average consumption)
	Causes the release of stored calcium from cellular sarcoplasmic reticulum and translocation of calcium, resulting in a decrease in intracellular calcium accumulation
	Affects neurotransmission because synaptic transmission depends on calcium influx into nerve endings
	In muscle tissue, restricts calcium uptake and storage by the sarcoplasmic reticulum; this action results in an increase in the strength and endurance of cardiac and skeletal muscles
Antagonism of $GABA_A$ receptors	Not common; occurs only at toxic levels
	Weak binding affinity to the benzodiazepine receptors and weak antagonistic effects on the $GABA_A$ receptors
	Changes and opposes the effects of benzodiazepines
Other peripheral effects	Blocks adenosine receptors in myocardial pacemaker cells, thus removing the braking effect of adenosine, leading to activation of cAMP and increased HR
	Stimulates the central sympathetic nervous system, thus increasing peripheral vasoconstriction and BP
	Inhibits sodium and water reabsorption in the renal tubules, thereby increasing urine output and possible dehydration
	Relaxes smooth muscle in bronchioles, opening airways, while also stimulating GI and colonic smooth muscle cells, thus promoting bowel movements, all of which is contributed by actin depolymerization
	Increases gastric acid secretion in the stomach by stimulating gastrin release and H_2 receptors, which can worsen ulcers
	Triggers the breakdown of triglycerides and release of free fatty acids, thus altering lipid metabolism
	Enhances muscle contraction strength by increasing calcium ion release from the sarcoplasmic reticulum, which can enhance athletic performance

BP indicates blood pressure; GI, gastrointestinal; H2, histamine type 2 receptor; and HR, heart rate.

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was a suggestion of acute detrimental effects immediately after caffeinated coffee consumption. Similarly, in a study of 45 Japanese participants with overweight, no improvement in glucose tolerance was reported after 8 weeks of 5 daily cups of caffeinated or decaffeinated coffee compared with water, but a small reduction was observed after 16 weeks.[36] Among 100 volunteers, daily randomization to caffeinated coffee versus caffeine avoidance failed to reveal any differences in mean daily glucose.[37,38]

The mechanisms underlying these observations may also be linked to constituents in coffee, unrelated to caffeine. Coffee contains chlorogenic acid, a polyphenol that improves glucose metabolism,[39] and 2 micronutrients, magnesium and chromium, both linked to insulin sensitivity and lower blood glucose concentrations.

Lipids

Consumption of unfiltered coffee raises serum cholesterol concentrations as a result of the coffee component cafestol.[40] In double-blind, placebo-controlled, randomized trials, cafestol capsules,[40] but not caffeine capsules,[41] increased low-density lipoprotein cholesterol concentrations. Cafestol is present in unfiltered coffee, including French press, Greek/Turkish, and Scandinavian boiled coffee, and to a lesser extent in espresso-based and Moka coffee.[40] However, cafestol is not present in substantial amounts in paper-filtered or instant coffee. Indeed, high consumption of unfiltered coffee consistently increased serum cholesterol in randomized trials, whereas consumption of filtered coffee did not.[42] Espresso-based coffee contains a smaller amount of cafestol than unfiltered coffee[40] and has been associated with modestly higher serum cholesterol concentrations.[43]

RELATIONSHIPS WITH CARDIOVASCULAR DISEASES

Arrhythmias

Observational studies and related meta-analyses have generally demonstrated that caffeine and caffeinated coffee consumption is associated with either no difference in risk or a lower risk for atrial fibrillation (AF), particularly in regular and moderate amounts (eg, 1–7 times a week and 1–3 cups of caffeinated coffee per day).[44,45]

Mendelian randomization studies similarly reveal no anticipated heightened risk of AF.[46,47] Among patients with AF who consumed at least 1 cup of caffeinated coffee at some point in the past 5 years scheduled for elective cardioversion, randomization to consume at least 1 cup of caffeinated coffee per day compared with avoidance of coffee and caffeine led to a statistically significant 39% reduced risk of recurrent AF.[48] Substantially fewer studies have focused on caffeinated tea and AF, with some suggestion that green tea consumers may experience a lower odds of AF.[49] It is important to note that multiple case reports and small case series have described acute episodes of AF in otherwise low-risk individuals (including young healthy people in their 20s) shortly after consuming caffeinated energy drinks.[50] On the whole, these data have resulted in a Class 3 recommendation in the updated American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines (albeit written before the randomized controlled trial data), admonishing clinicians to avoid recommending against caffeine consumption in order to reduce the risk of AF.[51]

Even fewer studies have focused on supraventricular tachycardia, comprising atrioventricular nodal reentrant tachycardia, atrioventricular reciprocating tachycardia, and atrial tachycardia, with the evidence favoring a reduced risk among caffeine consumers.[46]

Studies have generally revealed no relationship between caffeine when consumed in amounts found in natural substances such as coffee and tea and premature atrial contractions,[52] including a randomized controlled case-crossover study of caffeinated coffee examining premature atrial contraction frequency as the primary outcome.[38] In contrast, although several observational studies have failed to demonstrate a relationship between caffeinated beverages and premature ventricular contraction frequency, randomized trials have shown that caffeine, even when ingested in beverages in amounts commonly consumed in the general population, can increase premature ventricular contractions.[38,53]

Caffeinated coffee has been associated with a lower risk of ventricular tachycardia in a large cohort study.[46] However, extremely high doses of caffeine, such as when consumed in capsule or powder form in amounts >10 times that found in a typical cup of coffee, have been reported to result in ventricular fibrillation and sudden death in multiple individual case reports.[54,55]

Although bradyarrhythmias result in substantial morbidity, often require pacemaker implantation, and may have lethal consequences, relationships between either short-term use or long-term consumption of caffeine and such outcomes have not been rigorously examined.

Potential antiarrhythmic mechanisms of caffeine include vagolytic effects that may be especially relevant to AF, diuretic effects that may related to lowering of blood pressure, blockage of adenosine receptors, and anti-inflammatory effects.[56–60]

Coronary Artery Disease

The results of early epidemiological studies raised the concern that coffee consumption may increase the risk of coronary artery disease (CAD). However, more rigorous prospective studies conducted in recent decades did not confirm these results.[9] In a meta-analysis of 30 prospective cohort studies, consumption up to 6 cups of coffee per day was not associated with a higher risk of CAD. Furthermore, light (median, 1.5 cups/d) and moderate (median, 3.5 cups/d) coffee consumption was associated with an ≈10% lower CAD risk.[9] Similarly, a recent analysis in the UK Biobank showed that consumption of up to 5 cups of coffee per day was associated with a lower risk than nonconsumption, with the lowest risk for 2 to 3 daily cups.[56] Modest decaffeinated coffee consumption was also associated with a lower CAD risk in prospective cohorts.[56,61] Moreover, genetic predisposition to higher blood caffeine levels was not associated with CAD risk and did not modify the association between coffee consumption and CAD risk.[62] These findings suggest that caffeine intake within the commonly consumed range does not affect the risk of CAD but that other coffee components may slightly reduce CAD risk. Consistent with results for generally healthy populations, coffee consumption was not associated with a higher risk of cardiovascular diseases or mortality in individuals with a history of myocardial infarction.[63]

Heart Failure

Caffeine has various potential physiological effects that could influence heart failure risk. Although caffeine-induced changes in sympathetic tone, vascular resistance, and inotropy have been hypothesized, these effects are largely speculative and have not been rigorously studied, especially in the setting of chronic caffeine ingestion. Similarly, the association between caffeine and heart failure has not been evaluated in a randomized fashion.

Examination of the relationship between chronic caffeine consumption and heart failure risk has thus far been limited to large observational cohort studies. These studies were conceived to quantify the association between various exposures and cardiovascular outcomes; none were specifically designed to study the association between caffeine ingestion and heart failure risk. In addition, such investigations typically relied on administrative coding to identify heart failure outcomes, often limiting differentiation between heart failure with a reduced and heart failure with preserved ejection fraction. Last, most studies have focused primarily on coffee consumption, not overall caffeine ingestion.

Although an early observational study suggested an increased risk of heart failure with consumption of ≥5 cups of coffee per day,[64] multiple subsequent cohort studies, including the Physician's Health Study,[65] Swedish Mammography Cohort,[66] UK Biobank,[67] Framingham

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Heart Study,[68] Cardiovascular Health Study,[68] and Atherosclerosis Risk in Communities study,[68] have observed either no risk or a moderately lower risk of heart failure with chronic coffee consumption. In several studies, the association between coffee consumption and heart failure was not linear; after combining data from multiple cohorts, a meta-analysis has demonstrated a J-shaped curve with less heart failure observed with low to moderate coffee consumption.[69] The lowest heart failure risk was observed for ≈4 cups of coffee per day. Cohort-specific analyses that estimated overall daily caffeine consumption by combining all dietary sources (including tea) have similarly demonstrated a lower heart failure risk with higher daily caffeine intake.[68] Consistent with these results, an analysis of participants in the CARDIA study (Coronary Artery Risk Development in Young Adults) revealed that low to moderate daily coffee consumption from early adulthood to middle age was associated with better left ventricular systolic and diastolic function in midlife, whereas high daily coffee consumption (>4 cups/d) was associated with worse left ventricular function.[70]

Stroke

Evidence indicates a nuanced relationship between caffeine and caffeine-containing beverages and the risk of stroke. Mendelian randomization studies have found no causal link between plasma caffeine concentrations[71] or caffeine intake.[72] In contrast, observational cohort studies have generally found a lower risk of total and ischemic stroke among coffee drinkers compared with nondrinkers or those with low intake.[73] A dose-response meta-analysis of 20 cohort studies revealed a U-shaped association between coffee consumption and the risk of stroke, with the lowest risk observed at moderate coffee consumption (3–4 cups/d), corresponding to a 21% risk reduction.[73] In terms of coffee type, an inverse association was found for caffeinated coffee (based on 5 studies), whereas no significant association was observed for decaffeinated coffee (based on 3 studies).[73] However, a more recent analysis based on the UK Biobank showed that consumption of 4 or 5 or more cups of ground, instant, and decaffeinated coffee was associated with a lower risk of incident ischemic stroke.[56] Evidence from cohort studies also indicates a modest inverse association between tea consumption and stroke risk, with similar association for black and green tea.[74]

CLINICAL AND PUBLIC HEALTH IMPLICATIONS

The convergence of evidence from large cohort studies and small randomized controlled trials supports the conclusion that moderate caffeine or coffee consumption (up to 400 mg/d caffeine or ≈3–5 cups of coffee at 8 oz per cup) is safe for most adults and is associated with lower risk of cardiovascular disease, including coronary heart disease, stroke, heart failure, and AF, as well as hypertension and type 2 diabetes. Indeed, large prospective cohort studies with long-term follow-up consistently demonstrate modest inverse associations between habitual coffee consumption and all-cause mortality across diverse populations. These associations are typically nonlinear, with the lowest mortality risk observed at moderate levels of intake (2–4 cups/d), and are generally robust after adjustment for smoking and other lifestyle factors.[75] Similar inverse associations have been reported for both caffeinated and decaffeinated coffee, supporting the contribution of noncaffeine bioactive components.

The conclusions of this scientific statement are largely consistent with those from previous authoritative reviews[57,76] and the 2015 Dietary Guidelines Advisory Committee report.[77] According to this evidence, habitual moderate coffee consumption can be part of a healthy lifestyle. Although coffee is the main source of caffeine for most adults, tea, coffee, chocolate, and energy drinks also contribute to overall caffeine intake. Acute effects of caffeine can include transient increases in blood pressure, blood sugar, and alertness, as well as palpitations or sleep disruption in some individuals. Individual differences in genetic variation in caffeine metabolism partially explain the variability in caffeine tolerance and clinical response, although there is insufficient evidence to demonstrate that they modify the effects of habitual coffee consumption on chronic diseases or mortality. Large amounts of added sugar, flavored syrups, and dairy products can substantially increase caloric intake and counteract potential health benefits associated with coffee itself. Last, as alluded to throughout this scientific statement, limitations of various study designs used should be considered in the interpretation of these results. For example, "healthy user bias" may be especially operative among research participants who consume substances such as caffeinated coffee in moderation.

CONCLUSIONS AND RESEARCH NEEDS

Caffeine has heterogeneous effects that can meaningfully affect cardiovascular risk factors and cardiovascular diseases themselves (Figure 2). Many studies suggest potential protective effects, but these often come from studies of coffee as a beverage rather than caffeine per se in what are usually observational cohort studies. Several areas of future research are worth pursuing, made all the more important given the near ubiquity of caffeine consumption among the general public. This includes more research using the randomized controlled trial design such as crossover or pragmatic trials whenever feasible. Research priorities include disentangling caffeine from other components of the beverages such as polyphenols, assessing individual differences in response, and examining dose-response and thresholds

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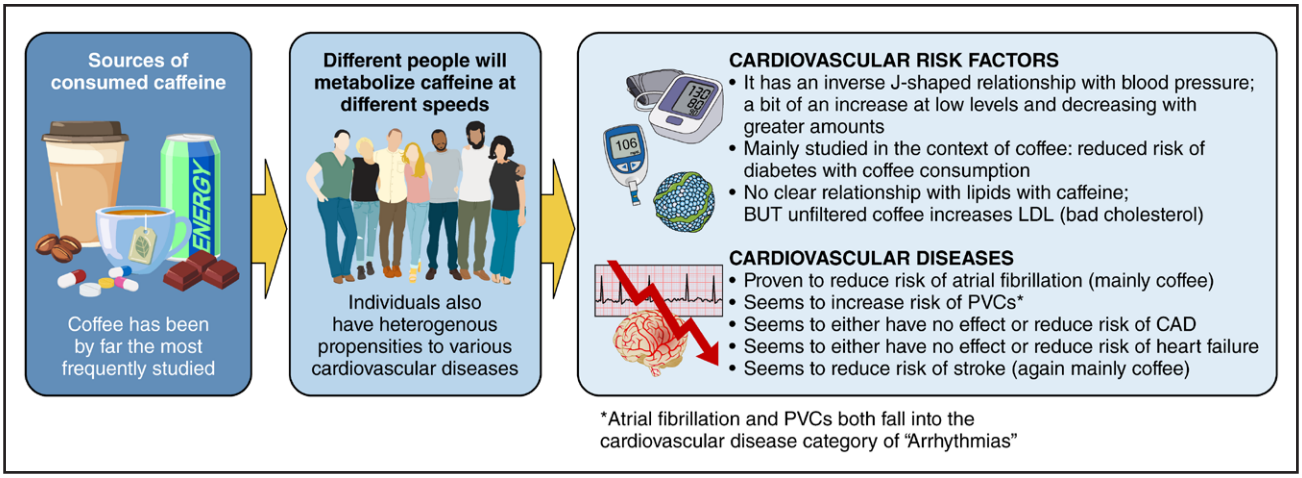


Figure 2. Relationships between caffeine, cardiovascular risk factors, and cardiovascular diseases.
CAD indicates coronary artery disease; LDL, low-density lipoprotein; and PVC, premature ventricular contraction.

in individuals with hypertension and other cardiovascular diseases. Because there is already substantial evidence of heterogeneous effects within individuals that may be genetically determined, elucidating those relationships will help the general public, health care professionals, and patients to tailor caffeine to individual risks and goals of care, improving risk stratification and personalization of recommendations. Potential health benefits that have been observed among individuals consuming caffeine that occurs in natural substances should not be extrapolated to synthetic products or high-dose caffeine. Indeed, although data on energy drinks are limited, available studies generally suggest cardiovascular harm. Last, in terms of applications of the potential beneficial effects of coffee intake, it is worth studying whether introducing or initiating regular coffee consumption among current abstainers yields positive cardiovascular health benefits.

ARTICLE INFORMATION

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This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on March 27, 2026, and the American Heart Association Executive Committee on May 28, 2026. A copy of the document is available at https://professional.heart.org/statements by using either "Search for Guidelines & Statements" or the "Browse by Topic" area. To purchase additional reprints, call 215-356-2721 or email Meredith.Edelman@wolterskluwer.com

The American Heart Association requests that this document be cited as follows: Marcus GM, Hu FB, van Dam RM, Cornelis MC, Dewland TA, Kang J, Larsson SC, Page RL II, Parekh N; on behalf of the American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Clinical Cardiology; and Stroke Council. Caffeine and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2026;154:e•••–e•••. doi: 10.1161/CIR.0000000000001454

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(*Continued*)

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

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This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

†Significant.

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