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ISCHEMIC HEART DISEASE (D MUKHERJEE, SECTION EDITOR)

Coffee Consumption and Cardiovascular Health: Getting to the Heart of the Matter

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Abstract As coffee-consumption is a widespread tradition, its possible impact on health has been of considerable interest. This review examines the effects of coffee on cardiovascular risk, outlines underlying biological mechanisms, and discusses implications for public health. In the past, coffee was often viewed as a cardiovascular risk-factor. However, in meta-analyses of recent well-controlled prospective epidemiologic studies, coffee-consumption was not associated with risk of coronary heart disease and weakly associated with a lower risk of stroke and heart failure. Also, available evidence largely suggests that coffee-consumption is not associated with a higher risk of fatal cardiovascular events. In randomized trials coffee-consumption resulted in small increases in blood pressure. Unfiltered coffee increased circulating LDL cholesterol and triglycerides concentrations, but filtered coffee had no substantial effects on blood lipids. In summary, for most healthy people, moderate coffee consumption is unlikely to adversely affect cardiovascular health. Future work should prioritize understanding the effects of coffee in at-risk populations.

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Introduction

Although studied for over 4 decades, the effect of coffee on cardiovascular health remains controversial. Scientific interest in the physiological effects of coffee was initially based on the hemodynamic and humoral effects of caffeine. Experimental data from short-term and animal studies suggested detrimental effects of caffeine on blood pressure, insulin resistance, and arrhythmia, and implicated coffee as a potential cardiovascular risk factor [1•, 2, 3•]. Also, cross-sectional studies showed an association between coffee and plasma cholesterol concentrations [4]. Additionally, epidemiologic evidence, primarily from case–control studies suggested that coffee consumption is associated with a higher risk of cardiovascular disease [5].

However, there has been growing recognition of a more nuanced relationship between coffee and cardiovascular disease risk based on several lines of evidence. First, prospective cohort studies, which are subject to less bias than retrospective case–control studies, generally do not support an association between coffee consumption and a higher risk of cardiovascular diseases (CVD) [6••]. Second, most habitual caffeine consumers appear to develop at least partial tolerance to the effect of caffeine on blood pressure [7]. Third, the discovery of myriad other bio-actives in coffee has led to the realization that the effect of coffee cannot be equated to those of caffeine. Indeed, some of these compounds may have insulin-sensitizing and anti-inflammatory effects [8–11] and emerging evidence suggests an inverse association between coffee and risk of type-2 diabetes mellitus [12••]. Fourth, the relative composition of coffee bioactives can vary substantially by coffee preparation method, and may underlie the heterogeneity

observed in coffee studies particularly in relation to serum cholesterol levels.

Recently, a number of meta-analyses on coffee and cardiovascular disease risk [6••, 12••, 13••, 14••, 15••, 16••, 17••, 18••] have been published, which further illuminate our understanding of this complex relationship. In this review, we will evaluate recent evidence, focusing particularly on cardiovascular mortality. We will also briefly summarize current understanding on pathways via which coffee influences cardiovascular disease risk, methodological issues to consider when interpreting the epidemiologic data, and discuss implications of recent findings for public health.

Pathways Linking Coffee Consumption to Cardiovascular Risk

Coffee is a complex brew with hundreds of phytochemicals such as caffeine, diterpenes, chlorogenic acid (CGA), trigonelline (a niacin-precursor), niacin, magnesium, and potassium, and roasted derivatives including melanoidins and quinides [8, 19]. The relative proportions of these compounds vary based on the coffee bean types, degree of roasting, and method of filtration (Table 1). Robusta coffee species contain higher levels of caffeine and CGA, and lower levels of diterpenes compared with Arabica species [20, 21]. Roasting can lead to a variety of chemical changes, including the transformation of CGA to phenols and quinides. Losses of CGA can be as high as 99 % [20]. Nevertheless, light to medium-dark roasted coffee contains a substantial concentration of CGAs (35–175 mg/100 mL), and CGA intake in frequent coffee drinkers is generally much higher than intake of abstainers [20]. Interestingly, reversal of quinides to CGA has been observed after exposure to alkaline digestive fluid, which may lead to a greater bioavailability of CGA than expected for darkly roasted coffee [20]. Coffee phytochemicals may have diverse effect on different cardiovascular risk factors, as discussed below.

Coffee and Serum Lipids

The effects of coffee on serum lipoprotein concentrations are largely dependent on the method of its preparation. Compared with filtered or instant coffee, unfiltered types of coffee such as Scandinavian boiled, Turkish/Greek, or French press coffee adversely modify the lipid profile. In a recent meta-analysis of 12 randomized trials, consumption of unfiltered coffee resulted in mean increases of 11.9 mg per dL for LDL cholesterol and 18.8 mg per dL for triglyceride concentrations [17••]. Filtered coffee consumption did not significantly change LDL cholesterol or triglyceride concentrations (Table 2). These findings are consistent with studies showing that the coffee diterpenes cafestol and kahweol are the primary hypercholestrolemic agents in boiled coffee [22], and their removal by filters reduces the lipid-raising potential of coffee [23]. The hypercholestrolemic effect of coffee appears to be more pronounced with higher daily

Table 1 Variability in the concentration of selected coffee bioactives based on coffee bean variety and preparation methods [a]

	Caffeine (mg)	Cafestol (mg)	Kahweol (mg)	Chlorogenic acid (mg)
Coffee bean variety	2-fold higher in Robusta vs Arabica [21]	Higher in Arabica vs Robusta [96]	Much higher in Arabica vs Robusta [96]	Higher in Robusta vs Arabica [20]
Roasting	Minor reductions on roasting [20]	Reduced by roasting [20]	Reduced by roasting [20]	Reduced by roasting [97]
Decaffeination				
Decaffeinated	3±2 [8]	-	-	79–242 [8]
Caffeinated	130±20 [8]	-	-	88–250 [8]
Method of preparation				
Boiled	-	2.40±2.24 [98]	3.12±2.72[98]	-
Turkish/Greek	-	3.12±2.56 [98]	3.12±3.12 [98]	-
French press	-	2.80±0.96 [98]	3.52±1.68 [98]	-
Instant	75 (60–85) [99]	0.2 (0.0-0.6) [98]	-	-
Drip, paper filtered	-	0.08±0.0 [98]	-	-
Metal filtered	-	0.05±0.04 [98]	0.03±0.03 [98]	-
Sock Filtered	-	0.09±0.06 [98]	0.01±0.02 [98]	-
Espresso	40 (30–50) [99] 140 (51–322) [100] (Commercial)	1.2±0.8 (Italian) [98] 0.96±0.72 (others) [98]	1.44±1.04 [98] 1.12±0.88 [98]	145 (24–422) [100]
Coffee pad [b]	-	0.76 (0.69–0.82) [101]	0.85 (0.77–0.94) [101]	-

[a] Concentrations are expressed per cup, which range in size from 120 mL [98] to 240 mL [8, 99] for standard size and from 30 mL [99] to 43 mL [100] for espresso shots. Values are means ± SD, median or mean (range), and range

[b] For coffee brewed via coffee machines using coffee pads, concentrations are expressed as mean (95 % CI) per liter

Table 2 Summary of recent meta–analyses investigating coffee consumption and cardiovascular health[a]

Study characteristics					Results					
Type	*N* studies	*N* (N cases)	Age (years)	Duration	Outcomes					
					Categories	Total (n)	Subgroup Analyses (n)			
RCT [17••] [b]	12	1017	26–49	45 d (mean)	Lipids	All (11–22) [c]	Men (5–11)	Men+Women (6–11)	Filtered (5–10)	Unfiltered (6–12)
					TC (mg/dL)	8.1 (4.5, 11.6)	4.5 (0.2, 8.8)	11.4 (5.7, 17.2)	3.6 (0.6, 6.6)	12.9 (6.8, 18.9)
					LDL–C(mg/dL)	5.4 (1.4, 9.5)	3.0 (0.2, 5.7)	10.7 (0.8, 20.7)	2.3 (−1.1, 5.6)	11.9 (3.2, 20.6)
					TG (mg/dL)	12.6 (3.5, 21.6)	0.7 (−5.5, 6.9)	25.3 (17.0, 33.7)	3.7 (−4.2, 11.7)	18.8 (4.8, 32.7)
RCT [2] [b,d]	16	1010	23–77	42 d (median)	BP	All (16)	≥ 50 % Men (17) [e]	< 50 % Men (8)	NBL (19)	HBL (6)
					SBP mm Hg	2.04 (1.10, 2.29)	1.53 (0.51, 2.55)	2.61 (1.75, 3.46)	2.09 (0.79, 3.40)	2.06 (−1.09, 5.20)
					DBP mm Hg	0.73 (0.14, 1.31)	0.42 (−0.32, 1.16)	1.86 (1.10, 2.62)	1.13 (0.38, 1.89)	0.75 (−1.05, 2.55)
RCT [18••] [b]	10	-	25–73	~ 60 d (median)	BP	All (10)	Men (4)	Women (3)	Decaffeinated (3)	Regular (12)
					SBP mm Hg	−0.55 (−2.46, 1.36)	−2.06 (−6.38, 2.26)	1.46 (−0.36, 3.28)	−1.07 (−2.89, 0.75)	−0.27 (−2.18, 1.64)
					DBP mm Hg	−0.45 (−1.52, 0.61)	−2.10 (−4.30, 0.11)	0.00 (−1.10, 1.09)	−0.19 (−1.87, 1.49)	−0.45 (−1.52, 0.61)
Cohort [13••]	6	172, 567 (37,135)	18–64	6–33 y	Hypertension	All (6)				
					<1 cups/d	1				
					1–3 cups/d	1.09 (1.01, 1.18)	–	–	–	–
					3–5 cups/d	1.07 (0.96, 1.20)				
					>5 cups/d	1.08 (0.96, 1.21)				
Cohort [12••]	18	457,922 (19319)	20–98	2–20 y	Diabetes	All	Men	Women	Registry/OGTTT	Self-report
					0 – ≤2 cups/d	1	1	1	1	1
					3– ≥4 cups/d	0.76 (0.69–0.82)	0.78 (0.70, 0.87)	0.71 (0.62–0.81)	0.85 (0.74–0.98)	0.72 (0.66–0.79)
Cohort [16••]	11	479,689 (10,003)	20–83	2–21 y	Stroke	All (11)	Men (5)	Women (5)	Ischemic (4)	Hemorrhagic (4)
					0 cups/d	1	1	1	1	1
					2 cups/d	0.86 (0.78, 0.94)	0.83 (0.73, 0.96)	0.84 (0.74, 0.95)	0.87 (0.79, 0.96)	0.86 (0.70, 1.06)
					4 cups/d	0.83 (0.74, 0.92)	0.80 (0.68, 0.94)	1.24 (0.52, 3.00)	0.82 (0.74, 0.91)	0.83 (0.63, 1.10)
					6 cups/d	0.87 (0.77, 0.97)	0.84 (0.71, 0.99)	–	0.82 (0.72, 0.92)	0.86 (0.63, 1.17)
					8 cups/d	0.93 (0.79, 1.08)	0.91 (0.70. 1.18)	–	0.82 (0.67, 1.00)	0.89 (0.62, 1.28)
Cohort [6••]	21	407,806 (15,599)	19-≥ 75	4–32 y	CHD	All (16 –20) [c]	Men (13–15)	Women (5–6)	Fatal (8–10)	Nonfatal (7)
					Light [f]	1	1	1	1	1
					Moderate	0.96 (0.87, 1.06)	1.01 (0.89, 1.14)	0.82 (0.73, 0.92)	1.01 (0.88, 1.15)	0.95 (0.89, 1.02)
					Heavy	1.04 (0.92, 1.17)	1.07 (0.91, 1.26)	0.87 (0.67, 1.13)	1.00 (0.85, 1.16)	1.08 (0.84, 1.38)
					Very heavy	1.07 (0.87, 1.32)	1.15 (0.91, 1.46)	0.90 (0.61, 1.34)	0.89 (0.78, 1.03)	1.23 (0.75, 2.00)
Cohort [14••]	5	140,220 (6522)	25–83	8–35 y	Heart failure	All (5)				
					0 cups/d	1	–	–	–	–
					3–4 cups/d	0.90 (0.82–0.99)				

Table 2 (continued)

Study characteristics				Results		
Type	*N* studies *N* (N cases)	Age (years)	Duration	Outcomes		
				Categories	Total (n)	Subgroup Analyses (n)
				7–8 cups/d	0.95 (0.87–1.05)	
				10–11 cups/d	1.01 (0.90–1.14)	

BP blood pressure, *CHD* coronary heart disease, *d* days, *HBL* high baseline blood pressure, *HF* heart failure, *HTN* hypertension, *NBL* normal baseline blood pressure, *OGTT* National registries or oral glucose tolerance test, *RCT* randomized controlled trials

[a] Values are weighted mean differences (95 % CI) [17••, 18••] or net change (95 % CI) [2] or relative risk (95 % CI) [6••, 12••, 13••, 14••, 16••]

[b] Range of coffee intake: 2.4–8 cups/d for [17••], 450–1235 mL (3–8 cups) for [2] and >3–6 cups/d for [18••]

[c] Number of study estimates included varied for the different outcomes measured [17••] or because separate meta-analyses were conducted for different levels of coffee consumption [6••]

[d] In subgroup analyses that stratified trials by using either coffee or caffeine as the intervention, mean changes (95 % CI) in SBP were 1.22 (0.52–1.92) for coffee and 4.16 (2.13–6.20) for caffeine, and in DBP were 0.49 (−0.06–1.04) for coffee and 2.41 (0.98, 3.84) for caffeine. There were 11 trials (18 strata) for coffee and 5 trials (7 strata) for caffeine included in this meta-analysis

[e] Values for subgroup analyses were adjusted for the following: age, type of intervention (coffee/caffeine), proportion of males, baseline BP, baseline caffeine intake, and caffeine dose

[f] Light drinkers (<1 cup/d US or≤2 cups/d Europe), moderate (1–3 cups/d, or 3–4 cups/d), heavy (4–5, 5–6 cups/d), and very heavy (≥ 6 or≥7 cups/d)

intakes of coffee, in people who have hyperlipidemia and in studies that included women [17••].

Coffee and Blood Pressure

The pressor effects of coffee are generally attributed to caffeine. At plasma concentrations of 5 to 50 μM, which can be readily obtained with consumption of 2 to 3 cups of coffee, caffeine acts to antagonize the effects of adenosine (as reviewed in [1•]). Due to its structural similarity to adenosine, caffeine can occupy its receptor, preventing adenosine-receptor binding. The resultant adenosine-inhibition leads to acute increases in blood pressure and insulin resistance [24]. Acute caffeine exposure (200–250 mg) can increase systolic blood pressure (SBP) by 7.3 mm Hg, and diastolic blood pressure (DBP) by 7.0 mm Hg in normotensive persons for up to 2 to 4 hours [25]. These effects are similar in hypertensive persons with reported average increases of 8 to 11 mm Hg in SBP and 6 to 8 mm Hg in DBP [15••, 25]. The pressor effect of caffeine is reduced with chronic exposure. For instance, in a meta-analysis of 5 randomized trials, caffeine (median intake, 410 mg/d) consumed over a median of 28 days increased SPB by 4.2 mm Hg and DBP by 2.4 mm Hg in largely normotensive adults [2]. This smaller effect of chronic caffeine exposure reflects a physiological adaptation to habitual caffeine intake, and is potentially mediated by increases in the number of adenosine receptors [26].

Caffeinated coffee can also increase blood pressure, but the effect appears to be substantially smaller than expected based on its caffeine content. An average increase of 1.2 mm Hg for SBP and 0.5 mm Hg for DBP in mostly normotensive adults who received a median of 5 cups of coffee for a median of 6 weeks was observed in a meta-analysis of 11 randomized trials compared with controls that received decaffeinated coffee or no coffee (Table 2) [2]. Since coffee may have compounds that can lower BP, it has been argued that comparing decaffeinated with caffeinated coffee assesses the effect of caffeine in a coffee milieu and not the effects of coffee itself [18••]. Only a small and statistically nonsignificant change in SBP and DBP was observed in a meta-analysis of 10 randomized trials that only used coffee-abstainers as the reference group (Table 2) [18••].

Recently, the effects of coffee consumption in persons with hypertension have been summarized [15••]. Drinking 3 to 5 cups of instant caffeinated coffee for 2 weeks did not increase blood pressure in younger hypertensive persons, but increased this in older hypertensive [27] compared with decaffeinated coffee or a caffeine-free diet [15••]. Although extensively investigated in cross-sectional studies, no consistent association between habitual coffee consumption and blood pressure has emerged. Increases, decreases or inverse U-shaped associations (eg, 1–2 cups/d being associated with a higher blood pressure than no consumption or 6–9 cups/d) have been

reported [28]. A meta-analysis of 6 prospective studies in normotensive and hypertensive populations (untreated, stage 1), observed a 7 % to 9 % higher risk of hypertension or initiation of hypertensive medications across categories of coffee consumption (Table 2) [13••]. It is not clear why the pressor effects of caffeine may be attenuated when administered via coffee. It has been suggested that other coffee compounds such as polyphenols favorably regulate blood pressure, negating the effects of caffeine. In addition, cell-culture studies suggest that coffee quinides may prevent adenosine re-uptake by adenosine transporters, increasing adenosine availability, thus, limiting adenosine-antagonistic effects of caffeine [29].

Interestingly, results from a limited number of randomized trials suggest that CGA (140-400 mg daily) from green coffee extract can substantially lower SBP and DBP in hypertensive persons [30, 31], possibly via nitric-oxide mediated vasodilatation [32]. It has been hypothesized that the antihypertensive effects of CGA are not noted with roasted coffee consumption due to the production of metabolites such as hydroxyhydroquinone, which can neutralize the effects of CGA. Indeed, findings from recent randomized trials suggest that hydroxyhydroquinone-free coffee with comparable levels of caffeine can lower blood pressure compared with hydroxyhydroquinone-containing coffee [33, 34].

Coffee, Oxidative Stress, and Inflammation

The large contribution of coffee to the total antioxidant capacity of the diet as estimated by in vitro methods in some countries [35], have led researchers to examine its effects on oxidative damage. The limited clinical studies done thus far have been somewhat promising, with increases in total ex vivo antioxidant capacity [36], ex vivo hemocyte antioxidant enzyme activity [36–38], and reductions in urinary 8-isoprostane concentration [9, 39], in vitro/ex vivo oxidative DNA damage [37, 38] and ex vivo LDL vulnerability to oxidation [40] observed for moderate coffee intakes (~3–4 cups). Some of these studies included coffees enriched for specific compounds such as CGA [39]. Observational [41–45] and clinical studies [9, 10] that have examined the effects of coffee on inflammatory markers such as C-reactive protein and interleukin-6 have yielded contradictory results with direct, inverse, and no associations being reported. Results for coffee consumption and plasma adiponectin concentrations have been more consistent. In most observational studies higher adiponectin concentrations were observed in high-coffee consumers compared with infrequent coffee consumers [11, 45, 46]. Similarly, higher coffee consumption increased adiponectin concentrations in several intervention studies [9, 10, 47]. Because LDL-oxidation and inflammation can promote atherosclerosis, the association of coffee with atherosclerotic markers is of interest. An inverse association between coffee and coronary calcification was noted in older Dutch women [48]. However, in a population of young US adults, coffee intake was not associated with carotid intima-media thickness or the presence, or progression of coronary arterial calcification [49].

Coffee, Insulin Resistance, and Risk of Type-2 Diabetes

Data from prospective cohort studies have rather consistently shown an inverse association between coffee consumption and risk of type-2 diabetes. In a meta-analysis of 18 prospective studies conducted in 2009, participants who consumed 3 to 4 cups of coffee per day had a 24 % lower risk of type-2 diabetes compared with those who consumed coffee less frequently (Table 2) [12••]. Estimates did not vary by sex or geographical region. Also, lower estimates in coffee consumers were observed regardless of the method of assessing diabetes incidence (self-report vs oral glucose tolerance test/population registry). This is noteworthy, as in many populations heavy coffee drinking is associated with less healthy behaviors and it is conceivable that the prevalence of undiagnosed diabetes is higher in this group [50]. Prospective studies published since 2009, have also supported the inverse association between coffee and type-2 diabetes risk [51–53].

The specific aspects of glucose metabolism influenced by coffee consumption are not clear. As previously reviewed [54], there is some suggestion from observational data that coffee has more pronounced favorable effects on post-prandial rather than on basal glucose metabolism. In 2 trials, lasting from 8 to 12-weeks coffee consumption did not improve fasting or post-prandial glucose metabolism, but increased circulating concentrations of adiponectin; an insulin-sensitizing adipokine [9, 10]. In a longer 16-week trial, reductions in 2-hour glucose concentrations were found in men consuming 5 cups of coffee per day compared with no coffee consumption [55]. In contrast, coffee consumption did not change fasting glucose and insulin concentrations. Improvements in postprandial glucose metabolism are consistent with evidence that CGA and its derivatives can decrease intestinal glucose absorption (reviewed in [8]). CGA may also decrease hepatic glucose output and have antioxidant effects [8]. Other compounds in coffee such as magnesium and lignans may also favorably influence glucose homeostasis [8]. In contrast, acute exposure to caffeine at physiologically relevant doses has been shown to reduce insulin sensitivity primarily mediated by its adenosine-inhibitory and sympathetic nervous system stimulatory effects [1•, 8, 56], which appear to persist with repeated exposure [1•]. Beneficial effects of coffee on glucose homeostasis are therefore unlikely to be mediated via caffeine. Consistent with this hypothesis, decaffeinated coffee consumption was associated with a lower risk of type-2 diabetes in a meta-analysis of 6 studies [12••].

Coffee Consumption and Other Biological Risk Markers

Data from randomized trials indicate that high coffee intakes substantially increase fasting plasma homocysteine concentrations [57, 58]. These effects occur for both filtered [57] and unfiltered [58] coffee, are likely to be mediated by both caffeine [59] and CGA [60] and are probably persistent [57, 61]. However, the etiological role of homocysteine in the development of CVD is debatable [62, 63] and the cardiovascular implications of elevations in plasma homocysteine concentrations remains unsettled. There is also concern that coffee intake can increase the risk of arrthymias. As reviewed in [3•] the limited available evidence suggest that habitual moderate coffee intake is not associated with the risk of arrthymias in most people. An increased risk of arrthymias has been noted at very high coffee intakes (more than 9 cups daily) in a cross-sectional study. Since caffeine consumption can increase catecholamine exposure, the authors recommend that physicians should use discretion for arrhythmias that are catecholamine-driven, or in persons who report sensitivity to caffeine [3•].

Methodological Challenges

Assessing the health effects of coffee is complex for a number of reasons [50]. First, some measurement error affects the assessment of coffee exposure. Variability in brew strength, serving size, and preparation methods can lead to misclassification, making it more challenging to establish dose–response relationships. Second, in many populations coffee consumption tends to correlate with unhealthy behaviors, particularly tobacco smoking [64, 65]. Smoking is an important confounder for the relationship between coffee consumption and CVD mortality, as coffee and smoking habits are correlated, and smoking substantially increases the risk of CVD mortality. This relationship is well-recognized and most studies control for categories of smoking. However, this adjustment may be incomplete due to misreporting of smoking habits. Also, within each smoking category, coffee consumption maybe associated with a greater intensity of smoking [66] because these behaviors appear to be mutually reinforcing. The biological basis for this is most likely related to the cytochrome P450 1A2 (CYP1A2) enzyme, which is responsible for metabolism of both nicotine and caffeine [66]. Caffeine intake can induce this enzyme resulting in faster clearance of nicotine and this may lead to increased smoking to maintain nicotine concentrations. Since the desirable effects of caffeine on attention may be dependent on caffeine dose it is possible that smokers increase their coffee intake to maintain caffeine concentrations [66, 67]. Coffee intake is also correlated with other unhealthy traits in some populations including poor dietary choices and psychological stress [65], which can act as confounders.

Third, recall bias in retrospective case–control studies can lead to inflated differences in coffee consumption in cases relative to controls, as cases are more likely to recall and report in detail exposures, which they think may be related to their disease [50]. Fourth, due to prevailing popular opinions about coffee, people diagnosed with conditions such as hypertension may reduce coffee intake or switch to decaffeinated coffee [50]. This can lead to confounded associations between coffee and cardiovascular outcomes. This “healthy-participant” bias may be particularly relevant for studies of coffee and mortality. People with less severe pre-existing conditions and less co-morbidity are more likely to be heavier coffee consumers. These people also have lower mortality risk resulting in potential under-estimations of risk at higher levels of coffee consumption. Nevertheless, prospective cohort studies that have addressed this issue either by looking at changes in coffee consumption on disease onset [64] or by adjusting for co-morbidities [68] have generally confirmed results of other cohort studies.

In addition to these biases, there is some evidence to suggest that the biological response to coffee may vary due to genetic factors. The best studied genetic variation is that of CYP1A2; a hepatic enzyme, which is responsible for as much as 95 % of caffeine metabolism [69]. Large inter-individual variability, ranging from 10- to 60-fold, in enzyme function yields substantial variations in the half-life of caffeine, ranging from 2.5 to 12 hours in adults [69]. Gene variants in CYP1A2 have been identified that are associated with altered enzyme activity and may distinguish between ‘fast’ and ‘slow-metabolizers’ of caffeine [70]. Results from a few studies have suggested that coffee consumption may be associated with risk of hypertension [71] and myocardial infarct (MI) [70] in slow-metabolizers but not in fast metabolizers, but confirmation of these findings in other studies is needed.

Coffee Consumption and CVD Incidence and Mortality

While understanding the effects of coffee on surrogate endpoints such as blood-pressure or plasma cholesterol provide valuable insights on intermediary physiological pathways, information on hard endpoints such as disease incidence and mortality are particularly compelling. This section summarizes findings of coffee consumption on risk of CVD incidence and mortality.

Coffee and Coronary Heart Disease Incidence and Mortality

Over the past decades, several meta-analyses on coffee and CHD risk have been reported. Most recently, Wu and co-workers summarized the results of 21 prospective studies [6••]. Similar to previous meta-analyses on cohort studies, they found no evidence for higher risk of CHD with higher

coffee consumption (Table 2). There was substantial heterogeneity in study estimates, and study-attributes such as shorter follow-up duration, higher proportion of nonsmokers and being of European origin tended to be associated with lower pooled estimates. In addition, sex-specific differences also contributed to study heterogeneity. Women (but not men) who drank moderate amounts of coffee had an 18 % lower risk of CHD events compared with those with low coffee consumption.

Some studies have evaluated whether the association between coffee and CHD risk differs by type of coffee. In the 5 cohorts that indicated filtered coffee as the main preparation method, moderate coffee consumption was not associated with a higher CHD risk [6••]. Consumption of decaffeinated coffee also does not seem to be associated with a higher risk of CHD [5]. A recent study which observed a 90 % higher risk of myocardial infarction (MI) in heavy decaffeinated coffee consumers compared with infrequent consumers, noted an attenuation of this association when events in the first 2 years were excluded [72]. This suggests that the higher risk in the decaffeinated group may have been driven by people at high-cardiovascular risk who possibly switched from caffeinated to decaffeinated coffee.

In contrast to cohort studies, case–control studies have fairly consistently supported an association between coffee consumption and a higher risk of CHD. In a meta-analysis of 13 case–control studies, compared with drinking less than 1 cup of coffee per day, drinking more than 4 cups of coffee each day was associated with a substantially higher risk of CHD (OR: 1.83, 95 % CI: 1.49–2.24) [5]. The differences in results for case–control and cohort studies have been attributed to methodological limitations of case–control studies, including recall bias, the failure to completely adjust for confounders such as smoking and selection bias as a result of using hospital-based controls [4]. Nevertheless, doubts persist about whether these biases are large enough to justify completely dismissing the elevated risk noted for coffee consumption in case–control studies. For instance, it has been suggested that the case–control design which queries coffee intake retrospectively is better suited to capture short-term effects of coffee consumption on the occurrence of CHD [4]. Conversely, the long lag-time between exposure and outcome, typical of most cohort studies, may dilute these associations. Consistent with this La Croix found higher risk estimates in heavy coffee drinkers with shorter follow-up times, and non-significant associations after 10-years of follow-up [73]. However, these concerns have not been supported by results of more recent studies. In a meta-analysis of 21 prospective studies, coffee consumption was not associated with a higher risk of CHD in both follow-up time subgroups (> 10-years, ≤ 10-years) [6••]. Moreover, cohort studies that updated coffee intake data every 2 years observed no associations between coffee consumption and CVD [74].

Several recent studies have investigated the association between coffee and CHD mortality. Wu et al. in a meta-analysis of 10 prospective studies, observed that CHD mortality risk in moderate, heavy, and very heavy coffee drinkers were comparable with persons drinking little or no coffee (Table 2). Since then, no association between coffee consumption and CHD mortality was observed in one Dutch [75] and 2 Japanese [65, 76] cohorts of men and an inverse association was observed in 2 cohorts of U.S. men [77, 78]. In contrast, a 9 % higher risk of CHD mortality in men per standard deviation increment in coffee consumption (~ 270 mL) was observed in a Dutch case-cohort study [79]. However, an inverse association between coffee consumption and CHD mortality was observed for women in that study and the authors cited residual confounding by smoking in men as a potential reason for this difference in association according to sex. In recent cohort studies of women, either no association [65, 75] or inverse associations [76–79] between coffee consumption and CHD mortality risk have been observed. In one of the largest prospective studies done to date, comprising of 402,260 US adults, women who drank 2 to 3 cups of coffee daily had a statistically significant 15 % and men a 14 % lower risk in heart disease mortality compared with abstainers [77]. Even consumption of 6 or more cups of coffee per day was associated with a lower risk of CHD mortality in this study compared with no coffee consumption.

No associations [75] or modest inverse associations [77, 78] of decaffeinated coffee intake on CHD and CVD mortality risk have been observed.

Coffee and Stroke Incidence and Mortality

Available evidence does not support an association between coffee consumption and a higher stroke risk. In contrast, a meta-analysis of 11 prospective studies suggested that moderate coffee consumption was associated with a slightly lower risk of fatal and nonfatal stroke events compared with abstinence (Table 2) [16••]. Heavy coffee consumption was not associated with risk of stroke [16••]. In sub-group analyses, women drinking 2 cups of coffee had a lower risk of stroke, while those who consumed 4 or more cups had a nonsignificantly higher risk compared with nondrinkers (Table 2). However, there were few women with high coffee intake resulting in wide confidence intervals. Similar estimates were obtained by region (US, Europe, Japan) and duration of follow-up. Risk estimates were significantly lower only for ischemic stroke (but not hemorrhagic stroke) sub-type. Recent findings from a large Japanese cohort also observed that participants who consumed 1 cup, or 2 or more cups of coffee daily had a 19 % to 20 % lower risk of stroke compared with abstainers [80].

Coffee intake was also modestly associated with an inverse risk of stroke mortality in a large cohort of 402,260 US adults

who were followed for 14 years [77]. The risk of fatal stroke events was 35 % lower in men and 18 % lower in women who consumed 4–5 cups of coffee daily compared with coffee nondrinkers [77]. In contrast, a Japanese study [65] observed a higher risk (HR 3.17, 95 % CI 1.50–6.69) for women who drank 3 or more cups compared with those that drank less than 1 cup each week. However, for men in this study coffee intake was associated with lower stroke mortality [65]. Other studies [75, 79] including those in East Asian populations [76] observed no associations between coffee intake and stroke mortality risk in either men or women.

The few studies that have examined the associations of decaffeinated coffee have generally noted weak inverse associations [81] or no associations [72, 77] with stroke morbidity or mortality.

Coffee and Risk of Heart Failure

In a meta-analysis of 5 European prospective studies, a J-shaped relationship was noted between coffee and risk of heart failure, with intakes 3 to 4 cups per day being associated with an 10 % lower risk of heart failure (Table 2) [14••]. Much lower or higher consumption was not associated with heart failure risk compared with no coffee consumption. Associations did not vary substantially by sex or by pre-existing MI or diabetes.

Coffee and CVD Mortality in High-Risk Populations

Given the acute detrimental effects of caffeine on blood pressure, insulin sensitivity, and blood lipids, the potential effects of coffee intake on CVD mortality in persons with pre-existing CVD or type-2 diabetes has been an area of interest. Also, recent observations that caffeine can compromise the cardio-protection afforded by ischemic preconditioning in animal and human in vivo models have led some researchers to speculate that post-MI outcomes rather than incidence of coronary events may be more appropriate to study in relation to coffee consumption [82]. In one of the earliest case–control studies to examine this association, very heavy coffee consumption (more than 10 cups/d) was associated with dramatically higher odds of having a sudden cardiac arrest in people with a history of CHD [83]. However, the study was limited by the low number of high-coffee consumers and its retrospective design. In a US cohort of people with a recent MI, Mukamal and colleagues noted a time-dependent association between coffee intake and all-cause mortality. Regular coffee drinkers had a lower risk of all-cause mortality within the first 90-days after MI and a higher risk beyond 90 days, up to a median follow-up of 3.8-years compared with abstainers [84]. However, these time-varying effects were not replicated in a Swedish cohort of participants with MI [68] in which an inverse association with total mortality and no association of coffee with cardiac mortality was observed [68]. Coffee consumption was not associated with risk of stroke, MI, sudden death, and CVD events (including fatal-events) in an Italian cohort of 11,231 participants with recent MI [85]. Similarly, Lopez-Garcia and colleagues, found no association between coffee consumption and all-cause or CVD mortality in US nurses with pre-existing CVD within 2-year periods or over longer follow-up [64]. Taken together these data do not provide clear support for either a beneficial or a detrimental effect of coffee consumption for CVD outcomes in persons with pre-existing CVD.

Limited evidence available in people with type-2 diabetes suggests either no association [86, 87] or modest inverse association [88] with fatal CVD or CHD events.

Coffee as a Trigger of Acute Cardiovascular Events

There is some evidence that transient coffee consumption can act as a trigger for cardiac events [89–91]. Case-crossover studies have shown that the risk of first MI [89], acute ischemic stroke [90] and sudden cardiac death [91] is elevated in the hour after coffee consumption. Results from 2 studies suggest that this association is pronounced in irregular coffee consumers (1 cup or less daily) and is not observed in people consuming at least 3 to 4 cups of coffee daily [89, 90]. Such elevated risk in occasional, but not habitual coffee-consumers is consistent with literature showing physiological adaptation of blood pressure and epinephrine levels with persistent caffeine exposure. However, case-crossover studies are vulnerable to within-person confounding by co-triggers such as stress or alcohol intake, and small numbers of cases in such studies often preclude adjustment for these factors [91]. Also, since the absolute risk of a cardiovascular event in an hour is very small, the absolute risk-increase is also low [92]. Given the biological plausibility of detrimental effects of caffeine in occasional coffee consumers, case-crossover studies with a larger number of cases and careful adjustment for confounders are warranted.

Conclusions

Evidence from recent meta-analyses suggests that for most people, regularly drinking 3 to 4 cups of filtered or instant coffee daily is unlikely to increase their risk of CHD, stroke, or heart failure Modest inverse associations between coffee consumption and risk of stroke and heart failure have been observed, but this requires further replication in other populations. Current evidence suggest that coffee consumption can potentially increase cardiovascular risk through small detrimental effects on blood pressure, homocysteine, and plasma lipids (for unfiltered types of coffee), but can potentially decrease risk through beneficial effects on glucose tolerance and inflammation. It is possible that the medical management of hypertension and dyslipidemia, the growing prevalence of obesity (a

proinflammatory condition), and insulin-resistance, and changes in type of coffee consumed from boiled to filtered, has rendered the effects of coffee on pathways of insulin-sensitivity/inflammation more relevant in contemporary times.

Current evidence must also be interpreted within the context of certain caveats. Most studies included participants who were free from cardiovascular disease at baseline, and investigations in at-risk populations are needed. Also, studies have been conducted in European and US populations. Given the growing popularity of coffee in Asia, and evidence that CYP1A2 activity is lower in some Asian compared with European populations [93], and potential differences in coffee preparation methods, more studies from this region are required. Certain types of coffees such as boiled unfiltered coffee can have profound detrimental effects on plasma LDL cholesterol and triglycerides, suggesting that this remains an important modifiable risk factor in populations with high consumption of these coffee-types. Also, since modest increases in blood pressure even with habitual coffee intake have been observed, coffee drinkers with uncontrollable hypertension can assess whether avoiding coffee results in better pressor control. Although results on potentially beneficial effects of coffee consumption on antioxidant status and glucose metabolism are promising, recommending coffee for health purposes is premature until more definite evidence from randomized trials is available. Nevertheless, prospective studies showing that replacing sweetened drinks with coffee is associated with a lower risk of stroke [94], and weight-gain [95] suggest that coffee (if consumed without much cream and sugar) in addition to tea and water may be a suitable alternative for such beverages.

Compliance with Ethics Guidelines

Conflict of Interest Salome A. Rebello is a co-investigator on Nestle Research Center funded clinical trial. Rob M. van Dam is a Principal Investigator on a Nestle Research Center funded clinical trial. He has received research funds from Nestle Research Center; has received travel/accommodation expenses covered for unpaid scientific talk.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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