The effect of coffee consumption on blood pressure and the development of hypertension: a systematic review and meta-analysis

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Context: Coffee is one of the most widely consumed beverages worldwide and is known to acutely raise blood pressure (BP), but the effects of chronic consumption on BP is unclear.

Objectives: To conduct a systematic review and meta-analysis of available randomized controlled trials (RCTs) and cohort studies to assess the effect of chronic coffee consumption on BP and the development of hypertension.

Data sources: *Ovid*, *MEDLINE* (from 1948), *EMBASE* (from 1988), and all of *Web of Science* and *Scopus*.

Study selection: RCTs and cohort studies of at least 1-week duration that assessed BP and/or the incidence of hypertension in coffee consumers compared with a control group that consumed less or no coffee.

Data extraction: Two authors independently reviewed abstracts and full-text articles for inclusion. Data were abstracted using standardized forms. Risk of bias in the RCTs was examined using the method described in the *Cochrane Handbook for Systematic Reviews of Interventions*. Quality of the cohort studies were assessed using the Newcastle–Ottawa quality assessment scale for cohort studies.

Data synthesis: Six hundred and ten articles were retrieved and a total of 15 (10 RCTs and five cohort studies) met inclusion criteria. Meta-analysis of RCTs demonstrated a pooled weighted difference in mean change in SBP of −0.55 mmHg [95% confidence interval (CI) −2.46 to 1.36) and DBP −0.45 mmHg (95% CI −1.52 to 0.61). Meta-analysis of the cohort studies demonstrated a pooled risk ratio for developing hypertension of 1.03 (95% CI 0.98–1.08).

Conclusion: Low-quality evidence did not show any statistically significant effect of coffee consumption on BP or the risk of hypertension. Given the quality of the currently available evidence, no recommendation can be made for or against coffee consumption as it relates to BP and hypertension.

Keywords: blood pressure, caffeine, coffee, hypertension

INTRODUCTION

Coffee is one of the most widely consumed beverages worldwide. In normotensive individuals, acute consumption of two to three cups of coffee has been shown to increase SBP by 3–14 mmHg and DBP from 4 to 13 mmHg [1]. There is evidence that the acute pressor effects of coffee consumption in chronic consumers are blunted as a result of adaptation in as little as 3–5 days [2,3]. Randomized trials on chronic consumption have shown mixed results with most showing only a small effect on blood pressure (BP) [4,5]. More recent prospective cohort data have suggested an inverse U-shaped relationship between coffee consumption and the development of hypertension with those that abstain from coffee and those that have the highest consumption levels being at lower risk than those who are low-to-moderate consumers [6–9]. Previous meta-analyses have examined the effects of both coffee and caffeine from randomized controlled trials (RCTs) with Noordzij *et al.* finding a smaller effect on BP than Jee *et al.* [4,5]. These reviews did not incorporate any of the available prospective cohort data, much of which has been published more recently. These reviews also included trials that used decaffeinated coffee as a control group, which essentially assesses the effect of the caffeine in coffee on BP but not the coffee itself. These trials were excluded from the current review. The objective of this systematic review was to examine the available literature including both RCTs and prospective cohort studies to investigate the effect of coffee on BP and the development of hypertension.

Journal of Hypertension 2012, 30:2245–2254

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Received 2 March 2012 **Revised** 13 July 2012 **Accepted** 25 July 2012

J Hypertens 30:2245–2254 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

DOI:10.1097/HJH.0b013e3283588d73

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METHODS

Study selection

Studies were considered eligible if they met the following criteria: were RCTs or cohort studies; included an intervention group that consumed coffee and a control group that consumed either no coffee or less coffee; included participants greater than 18 years of age; reported BP, change in BP, and/or an estimate of the risk of hypertension; duration greater than 1 week (to eliminate any acute pressor effect of coffee); and had a minimum coffee exposure of at least one cup.

Search strategy

An expert reference librarian developed the search strategy with input from study authors with expertise in conducting systematic reviews. We searched electronic databases on 23 February 2011 including *Ovid*, *MEDLINE* (from 1948), *EMBASE* (from 1988), *Web of Science*, and *Scopus*. The search resulted in 610 total results. The search strategy for *MEDLINE* is in eFigure 1 (http://links.lww.com/HJH/A199) and the search strategies for other databases are available from the authors.

Study selection

Abstracts and titles that resulted from executing the search strategy were independently evaluated by two reviewers for potential eligibility and the full-text versions of all potentially eligible studies were requested.

Two reviewers working independently and blindly considered the full-text reports (all available versions of each study) for eligibility. Disagreements were harmonized by consensus and if not possible by consensus through arbitration by a third reviewer. Agreement was measured using the κ-statistic as described by McGinn *et al.* [10].

Data collection

Using standardized forms, data were abstracted from each study. In the randomized trials, data abstracted included the following: study design (blinding methods, intervention/control type and amount, duration of intervention, instrument used to assess BP); sample size; study population characteristics (age, percentage males, prestudy coffee intake); and baseline BP, BP changes, and the measure of variance reported for each of these values.

For cohort studies, data abstraction included the following: description of cohort including percentage male, age, and baseline BP; number of participants and number lost to follow-up; outcome definition; and number of individuals with the outcome and/or the risk estimate.

Quality assessment

Risk of bias in the RCTs were examined using the method described in the *Cochrane Handbook for Systematic Reviews of Interventions* [11] using the tool provided in RevMan 5.0 [12]. The specific areas of bias addressed included selection, performance, detection, attrition, and reporting bias. In addition, as many trials involving coffee involve multiple phases or are cross-over trials, the run-in and wash-out periods, and the amount of coffee consumption were examined to assess for any risk of bias.

Quality assessment of the cohort studies were performed using the Newcastle–Ottawa quality assessment scale for cohort studies [13].

Statistical analysis

Effect of coffee on BP in parallel trials was calculated as the change in BP in the coffee group minus the change in BP in the control group, and in cross-over trials as BP at the end of the intervention period minus BP at the end of the control period. The standard error was obtained as reported or calculated from confidence intervals (CIs), *t*-statistics, or individual variances from intervention and control groups (parallel trials) or intervention and control periods (cross-over trials).

In cross-over trials, as individuals act as their own control, if only the SD of the experimental and control periods were reported the SD of the difference was calculated as described in the *Cochrane Handbook for Systematic Reviews of Interventions* [11] using the following formula:

$$SD_{\text{diff}} = \sqrt{SD_{\text{E}}^2 + SD_{\text{E}}^2 - (2 \times Corr \times SD_{\text{E}} \times SD_{\text{C}})}$$

in which SD_{diff} denotes SD of the difference, SD_{E} denotes SD of the experimental group, SD_{C} denotes SD of the control group, and *Corr* denotes correlation between the initial and final BP values. Correlation was estimated by calculations from Strandhagen and Thelle [14] who provided SD_{E}, SD_{C}, and SD_{diff} for multiple groups. Correlation values were calculated from this data and ranged from 0.56 to 0.78 with an average of 0.7. Sensitivity analysis was performed with different correlation values in this range and as it made no significant difference in the final analysis, a correlation of 0.7 was used. We used the I^2-statistic to assess variation across studies due to heterogeneity rather than chance [15]. We proposed predefined subgroups to assess the effect of participant and intervention characteristics on outcomes. These included type of coffee consumed, amount of coffee consumed, sex, and prestudy BP.

Cohort studies that met inclusion criteria reported the risk of developing hypertension with various amounts of daily coffee usage as relative risks (RRs), hazard ratios, or odds ratios (ORs). When reported, multivariate adjusted risks were used. We treated hazard ratios as RRs in the meta-analysis, but because of the relatively high incidence of hypertension (HTN) in some of the study populations, we did not assume that ORs were comparable to RRs.

The meta-analysis was performed in RevMan Version 5.0 using a random effects model as described by DerSimonian and Laird [16]. A random effects model was chosen due to the heterogeneity of the study designs, participant populations, and intervention types (amount and type of coffee).

RESULTS

Search results

Our initial search resulted in 610 publications and after abstract review by two authors this was limited to

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103 potentially relevant articles that were obtained and reviewed in full-text. Both authors agreed on inclusion of 15 publications and 88 were excluded for the reasons noted in eFigure 2 (http://links.lww.com/HJH/A199). There was initial disagreement on one publication that was resolved by consensus. The high consensus rate was likely driven by being overly inclusive in the abstract review in addition to well defined, unambiguous inclusion criteria. κ-Statistics was calculated as described in the methods and was 0.96.

Study characteristics and quality

Randomized controlled trials

Of the 15 articles selected for inclusion 10 were RCTs. Characteristics and results of these studies are summarized in Table 1 [14,17–25]. Of the 10 RCTs five were cross-over [14,19–21,23] and five were parallel trials [17,18,22,24,25]. Seven trials included two strata within each trial and these are denoted as parts (a/b) in Table 1 [18–22,24,25], five of these used the same control group when comparing BP in more than one strata, which is denoted as superscript (c) [18,19,21,24,25]. Most of the study populations were healthy, normotensive individuals; however, Rakic *et al.* [22] studied two groups of elderly patients: one that was normotensive and one that included those with treated or untreated hypertension, the latter being denoted with (a) in Table 1. They found a significant difference in elevation of BP in known hypertensive patients that consumed coffee but not in those that were normotensive. MacDonald *et al.* [21] included only participants with untreated resting BPs between 90 and 105 mmHg diastolic and found no significant effect of either caffeinated or decaffeinated coffee on BP in this group. Funatsu *et al.* [20] studied a group whose baseline BP was more than 120/80 mmHg and consumed alcohol regularly with an average of approximately 70 ml/day and the authors found significant decreases in BP in those who consumed coffee compared with those that did not consume coffee. Coffee consumption varied between trials and ranged from three to over six cups of coffee daily and only four used a standard amount of coffee consumption in the intervention [17,22,24,25], whereas the other trials defined a minimum amount of consumption but no maximum.

The quality of these studies were assessed using the *Cochrane* Risk of Bias Tool [11] as described in the methods section and are presented in eFigure 3 (http://links.lww.com/HJH/A199). Only two of the studies addressed allocation concealment in their method section and only four addressed blinding of the person measuring the BP when manual BP cuff was used. Six of the trials [14,18–21,23] instructed participants to consume a minimum amount of coffee but no maximum and only four [17,22,24,25] used a standardized amount. This makes determination of a dose response difficult, but may more accurately reflect actual consumption patterns in real life. Most of the trials had an adequate run-in and wash-out period between regimens. The two trials that did not were of significant enough duration that it likely had little to no effect on the result.

Prospective cohort studies

Five of the 15 included studies were prospective cohort studies that reported a multivariate adjusted risk of hypertension as either a RR, hazard ratio, or OR. Characteristics and results of these studies are summarized below and in Table 2 [6–9,26].

Klag *et al.* [7] examined a cohort of Johns Hopkins medical students graduating between 1948 and 1964 who had a normal BP measured at baseline and were followed with yearly questionnaires asking several questions including coffee intake and self-reported BP value. They defined HTN as one measure of more than 160/95 mmHg or two separate reported BPs more than 140/90 mmHg. If the definition of HTN was met, medical records were obtained and reviewed to confirm diagnosis. They had a median follow-up of 33 years and follow-up rate ranged from 87 to 94%.

Hu *et al.* [6] examined a cohort from a population study conducted in Finland in 1982, 1987, 1992, and 1997. They were initially screened with questionnaires and physical examination at study site to rule out pre-existing HTN. Participation was 74–88% and they had a mean follow-up of 13.2 years. Cases of HTN were defined as those who were treated with antihypertensive drugs according to the records of the Social Insurance Institution's nationwide registry, which every citizen must be registered with in order to get reimbursed for their medications.

Winkelmayer *et al.* [9] used the Nurses Health Cohorts (NHS) I and II, which are cohorts of female-registered nurses. They were assessed by questionnaire every 2 years. Diagnosis of hypertension in this study was done by self-report of physician diagnosed hypertension and the medical records for a subset of these were reviewed and found to have BP more than 140/90 mmHg 100% of the time. Follow-up exceeded 94% in both cohorts.

Palatini *et al.* [26] studied the Hypertension and Ambulatory Recording Venetian Study (HARVEST), which was a cohort initiated in 1990 of 18–45-year-old patients with a single BP measurement 140–159/90–99 mmHg who were never treated for HTN. The endpoint in this study was 'sustained hypertension', which was defined as SBP of at least 150 mmHg and/or DBP of at least 95 mmHg in two consecutive visits [27]. The mean follow-up was 6.4 years with a minimum follow-up of only 6 months for inclusion.

Uiterwaal *et al.* [8] examined a cohort from the Dutch city of Doetinchem who had participated in at least two chronic disease screening projects between 1987 and 2002, which included a screening examination and questionnaire. The definition of HTN used was BP more than 140/90 mmHg at two visits or if they were being treated with antihypertensive medications. Response rate for the screening project was 62% at baseline, 78% at first follow-up, and 78% at the third follow-up; also, only those that had two visits were included in the study. Risk was reported as an adjusted OR using three or more cups per day as a reference group rather than the none, unlike the other studies that reported either adjusted hazard ratio or RR with the lowest coffee-consuming group as the reference group.

The quality of these studies was assessed using the Newcastle–Ottawa scale [13] and results are included in Table 2 along with the other characteristics of the studies.

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TABLE 1. Characteristics of randomized controlled trials

References	Design	*N* (treatment/control)	Duration (weeks)	Age (years)	% Male	Coffee type	Coffee dose (cups per day)	SBP baseline (mmHg)	SBP change (SEM)	DBP baseline (mmHg)	DBP change (SEM)
Agudelo *et al.* [17]	P	28/30[c]	6	39.6	Not provided[d]	F	6	108.2	−4.0 (3.3)	72.3	−1.0 (2.3)
Agudelo *et al.*[a] [17]	**P**	**29/30[c]**	**6**	**39.6**	**Not provided[d]**	**F**	**4**	**107.6**	**−3.5 (3.3)**	**70.7**	**0.6 (2.4)**
Agudelo *et al.*[b] [17]	P	29/30[c]	6	39.6	Not provided[d]	F	2	105.7	−0.5 (3.1)	69.9	2.5 (2.3)
Bak and Grobbee [18]	P	33/34[c]	9	25	54	B	4–6	120.5	6.0 (2.1)	70.7	2.8 (1.7)
Bak and Grobbee[a] [18]	**P**	**34/34[c]**	**9**	**25**	**54**	**F**	**4–6**	**122.1**	**6.1 (2.2)**	**71.4**	**3.0 (1.5)**
Burr *et al.* [19]	**X**	**54/54[c]**	**12**	**35**	**65**	**I**	**≥5**	**119**	**1.3 (1.1)**	**81.9**	**0.4 (1.4)**
Burr *et al.*[a] [19]	X	54/54[c]	12	35	65	I/D	≥5	119	0.2 (1.1)	81.9	0.7 (1.4)
Funatsu *et al.* [20]	X	21/21	8	46	100	F	3.4	128.8	−5.1 (1.9)	81.5	−3.3 (1.9)
Funatsu *et al.*[a] [20]	X	21/21	8	46	100	F	3.4	132.9	−7.2 (2.6)	82.2	−3.8 (1.4)
MacDonald *et al.* [21]	**X**	**50/50[c]**	**8**	**47**	**46**	**I**	**>3**	**141.9**	**−4.8 (1.7)**	**92.2**	**−1.7 (0.9)**
MacDonald *et al.*[a] [21]	X	50/50[c]	8	48	47	I/D	>3	141.9	−3.0 (1.7)	92.2	−1.5 (0.9)
Rakic *et al.* [22]	P	12/9	4	72.6	29	I	5	121.9	0.4 (5.3)	68.5	3.0 (3.3)
Rakic *et al.*[a] [22]	P	14/13	4	72.6	29	I	5	133.2	5.2 (4.2)	69.9	2.7 (4.3)
Rosmarin *et al.* [23]	X	21/21	16	35	100	F	3.6	115.4	2.1 (2.2)	71.8	−2.4 (2.5)
Strandhagen and Thelle [14]	X	121/121	14	48.6	22	F	4	121	1.3 (1.0)	76.7	−0.5 (0.8)
Superko *et al.* [24]	**P**	**62/58[c]**	**8**	**45.5**	**100**	**F**	**4.5**	**114**	**1.3 (1.6)**	**73.5**	**0.2 (1.2)**
Superko *et al.*[a] [24]	P	61/58[c]	8	47	100	F/D	4.5	114.5	−1.4 (1.5)	73.5	0.9 (1.1)
VanDusseldorp *et al.* [25]	P	22/21[c]	11	39	50	B	6	122	3.5 (1.2)	78.5	0.9 (0.9)
VanDusseldorp *et al.*[a] [25]	**P**	**21/21[c]**	**11**	**39**	**50**	**B/F**	**6**	**122**	**0.4 (1.0)**	**79.0**	**0.4 (0.9)**

The data in bold represent the strata of the trial used in meta-analysis if the same control group was used for multiple comparisons. B, boiled; D, decaffeinated; F, filtered; I, instant; NA, ; P refers to parallel design; X refers to cross-over design.

[a]Different strata within the same trial.

[b]Different strata within the same trial.

[c]Study that used the same control group when comparing more than one group in a trial.

[d]Authors reported that there was no significant difference among gender between the groups but did not give gender breakdown.

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TABLE 2. Characteristics of cohort studies continued

Study	Coffee intake	Newcastle–Ottawa score	Number of cases of HTN	Number of participants	% Male	Age (mean, years)	Duration of F/U (years)	SBP baseline (mmHg)	DBP baseline (mmHg)	Risk type reported	Risk value (95% CI)
Klag *et al.* [7]	0	7	42	184	100	26.2	33	115	70	Adjusted RR	1
(a)	1–2		124	462	100	26.1		115	69		1.34 (0.90–1.99)
(b)	3–4		75	239	100	26.2		115	70		1.40 (0.94–2.09)
(c)	>5		39	132	100	27.4		116	69		1.43 (0.94–2.18)
Hu *et al.* [6] Total	0–1	6	183	2681	45.1	40.6	13.2	134.7	81.4	Adjusted HR	1
(a)	2–3		514	5336	40.6	43.6		136.3	82.5		1.30 (1.04, 1.63)
(b)	4–5		785	7430	42.6	44.4		135.8	82.2		1.28 (1.03, 1.59)
(c)	6–7		585	5084	49.3	44.7		135.6	81.6		1.26 (1.01, 1.59)
(d)	≥8		438	4179	63.6	42.5		134.8	81		1.12 (0.87, 1.43)
Hu *et al.* [6] Men	0–1	6	Not provided[a]	1209	100	Not provided[a]	13.2	Not provided[a]	Not provided[a]	Adjusted HR	1
	2–3		Not provided[a]	2168	100	Not provided[a]		Not provided[a]	Not provided[a]		1.14 (0.90, 1.44)
	4–5		Not provided[a]	3168	100	Not provided[a]		Not provided[a]	Not provided[a]		1.12 (0.90, 1.41)
	6–7		Not provided[a]	2508	100	Not provided[a]		Not provided[a]	Not provided[a]		1.10 (0.87, 1.40)
	≥8		Not provided[a]	2658	100	Not provided[a]		Not provided[a]	Not provided[a]		1.05 (0.82, 1.34)
Hu *et al.* [6] Women	0–1	6	Not provided[a]	1472	0	Not provided[a]	13.2	Not provided[a]	Not provided[a]	Adjusted HR	1
	2–3		Not provided[a]	3168	0	Not provided[a]		Not provided[a]	Not provided[a]		1.46 (1.13, 1.90)
	4–5		Not provided[a]	4262	0	Not provided[a]		Not provided[a]	Not provided[a]		1.40 (1.08, 1.81)
	6–7		Not provided[a]	2576	0	Not provided[a]		Not provided[a]	Not provided[a]		1.38 (1.05, 1.81)
	≥8		Not provided[a]	1521	0	Not provided[a]		Not provided[a]	Not provided[a]		1.19 (0.88, 1.60)
Winkelmayer *et al.* [9] NHS I	<1	5	8073	220 973	0	55.4	12	120.3	74.9	Adjusted RR	1
(a)	1		3261	83 525	0	55.4		121.4	75.5		1.06 (1.01, 1.10)
(b)	2–3		6190	171 274	0	55.4		121.4	75.6		1 (0.97, 1.04)
(c)	4–5		1431	45 044	0	55.4		121.4	75.4		0.93 (0.88, 0.99)
(d)	≥6		409	14 006	0	55.4		120.8	75.1		0.88 (0.80, 0.98)
Winkelmayer *et al.* [9] NHS II (e)	<1	5	6907	464 796	0	35.4	12	112	73.8	Adjusted RR	1
(f)	1		1905	123 668	0	35.2		112.6	74.1		1.06 (1.01, 1.13)
(g)	2–3		3571	241 352	0	35.9		112.6	74		1 (0.95, 1.04)
(h)	4–5		827	58 196	0	36.6		112.7	73.9		0.91 (0.84, 0.98)
(i)	≥6		258	17 462	0	37.1		112.8	74.1		0.91 (0.80, 1.04)
Palatini *et al.* [26]	0	4	Not provided[b]	294	72.5	30.9	6.4	144.6	93.1	Adjusted HR	1
(a)	1–3		Not provided[b]	704	72.4	33.7		146	93.9		1.27 (1.04–1.56)
(b)	>3		Not provided[b]	109	70.6	36.9		144.8	93.7		1.24 (0.94–1.66)
Uiterwaal *et al.* [8] Total	0	6	17	231	28	40.4	11	121.3	77.2	Adjusted OR	0.54 (0.31, 0.92)
(a)	0–<3		203	1173	32	40.4		121.3	77.2		1
(b)	>3–6		534	2737	44	40.4		121.3	77.2		0.93 (0.76, 1.12)
(c)	>6		202	1048	63	40.4		121.3	77.2		0.83 (0.65, 1.07)
Uiterwaal *et al.* [8] Men	0	6	6	65	100	40.7	11	125.6	79.4	Adjusted OR	0.60 (0.24, 1.49)
	0–<3		77	379	100	40.7		125.6	79.4		1
	>3–6		267	1195	100	40.7		125.6	79.4		1.08 (0.79, 1.47)
	>6		143	658	100	40.7		125.6	79.4		1.03 (0.72, 1.46)

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TABLE 2 (*Continued*)

Study	Coffee intake	Newcastle–Ottawa score	Number of cases of HTN	Number of participants	% Male	Age (mean, years)	Duration of F/U (years)	SBP baseline (mmHg)	DBP baseline (mmHg)	Risk type reported	Risk value (95% CI)
Uiterwaal *et al.* [8] Women	0	6	11	166	0	40.1	11	117.5	75.5	Adjusted OR	0.51 (0.26, 1.01)
	0–<3		126	794	0	40.1		117.5	75.5		1
	>3–6		267	1542	0	40.1		117.5	75.5		0.83 (0.64, 1.07)
	>6		59	390	0	40.1		117.5	75.5		0.67 (0.46, 0.98)

[a]Information provided only for total population.
[b]Only total number of cases reported as 561.

All scored between four and seven stars with the lowest being Palatini *et al.* [26], which had the shortest duration of follow-up with the minimum being only 6 months and used an endpoint of sustained hypertension that was not adequately excluded prior to inclusion in the cohort. For the diagnosis of hypertension, two studies used measured BP in a clinic setting [8,26]. As noted above, the others used self-report or record linkage that carries the potential of introducing detection and/or reporting bias. Self-reported HTN and BP measurements were validated in the NHS and Johns Hopkins medical student cohorts [28,29]; however, this may not be translatable to other populations. Finally, all of the cohort studies are limited by only being able to assess exposure to coffee through questionnaire that may introduce recall bias; however, this may be minimized by the habitual nature of coffee consumption in many individuals.

Meta-analysis

SBP and DBP

Six of the controlled trials used the same control group for more than one comparison in the same trial [17–19,21,24,25]. One of these compared differing amounts of daily consumption vs. no coffee [17], two compared boiled vs. filtered vs. no coffee [18,25], and three of these included a comparison of decaffeinated vs. regular vs. no coffee [19,21,24]. Figures 1 and 2 include the pooled analysis for SBP and DBP, respectively, showing all trials; however, as noted above, six of the trials had multiple strata using the same control group comparison of which only one of the strata was used. Sensitivity analysis was performed using multiple iterations of exclusion of one strata of each trial that used the same control group and it had no significant effect on the pooled result. The strata in each of these trials used in the final analysis are shaded in Table 1. These were chosen based on similarity to the other trials in the analysis, including amount of coffee consumed as well as to the most common type of coffee consumed among all trials (caffeinated/filtered).

The pooled weighted difference in mean change of SBP was −0.55 mmHg (95% CI −2.46 to 1.36) and of DBP was −0.45 mmHg (95% CI −1.52 to 0.61). There was significant heterogeneity in the pooled SBP analysis ($I^2 = 72\%$), but less so in the DBP analysis ($I^2 = 41\%$). This heterogeneity was explored with the planned subgroup analysis, including type of coffee, sex, and prestudy BP. Due to the variation in the amount of coffee consumed in the trials post-hoc subgroup analysis was performed on the six trials [14,18–21,23] that instructed participants to consume a minimum amount of coffee but no maximum compared with the four trials [17,22,24,25] that used a standardized amount.

Risk of hypertension

Of the five cohort studies that were included in this review, four were used in the meta-analysis. Uiterwaal *et al.* [8] reported a multivariate adjusted OR using the more than three cups as a reference group rather than the group consuming no coffee in their study due to the small

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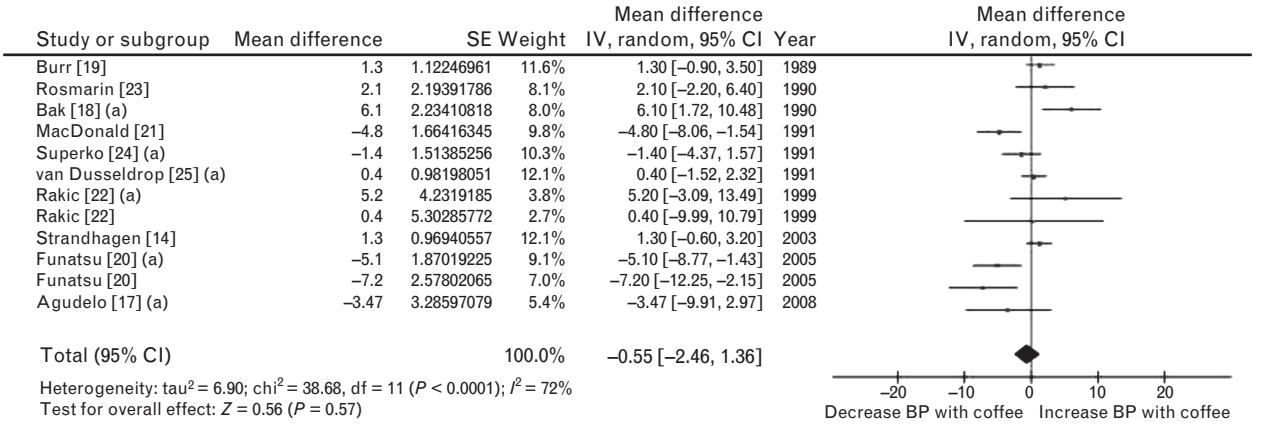

FIGURE 1 Mean difference between changes in SBP coffee vs. no coffee. *Pooled results are the mean difference calculated using inverse variance (IV) using a random effects model. CI, confidence interval.

numbers in that group. All other studies used the lowest consumption group as a reference group and reported RRs or hazard ratios. For this reason, the results of Uiterwaal *et al.* were not included in quantitative meta-analysis. Results from Uiterwaal *et al.* reveal a small but statistically significant decreased adjusted OR in women who consume more than six cups of coffee daily compared with those that consume more than three cups per day with an OR of 0.67 (95% CI 0.46–0.98) and in addition shows a small but statistically significant decrease in total coffee abstainers compared with those that consume more than three cups per day with adjusted OR of 0.54 (95% CI 0.31–0.92).

Meta-analysis revealed a pooled risk ratio for developing hypertension among all groups of coffee consumption was 1.03, but was not statistically significant (95% CI 0.98–1.08). This forest plot is shown in Fig. 3.

Subgroup analysis controlled trials

The subgroup analysis did not reveal any significant interactions. Results are summarized in eTable 1 (http://links.lww.com/HJH/A199).

Subgroup analysis cohort studies

Different studies reported differing amounts of coffee consumption as seen in Table 2. These were grouped into low (approximately one to three cups per day), moderate (approximately three to six cups per day), and high (approximately more than six cups per day). This allowed for minimal overlap between groups in each study other than Palatini *et al.* [26] whose highest consuming coffee group was more than three cups per day. Sensitivity analysis was performed considering this group into both the moderate and high coffee consuming groups and made no difference in the overall effect within or between groups, and this study was left in the moderate coffee consumption group due to the fact that the other studies done on European cohorts had the largest portion of their coffee consumers in the moderate consumption range. The results are shown in eTable 1. In the low coffee consumers, there was a very small increased rate of 1.05 (95% CI 1.00–1.10) with an identical but nonsignificant increased risk in moderate coffee consumers and no increased risk in those with high coffee consumption.

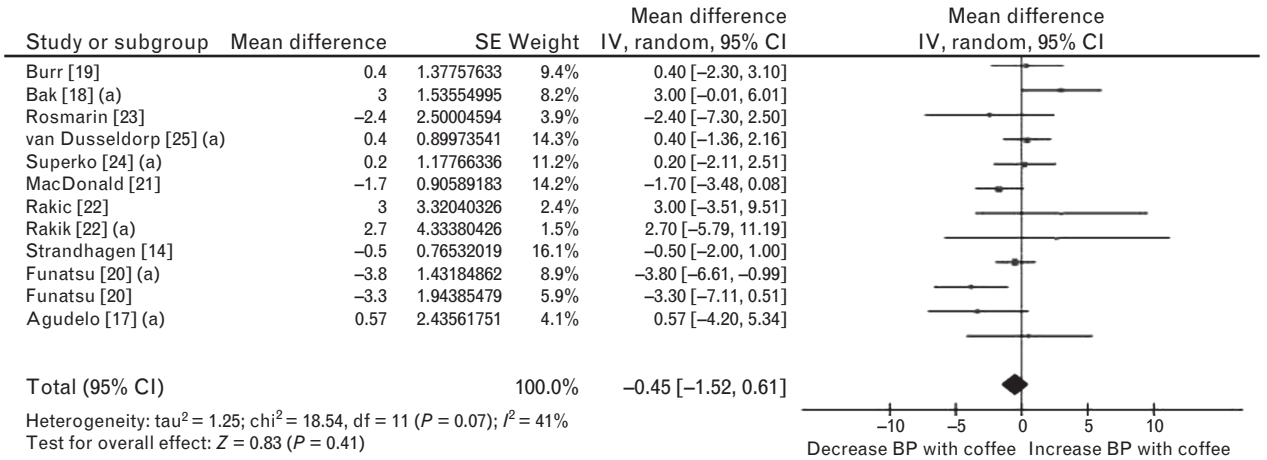

FIGURE 2 Mean difference between changes in DBP coffee vs. no coffee. *Pooled results are the mean difference calculated using inverse variance (IV) using a random effects model. CI, confidence interval.

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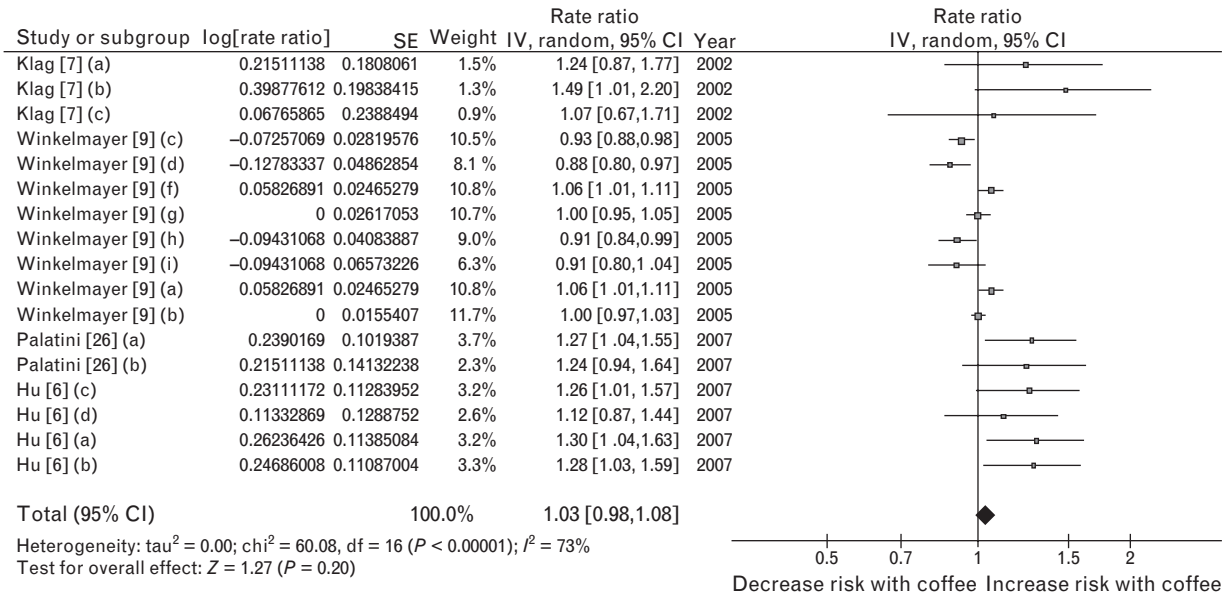

FIGURE 3 Forest plot for risk of hypertension with coffee consumption in cohort studies. *Pooled results are the inverse variance of the log of the risk ratio calculated using a random effects model. CI, confidence interval.

Subgroup analysis for differences between male and females in total and at all the above consumption levels revealed no significant differences. These results are summarized in eTable 1. There was not sufficient data to do subgroup analysis on coffee type or baseline BP.

DISCUSSION

This systematic review and meta-analysis of RCTs and prospective cohort studies revealed that coffee consumption was not associated with a significant change in SBP, DBP, or the risk of hypertension. There was no significant subgroup interaction to explain heterogeneity or identify a group of individuals who may demonstrate a different BP response to coffee or a certain type of coffee. All analyses were associated with significant heterogeneity.

Strengths and limitations

The strengths of this review relate to the comprehensive literature search, evaluating the evidence by independent reviewers and the exploration of heterogeneity in analysis. We also attempted to contact study authors to limit the effect of reporting bias. We included cohort studies as well as randomized trials to be more complete and allow the evaluation of the totality of the evidence, which increases precision, length of follow-up, and external validity (as randomized trials may have selected individuals followed for a short period).

Analyses were associated with significant heterogeneity that lowers the quality of the available evidence and limits the strength of inference. Heterogeneity also made the evaluation of publication bias not possible [30]. The methodologic quality of the studies was also limited, which increases the risk of bias. The ascertainment of coffee consumption and adherence to the quantity assigned is also difficult to confirm in studies that evaluate nutritional interventions especially over extended periods.

Implications for practice and research

Considering the overall low quality of evidence (weak inference), a strong recommendation for or against coffee consumption is not possible. However, at this point and with the available data, as it relates to BP and hypertension there is no compelling reason to limit coffee intake to a certain amount.

Some cohort studies had indicated an inverse U-shaped relationship between the amount of coffee consumed and the risk of HTN, wherein the highest risk of HTN was in those at the very lowest and highest levels of coffee consumption [6,8]. In the meta-analysis, there was a very small risk in the low coffee consumption group of 1.04 (95% CI 1.00, 1.09). Results in the moderate and high coffee consumption groups were again very small, 1.05 and 1.02, respectively, and there was no statistically significant difference between the groups ($P = 0.81$). These results do not indicate a significant relationship between coffee consumption and the development of hypertension. It is important to note that most of the cohort's studies included normotensive individuals. As noted previously, a recent follow-up study by Palatini *et al.* [31] studied genetic polymorphisms of *CYP1A2* and concluded that those with ∗1F allele are at higher risk of developing hypertension than those who are homozygous for ∗1A allele. With the high prevalence of prehypertension and hypertension globally, further research into the effect of coffee in these individuals may be needed.

Caffeine consumed from sources other than coffee has been associated with increased BP [5] and risk of HTN [9]. Recent research has identified chlorogenic acids (CGAs) that are present in coffee may have an antihypertensive effect and that this may be inhibited by hydroxyhydroquinone (HHQ), which is produced during the roasting of

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green coffee beans [32,33]. HHQ-reduced coffee has shown some promising results in lowering BP in those with prehypertenison or mild hypertension [34–36]; however, one study of patients being treated for essential hypertension revealed no effect on either raising or lowering BP [37]. This interaction of CGA and HHQ may help explain the differential effects of coffee vs. other caffeinated beverages on BP. More research is needed as there is little data on this currently.

Future clinical trials should focus on coffee consumption in those at highest risk for the development of hypertension, such as those with prehypertension; however, randomization in this population will be difficult given the ubiquity of coffee consumption and the likely reluctance among many to avoid coffee. Funding of such trials may also be difficult to secure. A possible future study design would be a historical cohort study that enrolls individuals with varying levels of coffee consumption (adolescents who are coffee naive and other individuals with a range of consumptions) and follow them prospectively. Such a study should adjust for related variables such as the risk of hypertension, baseline BP, BMI, and potential relevant genetic markers (e.g., *CYP1A2* polymorphism). Adequate outcome ascertainment (BP measurement and diagnosis of hypertension) is imperative in such study.

Low-quality evidence did not show any statistically significant effect of coffee consumption on BP or the risk of hypertension. Given the quality of the currently available evidence, no recommendation can be made for or against coffee consumption, as it relates to BP and hypertension until higher quality evidence is available.

ACKNOWLEDGEMENTS

There was no specific funding or support for this project.

Conflicts of interest

There are no conflicts of interest.

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Reviewers' Summary Evaluations

Reviewer 1

The National Coffee Association endorses that consumption has increased 7% from 2011, giving coffee a clear lead over soft drinks in the USA. Coffee-dependent sympathoactivation does not depend on caffeine and might be related with other components and/or processing. Thus, publication heterogeneity is not surprising. Coffee's acute pressor effect is blunted in habitual consumers. Therefore, variable results might also be associated with selected populations. This study revisited 20-year-long literature and no final answer is at sight. However, lack of evidence is not evidence against hypothesis. Studies should be targeted at potentially vulnerable populations such as resistant hypertensive individuals.

Reviewer 2

Previous meta-analyses have shown that the effects of chronic coffee drinking on BP, if any, were likely of small amplitude but might be important from a public health point of view. Besides the fact that the current work took into account the most recent reports, it addressed the issue of consistency according to the study design: controlled/cohort studies and BP level change/hypertension diagnosis. Whereas no significant association was disclosed, a large between-study heterogeneity was present in any subgroup analysis, which did not allow to conclude firmly on the absence of association but raised the quality issue of epidemiological work on common dietary habits.

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