

The effect of coffee on blood pressure and cardiovascular disease in hypertensive individuals: a systematic review and meta-analysis^{1–3}

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ABSTRACT

Background: The effect of coffee and caffeine on blood pressure (BP) and cardiovascular disease (CVD) in hypertensive persons is uncertain.

Objective: The objective was to summarize the evidence on the acute and longer-term effects of caffeine and coffee intake on BP and on the association between habitual coffee consumption and risk of CVD in hypertensive individuals.

Design: A systematic review and meta-analysis of publications identified in a PubMed and EMBASE search up to 30 April 2011 was undertaken. Data were extracted from controlled trials on the effect of caffeine or coffee intake on BP change and from cohort studies on the association between habitual coffee consumption and CVD.

Results: In 5 trials, the administration of 200–300 mg caffeine produced a mean increase of 8.1 mm Hg (95% CI: 5.7, 10.6 mm Hg) in systolic BP and of 5.7 mm Hg (95% CI: 4.1, 7.4 mm Hg) in diastolic BP. The increase in BP was observed in the first hour after caffeine intake and lasted ≥ 3 h. In 3 studies of the longer-term effect (2 wk) of coffee, no increase in BP was observed after coffee was compared with a caffeine-free diet or was compared with decaffeinated coffee. Last, 7 cohort studies found no evidence of an association between habitual coffee consumption and a higher risk of CVD.

Conclusions: In hypertensive individuals, caffeine intake produces an acute increase in BP for ≥ 3 h. However, current evidence does not support an association between longer-term coffee consumption and increased BP or between habitual coffee consumption and an increased risk of CVD in hypertensive subjects. *Am J Clin Nutr* doi: 10.3945/ajcn.111.016667.

INTRODUCTION

The association between coffee consumption and BP⁴ among normotensive individuals has been widely investigated. In a review of controlled trials, Nurminen et al (1) reported an acute increase in both SBP and DBP in the hours after the intake of caffeine; however, results on the effect of caffeine intake during ≥ 7 d were inconclusive. Also in a meta-analysis of 11 controlled trials that met many quality criteria, Jee et al (2) reported that coffee consumption for >1 d led to a slight increase in BP. Similarly, in a subsequent meta-analysis of randomized controlled trials of coffee or caffeine intake for ≥ 7 d, Noordzij et al (3) concluded that both interventions raised BP, although the effect of coffee was much smaller than that of caffeine. In contrast, cohort studies have found an association of habitual

coffee consumption with either an increased risk of hypertension (4–7) or a decreased risk (8, 9). Last, although recent coffee consumption may transiently increase the risk of acute myocardial infarction (10) and stroke (11), particularly among infrequent drinkers, longitudinal studies suggest that habitual coffee consumption does not increase the long-term risk of CVD (12, 13).

Unfortunately, the effect of coffee and caffeine on BP and CVD among individuals with hypertension is also uncertain. This is a relevant issue because, in these patients, even a slight increase in BP may raise it above levels considered safe. Moreover, coffee consumption might reduce the effectiveness of drug treatments for hypertension. Thus, this information would allow for an evidence-based clinical recommendation and for improving BP control in hypertensive patients. Of note, however, is that the most widely disseminated clinical guidelines on hypertension management do not comment on coffee consumption in the lifestyle recommendations (14, 15). Last, to our knowledge, no comprehensive and systematic overview of these topics has been published recently.

Thus, this article has systematically reviewed the studies on the acute and longer-term effects of coffee and caffeine intake on BP and on the association between habitual coffee consumption and risk of CVD among hypertensive individuals.

METHODS

This review has followed the recommendations of the PRISMA statement (16) and the MOOSE statement (17), as appropriate.

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⁴ Abbreviations used: BP, blood pressure; CGA, chlorogenic acid; CVD, cardiovascular disease; DBP, diastolic blood pressure; HHQ, hydroxyhydroquinone; SBP, systolic blood pressure.

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Literature search

A PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) and EMBASE (<http://www.embase.com>) search up to 30 April 2011 was conducted by using the key terms (words in the title or abstract of the manuscript) “coffee,” “caffeine,” “hypertension,” “hypertensive,” “hypertensives,” “high blood pressure,” “blood pressure,” and “mortality” and the CVD-related terms “ischemic heart disease,” “myocardial infarction,” “angina pectoris,” “arrhythmia,” “atrial fibrillation,” “stroke,” “heart failure,” “coronary heart disease,” “coronary bypass,” and “coronary angioplasty.” The complete PubMed and EMBASE searches are shown elsewhere (*see* Supplemental File 1 under “Supplemental data” in the online issue). Reference lists in articles retrieved from the electronic search were also scanned.

Study selection and data extraction

Two investigators (AEM and EL-G) independently selected the studies and extracted the data, and discrepancies were resolved by consensus. To examine the effect of coffee or caffeine consumption on change in BP, we selected controlled clinical trials, either randomized or nonrandomized, in which participants had an SBP ≥ 140 mm Hg and/or a DBP ≥ 90 mm Hg (18–25) or who were identified as having mild (26) or mild-to-moderate hypertension (27, 28). Trials with a co-intervention on other lifestyles factors, such as smoking or physical activity, were excluded. As was done in a previous review (3), the studies were classified into 2 groups, according to whether duration of coffee or caffeine intake was < 1 wk (indicating an acute effects) or ≥ 1 wk (indicating longer-term effects).

To explore the association between habitual coffee consumption and risk of CVD in hypertensive individuals, we selected cohort studies in which the outcome variables were CVD incidence or mortality. Both cohort studies of hypertensive individuals and larger cohorts that presented results in a subgroup of hypertensive individuals were included.

Quality assessment

The clinical trials were assessed to determine whether they were randomized, whether the intervention was blinded, whether losses to follow-up were identified, and whether each BP reading was made at least twice. The cohort studies were assessed to determine whether the diagnosis of hypertension was based on self-reports or measurements, whether repeated measurements of coffee consumption were made during follow-up, whether losses to follow-up were identified, how morbidity and mortality of CVD were measured or validated, and the degree of adjustment for potential confounders, particularly other predictors of CVD risk and antihypertensive drugs.

Synthesis of the data

In each clinical trial, the net effect of coffee/caffeine on BP was calculated as the difference in mean SBP and DBP change between the intervention and control groups. In crossover designs, the effect of coffee/caffeine was calculated as the difference in BP between the intervention and control periods.

In the meta-analysis of clinical trials on the acute effects of coffee/caffeine on BP, each period of time with BP measurements after the administration of coffee/caffeine was considered as an independent stratum (< 60 , 60 to < 120 , and 120 to 180 min). When a study had more than one measurement in the same period of observation, we used the mean of those measurements. For example, in the study by Freestone and Ramsay (26), 3 strata were considered, because measures after caffeine intake were available for the first (mean BP change at 5, 15, and 30 min), second (BP change at 60 min), and third (BP change at 120 min) periods of observation in both the intervention and control groups. However, protocols a and b in the study by Potter et al (21) were considered as independent studies because they considered different times of caffeine abstinence before the intervention and included a different number of participants. Because none of the studies selected presented the SD_i of the mean BP in each stratum, it was estimated by using the following formula:

$$SD_i = SEM_i \times (n_i)^{1/2} \quad (1)$$

where SEM_i is the SEM in each stratum and n_i is the size of each stratum. In studies without information on SEM or other sources to calculate the SD (19, 26), the SEM was imputed in a standardized way by using the prognostic method (29) with the following formula:

$$SEM_j^* = \Sigma_{i=1}^k SEM_i (n_i)^{1/2} / k(n_j^*)^{1/2} \quad (2)$$

where k is the total number of strata.

In the crossover studies, the SD of BP change in each period (intervention and control) was calculated by using the following formula:

$$SD_{\text{change}} = \left[(SD_{\text{baseline}})^2 + (SD_{\text{final}})^2 - \left(2 \times R \times SD_{\text{baseline}} \times SD_{\text{final}} \right) \right]^{1/2} \quad (3)$$

where R is the correlation coefficient (30). Because none of the studies presented information on individuals to obtain R , the most conservative estimate was assumed, a minimum correlation of 0.50. This value was used in a previous meta-analysis of the effect of coffee on BP (3).

Heterogeneity among studies was quantified by using the I^2 statistic (31). To pool the results of trials of the acute effects of caffeine on BP, fixed-effects models were used when heterogeneity was low or absent ($I^2 < 20\%$); when heterogeneity was greater and it was considered appropriate to pool the results, random-effects models were used. A sensitivity analysis was performed by repeating the analyses after the studies that had the largest effect on the overall result were excluded. In addition, the analyses were stratified by caffeine dose (200, 250, or > 250 –300 mg), time of abstinence from caffeine before beginning the trial (9, 12, or 48 h), and antihypertensive treatment (yes or no) to examine the influence of these variables on the effect of caffeine on BP. Differences in results across strata were tested by using meta-regression models.

Possible publication bias was explored with Begg's funnel plots (32) and with Egger's regression asymmetry test (33) in studies with a sufficient number of observations to allow for

a meaningful analysis. Data were analyzed by using Stata software version 10.0 (34).

Clinical trials of the longer-term effects of coffee consumption on BP were grouped according to the type of comparison examined: coffee compared with caffeine-free diet, coffee compared with decaffeinated coffee, and comparisons of coffees with different amounts of CGA and HHQ. Because of the small number of available studies and their heterogeneity, it was not considered advisable to pool their results by using meta-analytic techniques.

RESULTS

The flow of articles from the initial search to final inclusion in this systematic review is shown in **Figure 1**. The search of PubMed, EMBASE, and reference lists identified a total of 438 articles, 330 of which were excluded because their title or abstract was not related to the study associations. Of the 108 articles retrieved for critical review, 86 referred to the effect of coffee/caffeine on BP. Of these, 75 were excluded because they did not provide data among hypertensive individuals, were literature reviews, or had other specific criteria for exclusion detailed elsewhere (*see* Supplemental File 2 under “Supplemental

data” in the online issue). Accordingly, 5 studies on the acute effects and 6 studies on the longer-term effects of coffee/caffeine on BP were finally included. In addition, 40 studies were identified on the effects of coffee on CVD incidence or mortality. After the review articles were excluded (ie, those that did not provide specific data on hypertensive individuals and those with insufficient data), the review was based on 7 cohort studies.

Acute effects of caffeine on BP in hypertensive individuals

The characteristics of the 5 studies selected are shown in **Table 1**. All were conducted in English-speaking countries and included persons between 20 and 82 y of age who were habitual coffee drinkers. All of these studies had a crossover design. Study quality was heterogeneous. Three studies were randomized (18, 21, 27), and all of the studies were double-blind except for the oldest study (26). The BP measurements were based on ≥ 2 readings in 3 studies, but Freestone and Ramsay (26) and Vlachopoulos et al (27) did not report this information. No losses to follow-up were reported, although in the study by Potter et al (21) one person did not participate in the second protocol because of illness. The BP cutoffs to define hypertension varied among studies and were not reported in 2 studies (26,

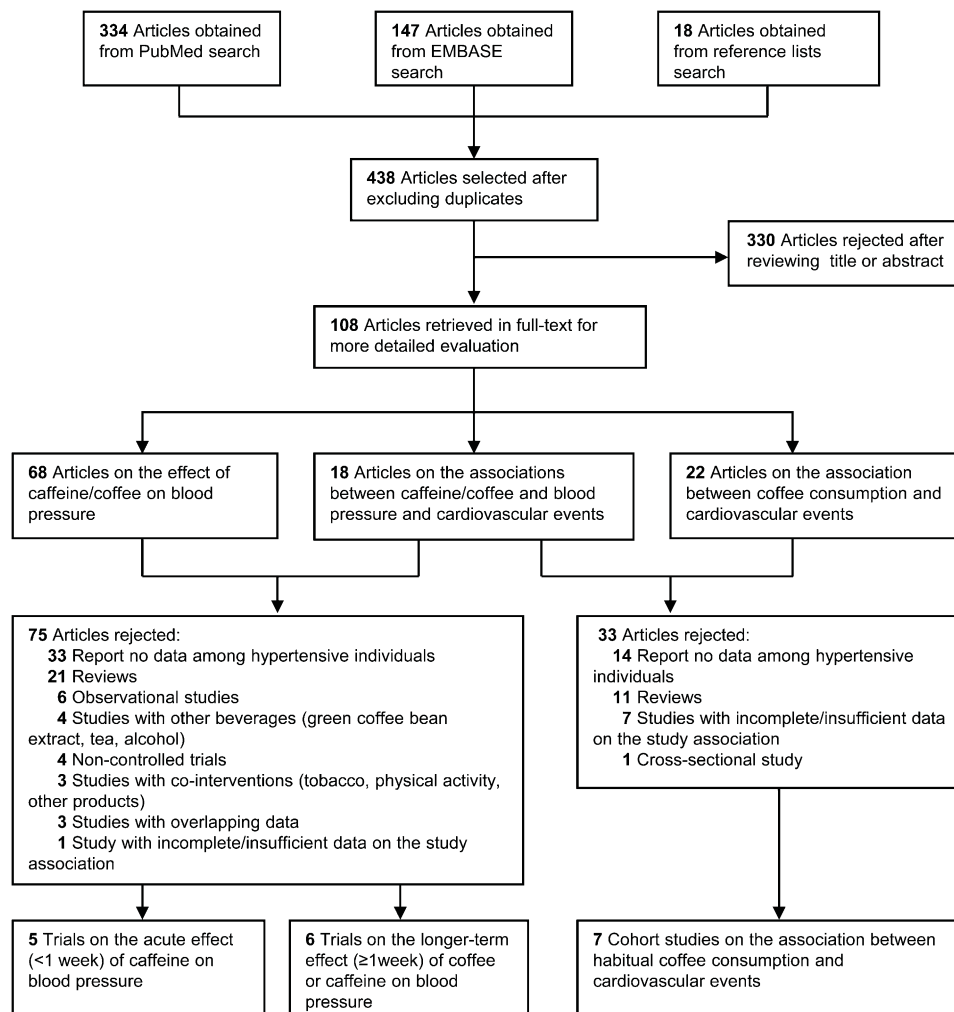


FIGURE 1. Flow of publications throughout the study. EMBASE, <http://www.embase.com>; PubMed, <http://www.ncbi.nlm.nih.gov/pubmed>.

TABLE 1
Clinical trials of coffee/caffeine on blood pressure in individuals with hypertension (HT)^y

Reference	Characteristics of participants							Antihypertensive medications	
	Country	Design	n	Age	Sex	Lifestyle/health status	Habitual coffee/caffeine intake before the trial		Criteria for inclusion as hypertensive
γ									
Acute effect of caffeine intake (trials <1 wk duration)									
Freestone and Ramsay (26), 1982	United Kingdom	C, X	16	30–65	M/F	Habitual smokers	4 cups/d ²	Mild HT	Yes
Potter et al (21), 1993 ^{a,b}	United Kingdom	R, DB, C, X	a: 8; b: 7	65–82	M/F	Nonsmokers with no history of IHD, stroke, diabetes, renal impairment, postural hypotension, anemia, or autonomic neuropathy	Coffee or tea drinkers	BP ≥160/95 mm Hg	No (antihypertensive therapy stopped 4 wk before)
Sung et al (19), 1994	United States	DB, C, X	18	30–45	M	<1 pack cigarettes/d, <2 alcoholic beverages/d	1–8 cups/d	BP 140–160/90–105 mm Hg	No
Pincomb et al (18), 1996	United States	R, DB, C, X	24	20–39	M	Smoking <10 cigarettes/d, with no aerobic functional impairment during exercise, medication use, CVD, or chronic disease	50–800 mg caffeine/d	BP 146–160/90–99 mm Hg	No
Vlachopoulos et al (27), 2003	United States	R, DB, C, X	12	60 ± 3	M/F	1 current smoker, 1 with non-insulin-dependent diabetes, 2 with hyperlipidemia, 6 with a positive family history of premature CVD, and all with HT controlled with medication in the past 6 mo	Caffeine consumers	Mild-to-moderate HT	Yes
Longer-term effects of coffee intake trials (≥1 wk duration)									
MacDonald et al (20), 1991 ^{a,b}	Scotland	R, DB, C, X	50	26–63	M/F	9 smokers with no biochemical, hematologic, electrocardiographic, or clinical abnormalities	≥3 cups/d	DBP 90–105 mm Hg	No
Eggertsen et al (28), 1993	Sweden	R, DB, C, X	23	28–74	M/F	Two smokers	3–4 cups/d	Mild-to-moderate hypertension	Yes
Rakic et al (22), 1999	Australia	R, C, P	27	≥50	M/F	Nonsmokers living in nursing homes with no diabetes mellitus, arrhythmia, heart failure, or renal disease	NA	BP 140–180/90–110 mm Hg and/or treatment of HT	Yes

(Continued)

TABLE 1 (Continued)

Characteristics of participants									
Reference	Country	Design	n	Age	Sex	Lifestyle/health status	Habitual coffee/caffeine intake before the trial	Criteria for inclusion as hypertensive	Antihypertensive medications
Chikama et al (23), 2008 ^{a,b,c,d}	Japan	R, DB, C, P	60	20–65	M/F	No heavy smokers or heavy alcohol consumers; no caffeine- or coffee-hypersensitive or allergic persons; no severe liver, kidney, cerebrovascular, or heart disease; no endocrine disorders, metabolic disturbances, diabetes, or potential pregnancy	NA	BP 140–159/90–99 mm Hg	No
Yamaguchi et al (24), 2008 ^{a,b,c,d}	Japan	R, DB, C, P	183	30–65	M/F	No heavy smokers or alcohol abusers and no history of medication use for HT, hyperlipidemia, diabetes mellitus, stroke, CVD, or renal or liver dysfunction	NA	BP 140–155/90–97 mm Hg	No
Ochiai et al (25), 2009 ^{a,b,c,d}	Japan	R, DB, C, P	21	30–64	M/F	Vascular failure and ≥2 of the following risk factors related to hypertension: smoking, waist circumference, triglycerides, total cholesterol, lipoprotein, and blood sugar	NA	BP 140–159/<100 mm Hg	No

¹ a, b, c, and d indicate different protocols in a study and are reported in detail in Figures 2 and 3 and in Table 3. BP, blood pressure; C, controlled; CVD, cardiovascular disease; DB, double-blinded; DBP, diastolic blood pressure; IHD, ischemic heart disease; NA, not available; P, parallel; R, randomized; X, crossover.

² 1 cup = 240 mL.

27). Moreover, participants in these 2 studies (26, 27) continued to take their antihypertensive medication, whereas patients in the other studies did not receive treatment. Participants abstained from coffee and caffeine consumption before the study for periods ranging from 9 to 48 h.

The meta-analysis of the acute effects of caffeine on SBP and DBP, respectively, grouped according to the time of observation (<60, 60 to <120, and 120 to 180 min) is shown in **Figures 2** and **3**. Certain assumptions were made in the meta-analysis. First, in the 2 studies in which caffeine doses were adjusted for body weight (18, 19), caffeine intake (mg) was estimated as the product of the dose/kg times the mean reported weight (19). Because weight was not reported by Pincomb et al (18), it was assumed to be 82 kg (mean value in white men aged 20–39 y in the United States) (35). Second, in the study by Potter et al (21), we used BP measured in the standing rather than in the supine position, because this is more frequent in clinical practice.

In all trials, 200–300 mg caffeine was administered (equivalent to ~1.5–2 cups filtered coffee). The overall change in SBP associated with caffeine over all studies and observation periods was 8.14 mm Hg (95% CI: 5.68, 10.61 mm Hg). SBP increased by 7.43 mm Hg in the first 60 min after coffee intake and remained elevated at the same level in the following periods. No heterogeneity among studies was detected in SBP elevation, either in each time period or over time ($I^2 = 0.0\%$) (Figure 2).

Given the large contribution of the study by Pincomb et al (18) to the overall results (Figure 2), the analyses were repeated after this study was excluded; similar results were found. Moreover, in the stratified analyses, the effect of caffeine on SBP did not vary with caffeine dose in the range of 200 to 300 mg (**Table 2**). The increase in SBP due to caffeine was similar regardless of whether or not participants were taking antihypertensive medication (**Table 2**).

For DBP, the overall change associated with caffeine intake was 5.75 mm Hg (95% CI: 4.09, 7.41 mm Hg). As for SBP, the increase in DBP was observed in the first 60 min and up to 3 h after caffeine intake (Figure 3). These results were obtained with random-effects models because some heterogeneity was observed in the results for the period 120–180 min ($I^2 = 36.1\%$). The heterogeneity is due to the larger increase in DBP observed in the study by Sung et al (19), which used higher doses of caffeine (300 mg) (Figure 3). The stratified and meta-regression analyses in Table 2 also suggest that DBP increased more in those who received >250 mg caffeine than in those who received smaller doses. The increase in DBP produced by caffeine did not vary with time of abstinence from caffeine before beginning the trial or with use of antihypertensive treatment (**Table 2**).

The Begg's funnel plots constructed with the 9 observations on the effect of 250 mg caffeine did not suggest publication bias for

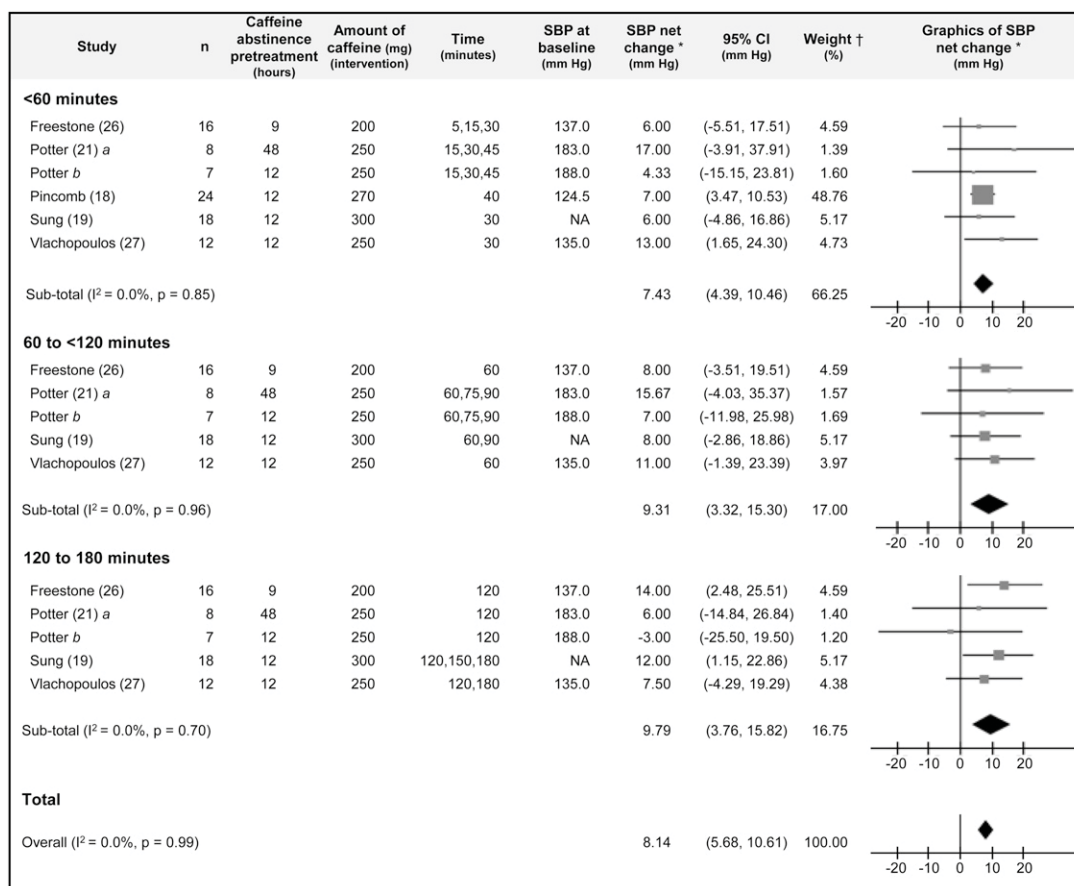


FIGURE 2. Meta-analysis of the acute effects of caffeine on SBP in hypertensive individuals, by time after caffeine intake. *The net change in SBP is the difference in SBP between the intervention period and the control period. †Weights are from fixed-effects models. In Potter's study, *a* indicates the protocol with a long caffeine abstinence period before the intervention, and *b* indicates the protocol with a short caffeine abstinence period before the intervention. NA, not available; SBP, systolic blood pressure.

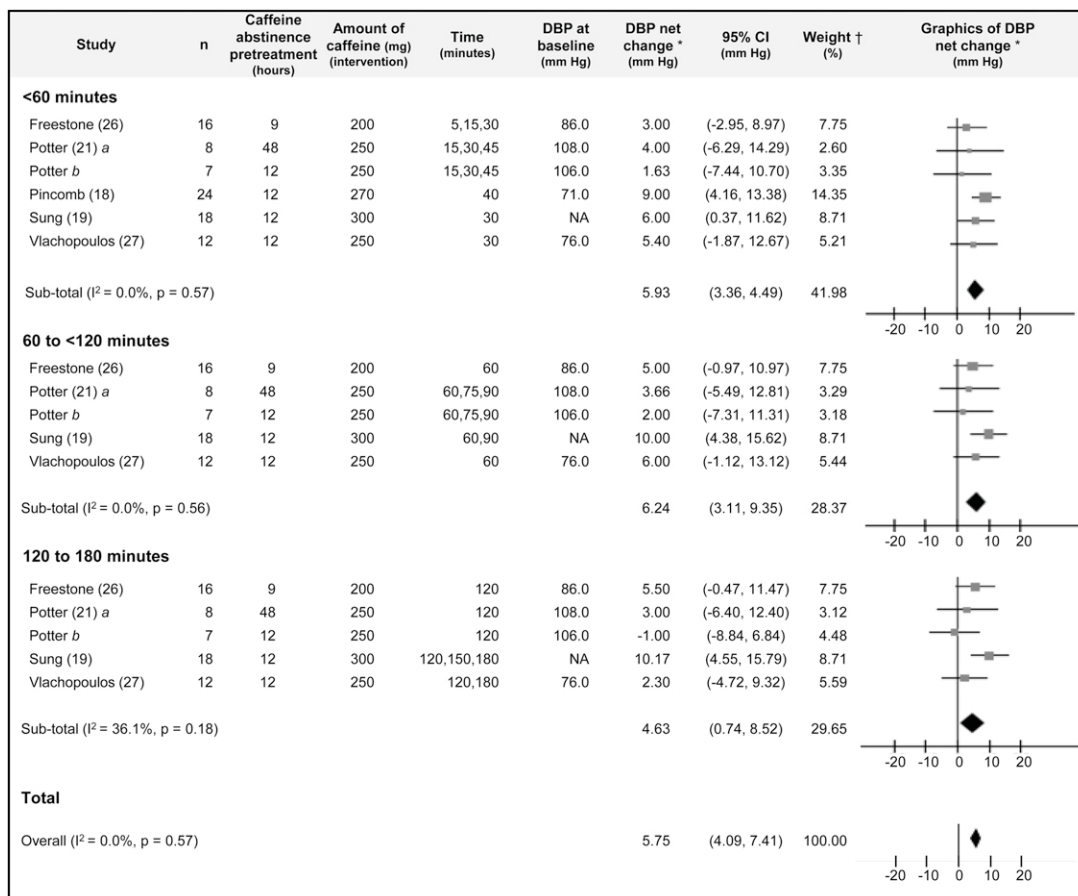


FIGURE 3. Meta-analysis of the acute effects of caffeine on DBP in hypertensive individuals, by time after caffeine intake. *The net change in DBP is the difference in systolic blood pressure between the intervention period and the control period. †Weights are from random-effects models. In Potter's study, a indicates the protocol with a long caffeine abstinence period before the intervention, and b indicates the protocol with a short caffeine abstinence period before the intervention. DBP, diastolic blood pressure; NA, not available.

the results on SBP or DBP. Moreover, the Egger's test P value was 0.411 for SBP and 0.583 for DBP. Thus, the results of the Egger's test did not support the existence of publication bias for the effect of 250 mg caffeine. Unfortunately, we had only 3 observations on the effect of 200 mg caffeine and 4 observations on the effect of >250–300 mg caffeine. Accordingly, a formal assessment of publications bias was not considered advisable for these caffeine doses.

Longer-term effects of coffee consumption on BP in hypertensive subjects

The characteristics of the 6 studies selected are shown in Table 1. The studies were conducted in different countries (20, 22, 28), with the 3 most recent studies carried out in Japan (23–25). All included persons of both sexes were aged ≥ 20 y. Four studies had a parallel design (22–25) and 2 were crossover studies (20, 28). The quality of the studies was high. All were randomized and double-blind, except for the study by Rakic et al (22), which did not report whether the intervention was blinded. Loss to follow-up was $<10\%$ in all studies, and in the study of Rakic et al (22) there were no losses. The BP values were based on the mean of 24-h ambulatory blood pressure monitoring in 3 studies (20, 22, 28), and on ≥ 2 BP readings in the remaining studies

(23–25). The cutoff points to define hypertension were heterogeneous, and the oldest study (20) considered only the DBP value. The study subjects continued with antihypertensive medication in 2 studies (22, 28), and they abstained from coffee and caffeine during 1 or 2 wk beforehand in 4 studies (22, 24, 28).

The longer-term effects of coffee intake on BP are shown in Table 3. Two of the studies (20, 28) presented BP data only at the end of the intervention and control periods. Thus, in the study by MacDonald et al (20), baseline BP was assumed to be the same as BP at the end of the period with the normal diet. In the study by Eggertsen et al (28), the effect of caffeine on BP was estimated by comparing only the final values of BP between the treatment branches. The duration of the intervention varied from 2 to 12 wk. No increase in BP was observed when coffee intake was compared with the caffeine-free diet and when coffee intake was compared with the decaffeinated coffee.

Three studies examined the effect of drinking coffee containing different amounts of HHQ and/or CGA on BP. Chikama et al (23) compared the effect of coffee with reduced HHQ with that of normal coffee. In comparison with normal coffee, the reduced-HHQ coffee resulted in a decrease in BP after 4–12 wk of consumption. In the second study, Yamaguchi et al (24) studied the effect of coffee without HHQ and with different

TABLE 2

Meta-analysis of the acute effects of caffeine on blood pressure in hypertensive individuals, stratified by caffeine intake, caffeine abstinence before the start of the trial, and use of antihypertensive medication

	Systolic blood pressure			Diastolic blood pressure		
	Net change ¹	95% CI	P value ²	Net change ¹	95% CI	P value ²
	mm Hg	mm Hg		mm Hg	mm Hg	
Amount of caffeine						
200 mg (26)	9.33	(2.69, 15.98)		4.50	(1.06, 7.94)	
250 mg (21, 27)	9.56	(4.30, 14.83)	0.958	3.11	(0.35, 5.87)	0.537
>250–300 mg (18, 19)	7.40	(4.32, 10.48)	0.605	8.82	(6.21, 11.43)	0.050
Caffeine abstinence before the trial						
9 h (26)	9.33	(2.69, 15.98)		4.50	(1.06, 7.94)	
12 h (18, 19, 21, 27)	7.68	(4.96, 10.41)	0.653	6.19	(3.87, 8.51)	0.353
48 h (21)	12.99	(1.18, 24.80)	0.597	3.53	(−2.00, 9.06)	0.770
Use of antihypertensive medication						
No (18, 19, 21)	7.49	(4.60, 10.37)		6.21	(3.77, 8.65)	
Yes (26, 27)	9.93	(5.16, 14.69)	0.391	4.51	(1.82, 7.16)	0.240

¹ The net change in blood pressure is the difference in blood pressure between the intervention and the control periods. Fixed-effects models were used for systolic blood pressure and random-effects models for diastolic blood pressure meta-analysis.

² Significance of the difference between the categories of the stratification variables, obtained from meta-regression analyses.

concentrations of CGA in comparison with normal coffee. The coffee without HHQ decreased BP, although the results did not show a clear dose-response with the concentration of CGA (24). Last, Ochiai et al (25) observed that, in comparison with a cup of coffee with a reduced concentration of HHQ and no CGA, a cup of coffee with a reduced concentration of HHQ but elevated concentration of CGA seemed to decrease SBP but did not modify DBP after 4, 6, and 8 wk of intervention.

Habitual coffee consumption and risk of CVD in hypertensive subjects

Five cohort studies (13, 36–39) were conducted in the United States, one in Finland (40), and the other in Sweden (41). Except for one study designed as a cohort of hypertensive individuals (36), the rest were large cohort studies in different populations with no clinical inclusion criterion, in which a subcohort developed hypertension during follow-up. Three cohorts included persons aged ≥ 30 y (13, 36, 38), and the others included those older than 48 y (37, 40, 41) and 64 y (39). The study quality was good. In 5 studies, hypertension was defined on the basis of measured BP values (36–40). Two studies were based on self-reported history of hypertension (41) or on a diagnosis of hypertension reported by nurses and were therefore very reliable (13). Habitual consumption of coffee was reported at the beginning of follow-up and in one study (13) was updated every 4 y. In all studies, information on CVD was confirmed by review of the medical record or death certificate. Length of follow-up varied from 4 to 25 y. Finally, in all cases, the results were adjusted for the main confounding factors.

The studies included in this section examined different end-points (Table 4). The 3 studies on CVD mortality found no excess risk of death associated with coffee or caffeinated drinks in hypertensive individuals (36, 38, 39). In contrast, the studies on coffee consumption and risk of stroke in hypertensive individuals yielded inconsistent results. Hakim et al (37) found

that those who consumed ≥ 20 oz coffee/d (600 mL coffee/d), ~ 4 cups, had double the risk of thromboembolic stroke than did noncoffee drinkers; however, Lopez-García et al (13) and Larsson et al (41) found no excess risk, even in those with higher consumption (≥ 4 cups/d). Finally, Larsson et al (40) observed a lower risk of cerebral infarction in those who consumed ≥ 6 cups/d than in those with lower consumption (< 2 cups/d). Only one study examined the effect of coffee on heart valve disease, and no association was found (39).

DISCUSSION

This review has shown that, in hypertensive patients, caffeine intake of 200 to 300 mg produced an important increase in BP, which was observed in the first 60 min after intake and persisted up to 180 min afterward. In contrast, drinking coffee for 2 wk did not appear to increase BP. These results are based on high-quality clinical trials. Finally, the cohort studies reviewed do not support an association between habitual coffee consumption and a higher risk of CVD in hypertensive individuals.

These results are unique because they extend the evidence of the effect of coffee on BP to hypertensive individuals. The most comprehensive review to date on the acute effects of caffeine in normotensive individuals reported BP elevations from 2 to 12 mm Hg for SBP and from 3 to 11 mm Hg for DBP (the results of the studies were not pooled statistically) (1). In our study, hypertensive individuals who received caffeine showed an overall increase of 8 mm Hg in SBP and of nearly 6 mm Hg in DBP. Thus, caffeine has a comparable effect on normotensive and hypertensive individuals.

In considering the longer-term effects of coffee consumption on normotensive individuals, 2 previous reviews showed elevated BP: 2.4 mm Hg in SBP and 1.2 mm Hg in DBP in the study by Jee et al (2) and 2.0 mm Hg in SBP and 0.7 mm Hg in DBP in the study by Noordzij et al (3). In our study, long-term coffee consumption did not show a clear increase in BP in hypertensive

TABLE 3
Longer-term effects (≥ 1 wk) of coffee consumption on BP in hypertensive individuals¹

Reference	No. of subjects	Coffee/caffeine		Amount of coffee (intervention)		Duration of the intervention	SBP		DBP		Conclusions
		No. of subjects before treatment	Coffee ²	Caffeine doses	Type and preparation		Baseline	Net change ³ (95% CI)	Baseline	Net change ³ (95% CI)	
			<i>cups/d</i>	<i>mg/d</i>		<i>wk</i>	<i>mm Hg</i>	<i>mm Hg</i>	<i>mm Hg</i>	<i>mm Hg</i>	
Coffee/caffeine-free diet											
MacDonald et al (20) ^a	50	No	≥3	NA	Instant	2	134.0	-0.9 (-2.3, 0.5)	86.3	0.5 (-1.3, 0.3)	Coffee consumption did not increase BP
Rakic et al (22)	27	2 wk	5	300	Instant	2	135.4	5.2 (-5.3, 15.7)	72.3	2.7 (-6.6, 12.0)	Coffee consumption increased BP
Coffee/decaffeinated coffee											
MacDonald et al (20) ^b	50	No	≥3	NA	Instant	2	134.0	-0.5 (-1.9, 0.9)	86.3	-0.2 (-1.0, 0.6)	Coffee consumption did not increase BP
Eggertsen et al (28)	23	2 wk	3-4	NA	Instant	2	131.6	1.5 (-6.6, 9.6)	80.3	0.7 (-3.9, 5.3)	Coffee consumption did not increase BP
Reduced HHQ coffee (active)/coffee (control)											
Chikama et al (23) ^a	60	No	1	77 (active group), 75 (control group)	Instant coffee with reduced HHQ	4	144.7	-5.1 (-9.6, -0.7)	90.5	-2.1 (-5.0, 0.8)	Reduced HHQ coffee consumption decreased BP
Chikama et al (23) ^b	60	No	1	77 (active group), 75 (control group)	Instant coffee with reduced HHQ	8	144.7	-4.0 (-8.3, 0.3)	90.5	-2.4 (-5.5, 0.7)	Reduced HHQ coffee consumption decreased BP
Chikama et al (23) ^c	60	No	1	77 (active group), 75 (control group)	Instant coffee with reduced HHQ	10	144.7	-4.2 (-8.3, -0.2)	90.5	-4.0 (-7.1, -0.9)	Reduced HHQ coffee consumption decreased BP
Chikama et al (23) ^d	60	No	1	77 (active group), 75 (control group)	Instant coffee with reduced HHQ	12	144.7	-6.0 (-11.0, -1.0)	90.5	-3.0 (-6.1, 0.1)	Reduced HHQ coffee consumption decreased BP
HHQ-free coffee with different levels of CGA/coffee											
Yamaguchi et al (24) ^a	183	2 wk	1	75-81	Instant HHQ-free coffee with zero dose of CGA	4	143.1	-0.9 (-3.2, 1.4)	90.6	0 (-0.7, 0.7)	HHQ-free coffee consumption decreased BP
Yamaguchi et al (24) ^b	183	2 wk	1	75-81	Instant HHQ-free coffee and low dose of CGA	4	145.0	-2.7 (-4.8, -0.6)	91.2	-2.2 (-2.8, -1.6)	HHQ-free coffee consumption decreased BP
Yamaguchi et al (24) ^c	183	2 wk	1	75-81	Instant HHQ-free coffee with middle dose of CGA	4	142.8	-2.8 (-5.2, -0.4)	90.6	-1.8 (-2.5, -1.1)	HHQ-free coffee consumption decreased BP

(Continued)

TABLE 3 (Continued)

Reference	No. of subjects	Coffee/caffeine		Amount of coffee (intervention)			Duration of the intervention	SBP		DBP		Conclusions
		No. of subjects before treatment	Coffee ²	Caffeine doses	Type and preparation	Instant HHQ-free coffee with high dose of CGA		Baseline	Net change ³ (95% CI)	Baseline	Net change ³ (95% CI)	
Yamaguchi et al (24) ^d	183	2 wk	1	75–81	Instant HHQ-free coffee with high dose of CGA		4	144.1	−3.3 (−5.6, −1.1)	91.2	−2.3 (−2.9, −1.7)	HHQ-free coffee consumption decreased BP
Reduced HHQ coffee and elevated CGA (active)/reduced HHQ and reduced CGA coffee (control)												
Ochiai et al (25) ^a	21	No	1	79 (active group), 59 (control group)	Instant coffee with reduced HHQ and elevated CGA content		2	147.3	3.5 (−2.3, 9.3)	88.4	2.6 (−4.7, 9.9)	Reduced HHQ coffee with ↑CGA consumption decreased SBP but did not modify DBP
Ochiai et al (25) ^b	21	No	1	79 (active group), 59 (control group)	Instant coffee with reduced HHQ and elevated CGA content		4	147.3	−2.1 (−8.5, 4.3)	88.4	0.8 (−5.4, 7.0)	
Ochiai et al (25) ^c	21	No	1	79 (active group), 59 (control group)	Instant coffee with reduced HHQ and elevated CGA content		6	147.3	−7.1 (−14.4, 0.2)	88.4	1.0 (−5.3, 7.3)	Reduced HHQ coffee with ↑CGA consumption decreased SBP but did not modify DBP
Ochiai et al (25) ^d	21	No	1	79 (active group), 59 (control group)	Instant coffee with reduced HHQ and elevated CGA content		8	147.3	−2.9 (−10.1, 4.3)	88.4	3.1 (−2.4, 8.6)	Reduced HHQ coffee with ↑CGA consumption decreased SBP but did not modify DBP

¹ In MacDonald et al's study, a and b indicate protocols with different comparisons in the control period. In Yamaguchi et al's study, a, b, c, and d indicate protocols with different interventions. In Chikama et al's and Ochiai et al's studies, a, b, c and d indicate protocols with different durations. BP, blood pressure; CGA, chlorogenic acid; DBP, diastolic blood pressure; HHQ, hydroxyhydroquinone; NA, not available; SBP, systolic blood pressure.

² 1 cup = 240 mL or 8 ounces.
³ The net change in BP is the difference in BP between the treated group and the control group for parallel trials and the difference in BP between the intervention period and the control period for crossover trials.

TABLE 4
Cohort studies of habitual coffee consumption and CVD in hypertensive individuals^a

Reference	Country, duration of follow-up	Population data	BP criteria for inclusion as hypertensive	Exposure/categories ²	Outcome (n)	Confounding factors	Multivariate-adjusted results	Conclusions
Martin (36), 1988	United States, 4 y	M/F, 30–69 y (n = 10,064)	DBP ≥ 90 mm Hg (n = 10,064)	Caffeinated beverage consumption: 0, >0–2, >2–4, or >4 cups/d	Total mortality (n = 589), cerebrovascular mortality (n = 64), other CVD mortality (n = 272)	Age, sex, race, body weight, initial DBP, fasting plasma glucose, total cholesterol, and marital status	RR of total mortality for categories of consumption: 1.0, 0.82 (0.65, 1.03), 0.82 (0.62, 1.82), and 0.90 (0.63, 1.28); RR of cerebrovascular mortality for categories of consumption: 1.0, 0.73 (0.37, 1.46), 0.61 (0.26, 1.44), and 1.30 (0.56, 3.04); RR of other CVD mortality for categories of consumption: 1.0, 0.93 (0.66, 1.30), 0.81 (0.53, 1.23), and 0.80 (0.46, 1.39)	Caffeinated beverage consumption not associated with increased cerebrovascular or other CVD mortality
Hakim (37), 1998	United States, 25 y	M, 55–68 y (n = 8006)	BP ≥ 140/90 mm Hg (n = 499)	Coffee consumption: 0, 4–8, 12–16, and ≥ 20 oz/d	Thromboembolic stroke (n = 76)	Age, SBP, total cholesterol, triglycerides, diabetes, physical activity, and alcohol consumption	RR for consumption of ≥ 20 oz/d: 2.1 (1.2, 3.7), <i>P</i> -trend = 0.006 (information for other categories not available)	Coffee consumption associated with increased risk of thromboembolic stroke
Greenberg (38), 2007	United States, 8.8 y	M/F, 32–86 y (n = 6594)	Stage 1: BP 140–159/90–99 mm Hg (n = 512); stage 2: BP ≥ 160/100 mm Hg (n = 290)	Caffeinated beverage consumption: <1.5 and ≥ 1.5 cups/d	Heart disease mortality (n = 147)	Age, sex, smoking, BMI, race, physical activity, alcohol consumption, income, educational level, and American-style diet	RR for consumption of ≥ 1.5 cups/d in stage 1 hypertensive subjects: 0.62 (0.39, 0.99); RR for consumption of ≥ 1.5 cups/d in stage 2 hypertensive subjects: 0.81 (0.47, 1.41)	Caffeinated beverage consumption not associated with increased heart disease mortality
Larsson (40), 2008	Finland, 13.6 y	M, 50–69 y (n = 26,556)	BP ≥ 140/90 mm Hg (number of hypertensive individuals not reported)	Coffee consumption: <2, 2–3, 4–5, 6–7, and ≥ 8 cups/d	Cerebral infarction (n = 1729 cases in those with SBP ≥ 140 mm Hg and 1455 in those with DBP ≥ 90 mm Hg)	Age, number of cigarettes smoked daily, BMI, leisure-time physical activity, alcohol intake, SBP and DBP at baseline, serum total cholesterol, serum HDL cholesterol, histories of diabetes and CHD, and tea consumption	RR for categories of consumption in those with SBP ≥ 140 mm Hg: 1.0, 0.92 (0.77, 1.10), 0.90 (0.76, 1.07), 0.79 (0.65, 0.95), and 0.76 (0.63, 0.93), <i>P</i> -trend = 0.001; RR categories of consumption in those with DBP ≥ 90 mm Hg: 1.0, 0.88 (0.72, 1.06), 0.88 (0.73, 1.06), 0.75 (0.61, 0.92), and 0.70 (0.57, 0.87), <i>P</i> -trend < 0.001	Coffee consumption was associated with lower risk of cerebral infarction
Greenberg (39), 2008	United States, 10.1 y	M/F, ≥ 65 y (n = 1354)	BP ≥ 160/100 mm Hg (n = 302)	Coffee consumption: 0 and ≥ 1 cups/d	CHD mortality (n = 39), heart valve disease (n = 20)	Age, sex, smoking, BMI, physical activity, alcohol consumption, marital status, BP, history of CVD, and antihypertensive medication use	RR of CHD mortality for consumption of ≥ 1 cup/d: 0.87 (0.44, 1.72), <i>P</i> -trend = 0.48; RR of heart valve disease for consumption of ≥ 1 cup/d: 1.72 (0.41, 7.25), <i>P</i> -trend = 0.04	Coffee consumption was not associated with increased risk of CHD mortality or heart valve disease

(Continued)

TABLE 4 (Continued)

Reference	Country, duration of follow-up	Population data	BP criteria for inclusion as hypertensive	Exposure/categories ²	Outcome (n)	Confounding factors	Multivariate-adjusted results	Conclusions
Lopez-Garcia (13), 2009	United States, 24 y	F, mean age: 56 y (n = 83,076)	BP $\geq$ 140/90 mm Hg (n = 12,960)	Coffee consumption: <1 cup/mo, 1 cup/mo to 4 cups/wk, 5–7 cups/wk, 2–3 cups/d, and $\geq$ 4 cups/d	Stroke (n = 900)	Age, smoking, BMI, physical activity, alcohol consumption, menopausal status, use of hormone replacement therapy, aspirin use, glycemic load, and intakes of total energy, calcium, potassium, sodium, folate, whole grain, fruit, vegetables, and fish	RRs for categories of coffee consumption: 1.0, 0.97 (0.76, 1.24), 0.90 (0.72, 1.11), 0.98 (0.77, 1.24), and 1.10 (0.76, 1.58), <i>P</i> -trend = 0.53	Coffee consumption not associated with increased risk of stroke
Larsson (41), 2011	Sweden, 10.4 y	F, 49–83 y (n = 34,670)	Self-reported history of hypertension (number of hypertensive individuals not reported)	Coffee consumption: <1, 1–2, 3–4, and $\geq$ 5 cups/d	Cerebral infarction (n = 482)	Age, smoking status, pack-years of smoking, education, BMI, total physical activity, history of diabetes, aspirin use, family history of myocardial infarction, and intakes of total energy, alcohol, red meat, fish, fruit, and vegetables	RR for categories of consumption: 1.0, 0.82 (0.61, 1.11), 0.95 (0.70, 1.29), and 0.73 (0.49, 1.09), <i>P</i> -trend = 0.29	Coffee consumption not associated with increased risk of cerebral infarction

¹ BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; NA, not available; SBP, systolic blood pressure.

² 1 cup = 240 mL or 8 ounces.

individuals. Finally, longitudinal studies in normotensive individuals (42), and the studies reviewed in this work in hypertensive individuals, suggest that habitual coffee consumption is not associated with a higher risk of cardiovascular events.

Our work makes some original methodologic contributions to the study of the acute effect of coffee and caffeine on BP. First, changes in BP after caffeine intake, from the beginning to the end of each study, were considered independently for each period of observation. This allowed evaluation of the temporal course of the effect of caffeine on BP in the first hours after its administration. Second, we found a suggestion of a dose-response relation between acute caffeine intake and DBP. Furthermore, the increase in BP was independent of the use of antihypertensive treatment.

Given the small number and the heterogeneity of the studies, it was not possible to calculate an overall estimator of the longer-term effect of coffee on BP in hypertensive individuals. However, no study found a significant increase in BP; moreover, modifying the concentrations of some components of coffee—specifically decreasing HHQ and increasing CGA—produced reductions in BP.

Coffee is a drink with a very complex chemical composition. Although the cardiometabolic effects of caffeine are well documented (1, 43–45), the effects of other substances in coffee are not yet well known. Recent studies suggest that some components of coffee, such as CGA and other phenolic compounds, magnesium, and trigonelline, improve glucose metabolism and reduce inflammation and endothelial dysfunction (46–48). In the long term, these effects would be seen in habitual coffee drinkers who have developed tolerance to caffeine. Thus, the harmful cardiovascular effects of caffeine would be offset by the beneficial effects of these other components. This may help explain the lack of association between coffee and long-term CVD risk in large cohort studies, in both normotensive (12, 40, 49–51) and hypertensive (13, 38, 39) persons.

The results of this review have clinical implications for the control of hypertensive patients. On the one hand, the acute increase in BP may temporarily increase the risk of a cardiovascular event (10, 11). This is consistent with the increased risk of coronary disease and stroke in the hours after coffee consumption. Thus, hypertensive patients with uncontrolled BP should avoid consuming large doses of caffeine. Furthermore, the consumption of coffee or other caffeinated substances in the hours before measuring BP may elevate it and give the erroneous impression that BP is poorly controlled. However, we found no evidence to justify avoidance of habitual coffee consumption in well-controlled hypertensive patients; therefore, in these patients, medical recommendations should prioritize modification of other lifestyles, such as quitting smoking, controlling weight, and increasing physical activity.

In conclusion, caffeine raises BP for $\geq$ 3 h after ingestion in hypertensive persons. However, the available evidence does not support the assertion that coffee consumption for 2 wk increases BP or that habitual coffee consumption raises the risk of CVD. Nonetheless, studies of the effect of prolonged coffee consumption ($>$ 2 wk) on BP are needed (Table 3). It is also necessary to investigate directly the influence of coffee or caffeine on the degree of BP control in hypertensive individuals and its possible variation with type of antihypertensive medication (eg, renin-angiotensin-aldosterone inhibitors, calcium

antagonists, and β -blockers). Such evidence would make it possible to fine tune recommendations about coffee consumption in hypertensive individuals. Last, given that the studies on the association between coffee and risk of stroke found inconsistent results, further research is needed before we can rule out a deleterious effect of coffee consumption on each type of CVD.

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