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Cardiovascular effects of caffeinated beverages ☆,☆☆

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ABSTRACT

Caffeine is the world's most popular 'drug', with tea and coffee a ubiquitous part of daily life. As a psychoactive stimulant, there are potential concerns regarding adverse cardiovascular squeal. Cardiovascular conditions, encompassing hypertension, coronary artery disease, rhythm disorders and heart failure affect billions of patients worldwide. We aim to provide a patient-centered comprehensive review of the cardiovascular effects of caffeinated beverages as they pertain to various common cardiovascular conditions. We conclude that intake of tea and coffee, particularly in moderate doses, does not appear to be harmful and may even be beneficial in a range of cardiovascular conditions, including coronary artery disease, heart failure and arrhythmias.

Introduction

Tea and coffee are consumed on a daily basis by more than half of the American population. Attention to modifiable lifestyle-related factors is an important approach to the management of cardiovascular disease. Generally there is a public perception that the physicians approach is to prohibit perceived pleasures in life such as alcohol, tobacco and "junk food" however the situation may be different for caffeine. Due to their 'stimulant' properties, some patients and physicians alike are cautious regarding the intake of caffeinated beverages particularly in the presence of cardiovascular disease. However the 2015–20 Dietary Guidelines for Americans report a reduction in the risk of type 2 diabetes and cardiovascular disease with the consumption of 3–5 cups of coffee per day. We provide a concise, patient-centered review of key studies to determine the interaction between various caffeinated beverages and a broad spectrum of cardiac conditions. We hope this review will help guide clinicians in appropriately counselling patients with a range of cardiovascular conditions regarding caffeine intake, in particular tea, coffee and energy drinks.

Methods

We performed a comprehensive literature search in July 2018 of EMBASE, Web of Science, Medline and PubMed focusing on human and animal studies published in English examining effects of caffeine on cardiovascular disease. Key search terms were 'caffeine, 'coffee, 'tea', 'energy drinks' in combination with 'diabetes', 'coronary artery disease', 'mortality', 'heart failure', 'arrhythmias', 'atrial fibrillation', 'sudden death', 'ectopy' and 'ventricular arrhythmias'. The highest quality studies were included in the review, encompassing prospective cohorts, interventional studies and meta-analyses.

Pharmacology of caffeine

Caffeine, a methylxanthine alkaloid, is the key constituent in tea (1 cup ~45 mg), coffee (1 cup ~95 mg) and energy drinks (which often contain higher concentrations). Peak concentrations are reached 1 h following intake, with a half-life of ~6 h. Table 1 summarizes the caffeine content of commonly consumed beverages. Caffeine interacts with different receptors in the cardiovascular system in a dose dependent manner. The physiological

Abbreviations: CAD, Coronary artery disease; RR, Relative risk; HR, Hazard ratio; OR, Odds ratio; CI, Confidence interval; RCT, Randomized controlled trial; AF, Atrial fibrillation and/or flutter; SCD, Sudden cardiac death; BP, Blood pressure.

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Table 1
Estimated caffeine content of commonly consumed beverages.

Beverage	Caffeine (g)	Volume (mL)
Cup of hot chocolate	10 mg	250 mL
Arizona green iced tea	15 mg	470 mL
Arizona black iced tea	32 mg	470 mL
Can of Coca Cola	32 mg	375 mL
Cup of Lipton green tea	35 mg	150 mL
Cup of Lipton black tea	55 mg	150 mL
Starbucks Café Latte – short	75 mg	236 mL
Red Bull Energy drink	80 mg	250 mL
Iced coffee	99 mg	500 mL
Espresso shot	106 mg	25 mL
Starbucks Café Latte – grande	150 mg	473 mL
Monster Energy drink	160 mg	473 mL
Wired X344 Energy drink	344 mg	473 mL
Fixx Energy drink	500 mg	591 mL

effects of caffeine on the cardiovascular system are summarized in Fig. 1.

While acute sympathomimetic effects are mediated by phosphodiesterase inhibition and increases in cytosolic calcium concentration and a rise in catecholamine activity, tolerance develops rapidly. Hence habitual consumption does not necessarily result in changes in heart rate, electrocardiogram parameters, heart rate variability nor cardiac output. Potential beneficial effects relate to selective inhibition of adenosine A_1 and A_{2A} receptors which may result in coronary vasodilation and anti-arrhythmic effects. Caffeine promotes expression of endothelial nitric oxide synthase, enhancing endothelial nitric oxide release which promotes vasodilation of vascular smooth muscle. Moreover, coffee contains polyphenols (e.g. chlorogenic acid) while tea is rich in the catechin epigallocatechin gallate (EGCG) which have antioxidant and anti-inflammatory properties [1].

Cardiovascular risk factors

Hypertension

Regular consumption of tea or coffee has not been associated with long term effects on blood pressure. Acute rises in blood pressure have been reported early after coffee however are not sustained. In a meta-analysis of 5 randomized trials in hypertensive individuals, 200 –300 mg of caffeine acutely increased systolic BP by 8 mmHg (95% CI 5.7–10.6 mmHg) and diastolic BP by 5.7 mmHg (95% CI 4.1–7.4 mmHg) between 1 and 3 h post-ingestion. However tolerance develops quickly, and no difference in blood pressure effect was observed with ongoing caffeine intake at these doses after just 2 weeks [2]. Analysis of urine caffeine metabolites in the acute setting have demonstrated small but significant (~1 mmHg) reductions in systolic blood pressure with each doubling of urinary caffeine excretion [3].

Black and green tea consumption in hypertensive patients have been associated with overall reductions in blood pressure. In a meta-analysis of 10 randomized trials significant reductions in systolic and diastolic blood pressures (~2 mmHg each) were observed with tea consumption. Postulated mechanisms include vasodilation in response to prostacyclin release, enhancement of nitric oxide production and reduction in oxidative stress [4]. Moreover, risk of incident hypertension has not been consistently associated with higher caffeine intake. In a large prospective cohort with 5566 cases of incident hypertension over 112,935 person-years of follow-up, neither caffeinated nor decaffeinated coffee were associated with changes in blood pressure [5].

Diabetes mellitus and metabolic syndrome

Regular coffee and caffeine consumption may have beneficial effects on glucose homeostasis. Coffee intake increases secretion of gastrointestinal peptides such as gastric inhibitory polypeptide (GIP) and decreases glucagon-like peptide-1 (GLP-1) secretion, reducing small intestinal glucose absorption. Anti-inflammatory biomarkers (adiponectin, IL-4, IL-10) are also increased with an associated reduction in pro-inflammatory mediators (IL-1β and TNF-α) and anti-oxidant phenols reducing pancreatic β-cell inflammation. Phenols in coffee also stimulate insulin-mediated cellular glucose uptake through GLUT4 and insulin receptor activation [6].

These mechanisms are the probable explanation for the dose-related reduction in incident type 2 diabetes mellitus (T2DM) in coffee drinkers. In a meta-analysis of 28 prospective studies with 1,109,272 study participants and 45,335 new cases of T2DM, each additional cup of coffee per day was associated with a progressive reduction in T2DM risk compared to non-drinkers. The lowest risk was observed in those consuming 6 cups/day (RR 0.67; 95%CI 0.61 – 0.74), regardless of whether coffee was caffeinated or decaffeinated [7]. In a combined prospective cohort encompassing 1,663,319 person-years of follow-up and 7269 new T2DM cases, a 1 cup/day increase in coffee intake over a 4-year period lowered the risk of T2DM by 12% (95% CI 4 – 19%), while a reduction in coffee intake by 1 cup/day increased the risk by 18% (95% CI 10 – 28%). There was no association found with respect to tea intake [8]. Further studies are required to examine the impact of caffeine consumption in patients with established T2DM. There is a reported tendency to hyperglycemia 1–3 h after coffee related to adenosine A1 receptor antagonism reducing skeletal muscle glucose uptake, however glucose metabolism appears improved long-term [9].

Acute and habitual caffeine consumption has been associated with protection from weight gain. At 4 h post consumption, caffeine increases lipid-turnover twofold and increases energy expenditure by $13.3 \pm 2.2\%$ [10]. Animal studies suggest that long-term consumption of polyphenols and caffeine may have an anti-obesity effect owing to a reduction in leptin thereby suppressing hunger [11]. Caffeine inhibits short chain fatty acid gut absorption which activates the key energy-sensing molecule AMPK which downregulates lipogenesis and promotes lipolysis. Meta-analyses of 32 randomized trials demonstrate tea consumption as associated with overall minor weight loss of ~1 kg over 8–12 weeks. Weight loss was particularly reported in studies involving green tea whereby caffeine and catechins were synergistic in the overall benefit [12]. Large scale cross-sectional studies have also demonstrated a significant inverse relationship between coffee consumption and obesity. In a Danish cohort study of 83,436 individuals followed for 9 years, consumption of 1–4 cups of coffee per day was associated with significant reductions in incident diabetes, obesity and metabolic syndrome, compared with non-drinkers [13].

Dyslipidemia

Short-term consumption of unfiltered coffee appears to increase serum triglycerides, cholesterol and Low Density Lipoprotein (LDL) [14]. In a meta-analysis of 12 randomized trials of 1017 people drinking coffee for a mean of 45 days, significant increases were observed in total cholesterol (8.1 mg/dL), LDL (5.4 mg/dL) and triglycerides (12.6 mg/dL) but not High Density Lipoprotein. Adverse effects on lipids were particularly observed with pre-existing dyslipidemia, unfiltered and caffeinated coffee and in those who drank > 6 cups per day [15]. These effects have been attributed to bioactive molecules within coffee such as cafestol which inhibits

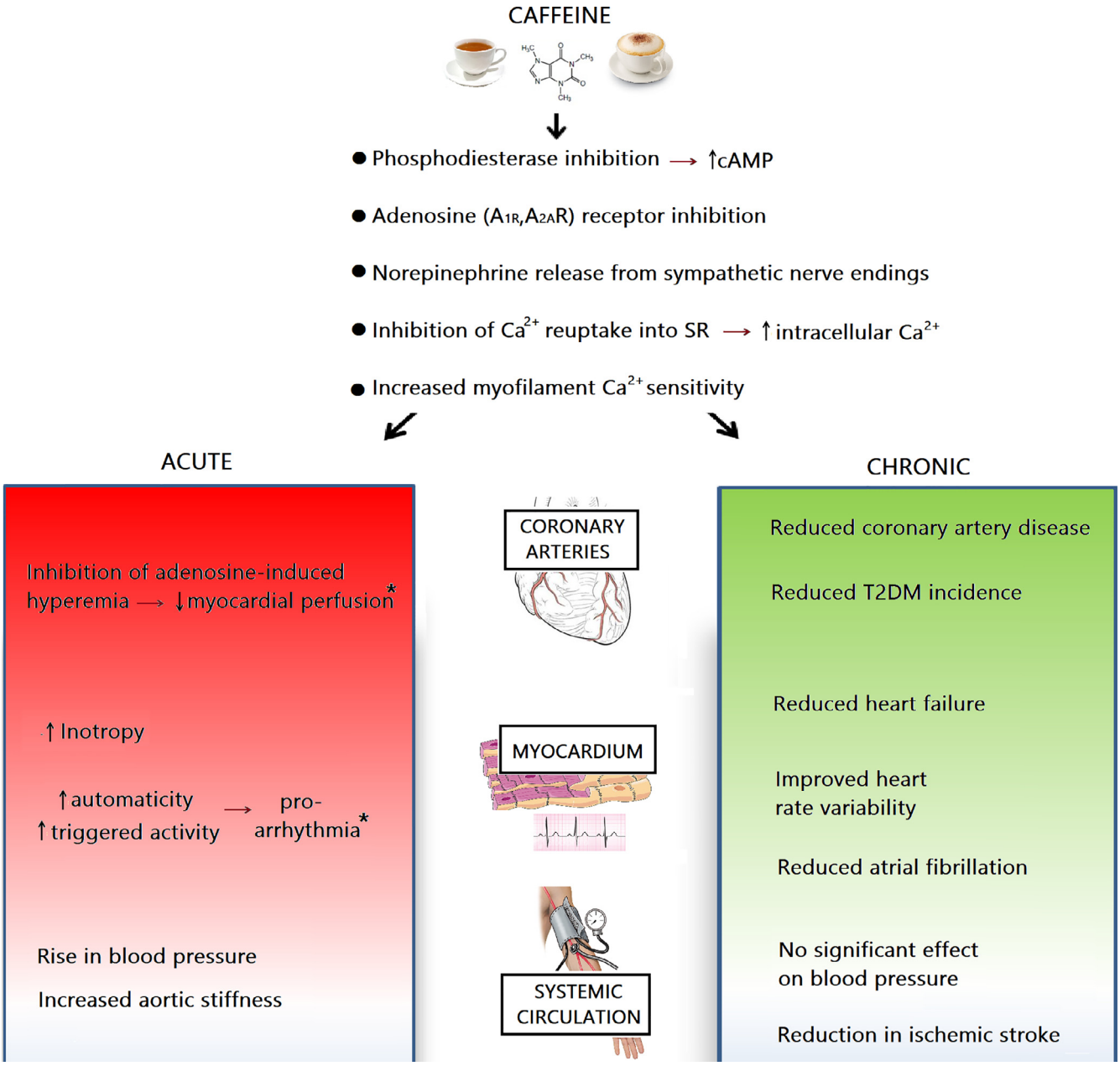

Fig. 1. Physiological effects of caffeine on the cardiovascular system with acute and chronic sequelae, Legend: *denotes very high doses required.

cholesterol 7α-hydroxylase involved in bile acid synthesis [16]. In contrast filtered coffee has no substantial effects on serum lipids as the filter paper retains the oil droplets containing the diterpenes.

More favourable effects on lipid profile have been reported with tea consumption due to phenol and catechin-related antioxidant effects on lipid metabolism and inhibition of lipid absorption. In a systematic review of 17 trials involving 1356 patients, green tea epigallocatechin gallate (EGCG) at doses of 107–856 mg/day for 4–14 weeks significantly lowered LDL by 9.3 mg/dL [17]. A recent cohort study of 80,182 healthy individuals demonstrated that tea consumption slowed the age-related decline in HDL cholesterol compared with non-drinkers (adjusted mean difference 0.01; 95% CI 0.008–0.012), with the greatest benefits observed in those at higher cardiovascular risk, including men, the elderly and those with metabolic syndrome [18].

Coronary artery disease

There are inconsistent and conflicting results regarding the impact of coffee consumption on coronary disease in part explained by evidence largely based on case control and cohort studies. Adenosine is a coronary vasodilator and its acute antagonism by caffeine impairs the expected increase in myocardial flow during exercise and has been shown in some studies to attenuate adenosine-induced hyperemia fractional flow reserve measurements during coronary angiography [19]. PET scan studies have also demonstrated a 14% reduction in myocardial perfusion reserve in controls and 25% drop in those with CAD following 200 mg oral caffeine [20]. Interestingly, a recent meta-analysis of 17 studies examining the risk of myocardial infarction (MI) alone demonstrated that while 2–3 cups/day did not affect risk,

consumption > 4 cups/day significantly increased risk of MI (RR 1.48; 95%CI 1.22–1.79) [21]. These findings suggest that coffee consumption should not exceed 3 cups/day in patients with coronary artery disease.

Nevertheless in the primary prevention setting, long-term coffee consumption at moderate levels appears to reduce the risk of incident cardiovascular disease. A meta-analysis of 36 studies incorporating 1,279,804 participants and 28,347 new cases of coronary artery disease demonstrated a U-shaped relationship with the second (median 3.5 cups/day; RR 0.89) and third (median 5 cups/day; RR 0.90) highest categories of consumption associated with a significant risk reduction compared to non-drinkers. Interestingly, Miranda et al observed that the benefits of coffee consumption on coronary artery disease may be ameliorated by smoking. In a cross-sectional analysis of 4426 individuals undergoing CT coronary artery calcium (CAC) measurement, an inverse association was observed between CAC score ≥ 100 and coffee intake, with the greatest protection against coronary artery calcification apparent in those consuming > 3 cups/day (OR 0.33; 95% CI 0.17–0.65). However following stratification, this benefit was only observed in never smokers, suggesting the deleterious effects of smoking on atherosclerosis negate any potentially beneficial effects from coffee and caffeine-derived antioxidants [22].

In a large prospective cohort of 487,375 participants with 24,665 new cases of CAD (RR 0.92; 95%CI 0.88–0.95) and 3959 major coronary events (RR 0.90; 95%CI 0.82–0.99) over 7.2 years, tea consumption at all levels was also protective [23], with other studies demonstrating an inverse relationship with coronary artery calcification progression ($p = 0.04$) [24].

Cerebrovascular disease

Regular coffee consumption is associated with a significant reduction in stroke. In healthy individuals, a meta-analysis of 11 prospective studies reported coffee consumption of up to 6 cups/day was associated with a significant reduction in stroke risk (lowest with 3–4 drinks/day – RR 0.84; 95%CI 0.77–0.91) [25]. Both green and black tea were also found to be protective demonstrating a significant dose-related reduction in risk of ischemic stroke with moderate consumption of 3 cups/day (RR 0.76; 95%CI 0.69–0.84) [26]. Caffeine is a weak cerebral vasoconstrictor as a result of blocking adenosine receptors. A single dose of 250 mg of caffeine reduces cerebral blood flow by ~20%, particularly in caffeine-naïve patients. However, polyphenols found in tea and coffee may counteract these effects through improvements in endothelial function and increased nitric oxide bioavailability [27]. In addition coffee and tea may reduce stroke by effects on lipid and glycemic profile and catechin-related improvements in endothelial function.

Heart failure

Habitual coffee consumption is associated with reductions in incident hypertension and CAD, so it is not unexpected that observational studies indicate a lower incidence of heart failure (HF). In a meta-analysis of 5 prospective studies including 6522 heart failure events, a statistically-significant J-shaped relationship between coffee and HF was described, with the strongest benefit observed for 4 cups/day with an 11% lower risk [28]. An artistic rendering of potential benefits of moderate habitual coffee consumption with respect to incidence of various cardiovascular conditions is shown in Fig. 2.

Caffeine may be beneficial in those with established HF. Intravenous caffeine (4 mg/kg ~2 cups of coffee) increased peak minute ventilation and mean exercise time (511 to 560 s; $p = 0.004$) without affecting peak oxygen consumption in patients with heart failure. Adenosine, present in higher levels in HF is a by-product of muscle metabolism and stimulates the muscle metaboreflex which enhances sympathetic discharge to skeletal muscle. This reflex is exaggerated in HF, and caffeine's antagonism of afferent neural adenosine thereby improves oxygen uptake [29]. Acute ingestion of ~300 mg caffeine has a diuretic effect owing to increases in glomerular filtration (antagonism of adenosine-mediated vasoconstriction of afferent arterioles) and inhibition of proximal tubule sodium reabsorption, although tolerance develops with habitual consumption [30]. In a double-blinded crossover trial of 51 patients with moderate-severe cardiomyopathy, consumption of 500 mg of caffeine did not portend a higher risk of atrial or ventricular arrhythmias compared to placebo [31].

Arrhythmias

While caffeine is commonly considered a trigger for arrhythmias by physicians and patients alike there is minimal evidence to support this misconception. Rather caffeine is associated with a mild reduction in the incidence of atrial fibrillation in observational studies. Electrophysiological and ambulatory monitoring studies in humans have failed to demonstrate proarrhythmia even at acute doses as high as 400 mg. Caffeine does not alter atrial or ventricular refractory periods, SVT or VT inducibility, interatrial and intra-atrial conduction, P-wave duration and dispersion, and burden of atrial & ventricular ectopy [32]. At very high doses, caffeine may be pro arrhythmic by increasing intracellular calcium which enhances atrial automaticity and after depolarization-induced triggered activity. Administration of 15 mg/kg/min in a murine model resulted in sympathetic overactivity with ventricular ectopy culminating in ventricular fibrillation in all [33].

In fact, population based studies support an antiarrhythmic effect likely explained by antagonism of adenosine which shortens atrial refractoriness and antioxidants contained in tea and coffee. A recent meta-analysis incorporating 176,675 subjects and 9987 new atrial fibrillation diagnoses demonstrated a lower incidence of AF in those whose intake of caffeine from coffee exceeded 436 mg/day [34]. Caffeine consumption also had no impact on ventricular ectopy in a meta-analysis of 7 studies [35]. In 103 MI survivors, regular caffeine (mean intake 353 mg/day) improved heart rate variability and increased parasympathetic activity without increasing arrhythmia risk [36].

Energy drinks and cardiovascular disease

There are increasing reports of adverse cardiovascular effects related to energy drinks (EDs). While a safe 'acute' dose of caffeine is considered to be 200–300 mg, some energy drinks contain up to 505 mg. Pro-arrhythmic effects are likely mediated by phosphodiesterase inhibition with increased intracellular calcium release and myofilament sensitivity. Heightened risk of AF, SVT, ventricular tachyarrhythmias, QTc interval prolongation and unmasking of Brugada syndrome have all been reported. However, not all of these can be attributed to caffeine. In addition to other 'energy-boosting' ingredients (guarana, glucuronolactone, ginseng, yohimbine and ephedra), many consume EDs in a high adrenaline state (e.g. nightclub, post exertion, or sleep deprivation) with alcohol or illicit drugs [37].

Excessive ED consumption may also cause myocardial ischemia due to either coronary spasm or thrombosis. This is likely mediated by increased platelet aggregation, blood pressure elevation and endothelial dysfunction. There is a significant increase in arachidonic acid-induced platelet aggregation activation acutely after ED consumption [38]. A meta-analysis of 15 studies (including double blind RCTs) examining acute BP effects of EDs

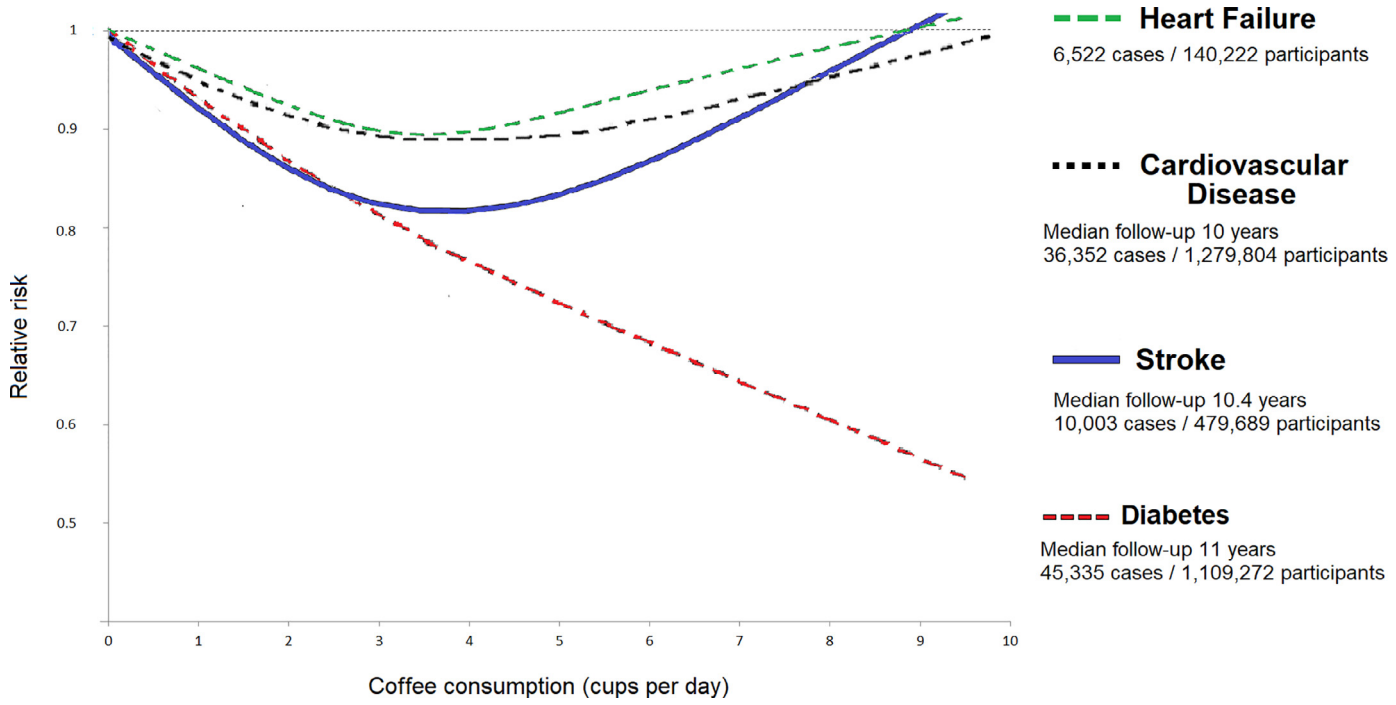

Fig. 2. Habitual caffeine consumption and incident risk of major cardiovascular conditions (based on large meta-analyses (7,26,28)).

(30 min – 6 h) demonstrated significant rises in systolic and diastolic blood pressures, with the greatest rises observed with caffeine doses exceeding 200 mg [39]. Given numerous adverse events in individuals without structural heart disease, many major society guidelines suggest that patients with pre-existing cardiovascular conditions avoid ED consumption altogether.

Mortality

Large scale prospective cohort studies suggest that tea and coffee consumption reduce cardiovascular and all-cause mortality. In the NIH–AARP Diet and Health Study spanning 5,148,760 person-years of follow-up with 52,515 deaths, coffee consumption was inversely associated with death ($p < 0.001$ for trend). Consumption as high as 4–5 cups/day was associated with the greatest benefit among both men (HR 0.88; 95%CI 0.84–0.93) and women (HR 0.84; 95% CI 0.79–0.90). Benefits from caffeinated coffee were observed for deaths attributed to heart disease, diabetes, stroke, infections and respiratory diseases, but not malignancy [40]. Mortality data from the UK Biobank (~500,000 participants) also demonstrated an inverse relationship between coffee consumption and mortality. Benefits were observed even at consumption of 8 cups/day (HR 0.86; 95% CI 0.77–0.95), whether coffee was ground, instant or decaffeinated and regardless of caffeine metabolism genetic polymorphisms, suggesting non-caffeinated components were potentially important factors [41].

Similarly, consumption of both black and green tea have been associated with reductions in both cardiovascular and all-cause mortality. In a meta-analysis of 18 prospective studies, the highest vs lowest categories of consumption were associated with reduced all-cause mortality for both green (RR 0.80; 95%CI 0.68–0.93) and black tea (RR 0.90; 95%CI 0.83–0.98). Moreover, there was a dose-related effect with each cup/day of green tea reducing risk of mortality by 5% from cardiovascular disease [42].

Future directions

Recommendations are largely based on epidemiological studies subject to publication bias and confounding, and more high-quality randomized trials with longer follow-up are needed particularly in patients with pre-existing cardiovascular conditions. The long term safety of newer beverages with higher concentrations of caffeine and greater calorie content require further clarification.

Genetic variations in Cytochrome P450 enzyme 1A2 (CYP1A2), the enzyme responsible for 95% of caffeine metabolism, have already been linked with cardiovascular outcomes. Observational studies suggest that slow metabolisers may have a heightened risk of hypertension and non-fatal myocardial infarction [43,44]. There is ongoing interest in the field of 'nutrigenetics' aiming to identify genetic polymorphisms that may affect an individual's response to caffeine.

Conclusion

Mild-to-moderate habitual consumption of caffeinated beverages, particularly a daily intake of 2–3 cups of coffee or tea, appears to be safe across a broad range of cardiovascular conditions, and may even be beneficial with respect to diabetes mellitus, atherosclerosis, heart failure, arrhythmia and total mortality. Acute consumption of high doses of caffeine, particularly in the form of energy drinks is best avoided.

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