Blood pressure response to chronic intake of coffee and caffeine: a meta-analysis of randomized controlled trials

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Purpose **Coffee is a widely consumed beverage and small health effects of substances in coffee may have large public health consequences. It has been suggested that caffeine in coffee increases the risk of hypertension. We performed a meta-analysis of randomized controlled trials of coffee or caffeine and blood pressure (BP).**

Data identification **BP trials of coffee or caffeine published between January 1966 and January 2003 were identified through literature databases and manual serach.**

Study selection **A total of 16 studies with a randomized, controlled design and at least 7 days of intervention was selected, comprising 25 strata and 1010 subjects.**

Data extraction **Two persons independently obtained data on sample size, type and duration of intervention, changes in BP and heart rate (HR), and subjects' characteristics for each trial. Meta-analysis was performed using a random-effects model.**

Results **A significant rise of 2.04 mmHg [95% confidence interval (CI), 1.10–2.99] in systolic BP and 0.73 mmHg (95% CI, 0.14–1.31) in diastolic BP was found after pooling of coffee and caffeine trials. When coffee trials ($n = 18$, median intake: 725 ml/day) and caffeine trials ($n = 7$, median dose: 410 mg/day) were analysed separately, BP elevations appeared to be larger for caffeine [systolic: 4.16 mmHg (2.13–6.20); diastolic: 2.41 mmHg (0.98–3.84)] than for coffee [systolic: 1.22 mmHg (0.52–1.92) and diastolic: 0.49 mmHg (−0.06–1.04)]. Effects on HR were negligible.**

Conclusions **Regular caffeine intake increases BP. When ingested through coffee, however, the blood pressure effect of caffeine is small.** *J Hypertens* **23:921–928 © 2005 Lippincott Williams & Wilkins.**

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Introduction

A large number of people consume coffee on a daily basis and even small health effects of substances in coffee may have large public health consequences. High intake of caffeinated coffee may influence blood pressure (BP) [1–3] or the risk of coronary heart disease [4,5]. A single dose of caffeine of 200–250 mg, equivalent to 2–3 cups of coffee, has been shown to increase systolic BP by 3–14 mmHg and diastolic BP by 4–13 mmHg shortly after intake in normotensive subjects [3]. However, the cardiovascular system may develop tolerance for caffeine and little is known about the long-term effects of coffee and caffeine intake.

The objective of this meta-analysis was to quantify the chronic effect (≥ 7 days) of regular coffee and caffeine intake on BP, using data from randomized controlled trials. In addition, we performed subgroup analyses to examine whether heterogeneity in BP response could be explained by type of intervention (coffee or caffeine) or subjects' characteristics.

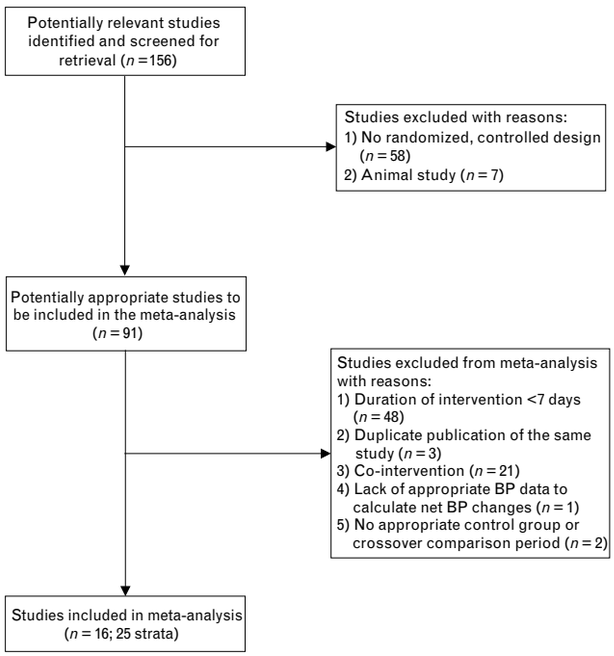
Methods

Selection of studies

We performed a systematic search for publications between January 1966 and January 2003 using the literature databases of Medline, Embase, Lilacs and Current Contents. A search was performed for the text words 'coffee or caffeine', 'blood pressure or hypertension' and 'trial or intervention or random* or study' in studies that were published in English-language journals. The Medline search was restricted to studies classified as randomized controlled trials. An additional manual search was conducted using reference lists from original research papers, former meta-analyses and review articles.

Studies that met the following criteria were eligible for meta-analysis: (1) conducted in humans; and (2) random

Fig. 1



Progress through the stages of the meta-analysis for randomized controlled trials of coffee or caffeine and blood pressure (BP).

allocation of study participants to intervention and control groups. A total of 91 out of 156 reports that were identified fulfilled these criteria. Reasons for the exclusion of studies were: (1) duration of intervention of less than 7 days ($n = 50$); (2) duplicate publication of the same study ($n = 3$); (3) co-intervention (e.g. caffeine combined with ephedrine, nicotine or stress) from which the effect of coffee or caffeine could not be separated ($n = 21$); (4) lack of concurrent control group or balanced crossover comparison period ($n = 2$); and (5) lack of data to calculate the net changes in BP ($n = 1$). A reference list of excluded trials is available from the authors. Sixteen trials [6–21] comprising 25 relevant strata proved to be eligible for meta-analysis (Fig. 1).

Data extraction

Two authors (M.N., J.M.G.) independently abstracted data from original reports using standard forms. In case of disagreement, consensus was reached. Data collection included: (1) sample size; (2) characteristics of the study population, i.e. age, gender distribution (% males), baseline BP, baseline heart rate (HR), habitual coffee consumption and caffeine intake, use of antihypertensive medication; (3) study design (parallel or crossover), blinding procedures, duration of intervention, type of intervention and control treatment; and (4) BP and HR changes and associated measures of variance.

For parallel trials the net BP effect of coffee or caffeine intake was calculated as BP change from baseline in the intervention group *minus* BP change from baseline in the control group. For crossover trials, BP level at the end of the control period was subtracted from BP at the end of the intervention period. Net effects of coffee or caffeine on HR were obtained similarly. In addition, the standard error (SE) for the net BP effect was obtained. If not reported, SEs were derived from 95% confidence intervals (95% CI), *t*-statistics or the individual variances for intervention and control groups (parallel trials) or intervention and control periods (crossover trials). Variances during the trial were assumed to be equal, and a correlation of 0.50 was assumed between baseline and final BP values, according to Follmann *et al.* [22] using the formula:

$$SE_{\Delta BP} = \sqrt{\{SE^2_{baseline} + SE^2_{final} - (2 \times 0.5 \times SE_{baseline} \times SE_{final})\}}$$

If different treatments were tested within the same trial, they were analysed as separate strata (delineated by a and b suffixes in tables and figures). Studies in which the active treatment consisted of caffeine tablets, either as the sole treatment or combined with decaffeinated coffee, were classified as caffeine trials. Caffeine intake at baseline was derived from the paper or, if not reported, estimated from pre-treatment coffee consumption, assuming that 150 ml of coffee contains 90 mg of caffeine [3]. Cup size was considered equal to 150 ml if the actual size was not reported. In one trial [14] among 36 subjects with a mean age of 23 years, caffeine doses were reported in mg/kg per day and we estimated the actual dose assuming an average body weight of 78 kg in men and 64 kg in women. Four reports of crossover studies [9,12,14,15] did not provide baseline BP data, and we used mean BP in the control period as the pre-treatment BP level. Data on BP and HR could not be obtained from text or tables for one trial [13] and we abstracted this information from graphs. Data on net changes in HR were missing in four trials [6,15,17,18].

Statistical analysis

Statistical analyses were performed using SAS, version 8 (SAS Institute Inc., Cary, North Carolina, USA). Homogeneity of effect size across trials was tested by Q-statistics [23]. Because of significant heterogeneity in BP effect among trials ($P < 0.001$ for systolic BP and $P = 0.044$ for diastolic BP), a random-effects model was used to calculate the effect of coffee and caffeine on BP and corresponding 95% CI. To calculate the pooled net effect size, each study was weighed by the reciprocal of the variance for BP change. Both within- and between-study variation were taken into account, according to DerSimonian and Laird [23]. We applied a statistical

technique for meta-analysis of continuous outcomes using the SAS PROC MIXED statement, as reported by Van Houwelingen *et al.* [24].

Heterogeneity in BP response was examined by performing stratified meta-analyses. Predefined subgroups were created on the basis of type of intervention (coffee versus caffeine), age (<40 years versus ≥ 40 years), gender ($<50\%$ males versus $\geq 50\%$ males), baseline BP ($<130/85$ mmHg versus $\geq 130/85$ mmHg), baseline caffeine intake (<400 mg/day versus ≥ 400 mg/day), caffeine dose during intervention (<410 mg/day versus ≥ 410 mg/day), study design (parallel versus crossover), blinding (open versus double blind) and study duration (<6 weeks versus ≥ 6 weeks). Within coffee trials, additional analyses for brewing method were performed (boiled versus filtered versus instant). Analyses in subgroups for age, baseline caffeine intake, caffeine dose and study duration were based on the median of the frequency distributions of these variables. Because only two of 25 strata included hypertensive subjects ($\geq 140/90$ mmHg), stratification for baseline BP was based on the cut-off for high normal BP ($\geq 130/85$ mmHg) according to WHO/ISH Hypertension Guidelines 1999.

Stratified analyses were repeated using a multivariate model with adjustment for the following variables (except when used as a stratification factor): age (years), gender (% males), baseline BP (mmHg), type of intervention (coffee or caffeine), baseline caffeine intake (mg/day) and caffeine dose during intervention (mg/day). Baseline coffee consumption or caffeine intake were not reported in two trials [16,17], and we imputed these missing data by mean values of the remaining 21 trials, to retain the trials in the multivariate analysis.

Funnel graphs were constructed in which BP effects of individual trials were plotted against their weight factors. The plots were visually examined to detect potential publication bias.

Results

Overview of trials included in meta-analysis

Study design features and characteristics of study populations for 11 coffee trials (18 strata) and five caffeine trials (7 strata) included in meta-analysis are presented in Tables 1 and 2, respectively. Trials were published between 1984 and 2000 and varied in sample size from 10 to 123 participants (median: 45). The analysis included 1010 subjects in total. All trials were performed in adult populations, with mean ages between 23 and 77 years. A crossover design was used in seven trials and treatment was double blind in all caffeine trials and in two coffee trials. Trial duration varied from 7 to 84 days (median: 42 days). Seventeen strata (68%) included $\geq 50\%$ men. Six strata (24%) included study populations with high normal BP or hypertension, with two strata having subjects on antihypertensive treatment. Intervention groups in coffee trials consumed instant coffee ($n = 8$), filtered coffee

Table 1 **Study and population characteristics of randomized controlled trials of coffee consumption and BP**

								SBP (mmHg)		DBP (mmHg)		HR (bpm)	
First author, year of publication	Design[a]	*N*[b]	Duration (days)	Age (year)	Males (%)	Type of coffee/ control[c]	Coffee dose (ml/day)[d]	Baseline	Change (SE)	Baseline	Change (SE)	Baseline	Change (SE)
Bak 1990a [7]	P-open	66[e]	63	26	53	F/N	700 (469)	122	6.1 (2.27)	71	3.0 (1.56)	76	4.0 (2.45)
Bak 1990b [7]	P-open	62[e]	63	26	54	B/N	700 (441)	121	6.0 (2.17)	71	2.8 (1.77)	75	5.7 (2.90)
Burr 1989a [9]	X-open	54[e]	28	35	65	I/D	1235 (741)	116	1.7 (1.20)	70	−1.1 (1.20)	64	−1.1 (1.10)
Burr 1989b [9]	X-open	54[e]	28	35	65	I/N	1235 (741)	114	2.9 (1.40)	70	−0.9 (1.20)	63	0.3 (1.10)
Dusseldorp 1989 [10]	X-db	45	42	38	49	F/D	750 (435)	124	1.5 (0.40)	76	1.0 (0.40)	66	−1.3 (0.60)
Dusseldorp 1991a [11]	P-open	43[e]	79	39	51	B/N	900 (774)	122	3.5 (1.18)	79	0.9 (0.92)	70	0.9 (0.89)
Dusseldorp 1991b [11]	P-open	42[e]	79	39	52	B + F/N	900 (798)	122	0.4 (0.98)	79	0.4 (0.90)	74	0.2 (1.00)
Eggertsen 1993 [12]	X-db	23	14	56	57	I/D	525 (263)	135	0.3 (3.20)	84	−0.1 (1.61)	75	0.4 (1.87)
Höfer 1994 [13]	P-open	120	9	32	50	I/D	998 (335)	114	−0.7 (0.66)	71	−1.0 (0.99)	72	−0.3 (1.87)
MacDonald 1991a [15]	X-open	50[e]	14	47	46	I/N	450 (225)	143	−0.7 (1.45)	94	0.1 (0.88)	–[f]	–[f]
MacDonald 1991b [15]	X-open	50[e]	14	47	46	I/D	450 (225)	143	−0.8 (1.45)	94	−0.3 (0.88)	–[f]	–[f]
Rakic 1999a [16]	P-open	27	14	77	15	I/N	750 (300)	136	3.6 (1.60)	72	4.7 (1.20)	73	3.3 (5.11)
Rakic 1999b [16]	P-open	21	14	72	29	I/N	750 (300)	125	−1.6 (6.87)	71	−0.2 (4.18)	78	4.6 (3.01)
Rosmarin 1990 [18]	X-open	21	56	36	100	F/N	540 (270)	115	2.1 (2.15)	72	−2.4 (2.45)	–[f]	–[f]
Superko 1991a [19]	P-open	123[e]	56	47	100	F/D	1090 (629)	115	2.7 (1.65)	74	−0.7 (1.15)	61	−0.1 (1.29)
Superko 1991b [19]	P-open	120[e]	56	46	100	F/N	1067 (615)	114	1.3 (1.57)	74	0.2 (1.18)	61	1.3 (1.07)
Superko 1994a [20]	P-open	99[e]	56	44	100	F/N	1067 (615)	116	1.4 (1.51)	74	0.7 (1.29)	64	1.2 (1.18)
Superko 1994b [20]	P-open	103[e]	56	47	100	F/D	1067 (615)	117	1.6 (1.70)	75	1.1 (1.25)	64	0.5 (1.46)

BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate in beats per minute. [a]P, parallel; X, crossover; db, double blind; [b]*N*, number of subjects that completed the study; [c]F, filtered coffee; B, boiled coffee; I, instant coffee; N, no coffee; D, decaffeinated coffee; [d]Caffeine dose in parentheses. For five trials in which cup size was not reported, an amount of 150 ml was assumed.[10,12,15,16,18]; [e]Different interventions were compared with the same control group or placebo treatment; [f]Data were not given in trial report.

Table 2 Study and population characteristics of randomized controlled trials on caffeine intake and BP

First author, year of publication	Design[a]	*N*[b]	Duration (days)	Age (year)	Males (%)	Treatment/control[c]	Caffeine dose (mg/day)	SBP (mmHg)		DBP (mmHg)		HR (bpm)	
								Baseline	Change (SE)	Baseline	Change (SE)	Baseline	Change (SE)
Arciero 1998 [6]	X-db	10	28	71	1.00	T/P	295	130	12.0 (6.00)	75	2.0 (3.00)	62	–[f]
Bak 1991 [8]	P-db	62	63	25	0.55	T/P[d]	375	124	−0.6 (2.65)	74	0.6 (1.75)	73	1.4 (2.25)
James 1994a [14]	X-db	18	7	23	1.00	T/P	410[e]	119	2.1 (2.12)	68	1.6 (1.12)	69	−1.3 (2.17)
James 1994b [14]	X-db	18	7	23	0.00	T/P	336[e]	109	1.5 (1.27)	65	1.3 (1.12)	76	−2.7 (1.77)
Robertson 1984 [17]	P-db	17	7	30	0.41	T/P	750	129	8.5 (1.56)	79	5.0 (1.56)	71	–[f]
Watson 2000a [21]	X-db	22	84	38	1.00	T/P	400	130	2.0 (4.00)	69	1.0 (2.00)	67	0.0 (2.65)
Watson 2000b [21]	X-db	12	84	38	0.00	T/P	400	113	5.0 (4.00)	66	−1.0 (2.65)	76	−1.0 (3.00)

BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate in beats per minute. [a]P, parallel; X, crossover; db, double blind; [b]*N*, number of subjects that completed the study; [c]T, caffeine tablets; P, placebo tablets; [d]Treatment consisted of caffeine tablets combined with decaffeinated coffee; [e]Estimated from caffeine dose/kg body weight per day (details given in text); [f]Data were not given in trial report.

($n = 7$), boiled coffee ($n = 2$) or coffee that was boiled and subsequently filtered ($n = 1$). Daily coffee dose in active treatment groups varied from 450 ml to 1235 ml, which corresponds to a caffeine dose of 225–798 mg/day. In caffeine trials, the doses of caffeine from tablets ranged from 295 to 750 mg/day. In coffee and caffeine trials combined, the median caffeine dose was 410 mg/day. The control groups of coffee trials either received no coffee (11 strata) or decaffeinated coffee (seven strata). In the caffeine trials all control groups received placebo tablets.

Effects on BP and HR

Average pre-treatment BP ranged from 109 to 143 mmHg for systolic BP (median 122 mmHg) and from 65 to 94 mmHg for diastolic BP (median 74 mmHg). Mean pre-treatment HR was available for 22 studies and ranged from 61 to 78 bpm (median 71 bpm). Net BP changes in coffee and caffeine trials ranged from −1.6 to 12.0 mmHg for systolic BP and from −2.4 to 5.0 mmHg for diastolic BP.

Meta-analysis yielded an overall BP effect of increased coffee or caffeine intake of 2.04 mmHg (95% CI, 1.10–2.99) for systolic BP and 0.73 mmHg (95% CI, 0.14–1.31) for diastolic BP (Fig. 2). After excluding nine coffee trials with an open design, BP estimates were: systolic, 2.81 mmHg (1.08–4.53); and diastolic, 1.17 mmHg (0.54–1.81). A non-significant increase in HR during coffee or caffeine treatment was observed, with an overall estimate of 0.15 bpm (−0.52–0.83).

Stratified analyses

BP effects of coffee and caffeine in strata of subjects' characteristics and study design features are summarized in Table 3. When coffee and caffeine trials were analysed separately, BP elevations in caffeine trials appeared to be larger for systolic BP ($P = 0.087$) and diastolic BP ($P = 0.091$) when compared to coffee trials. In trials with a high caffeine dose ($\geq$ 410 mg/day), the rise in systolic BP was larger than in trials with a lower caffeine dose ($P = 0.029$).

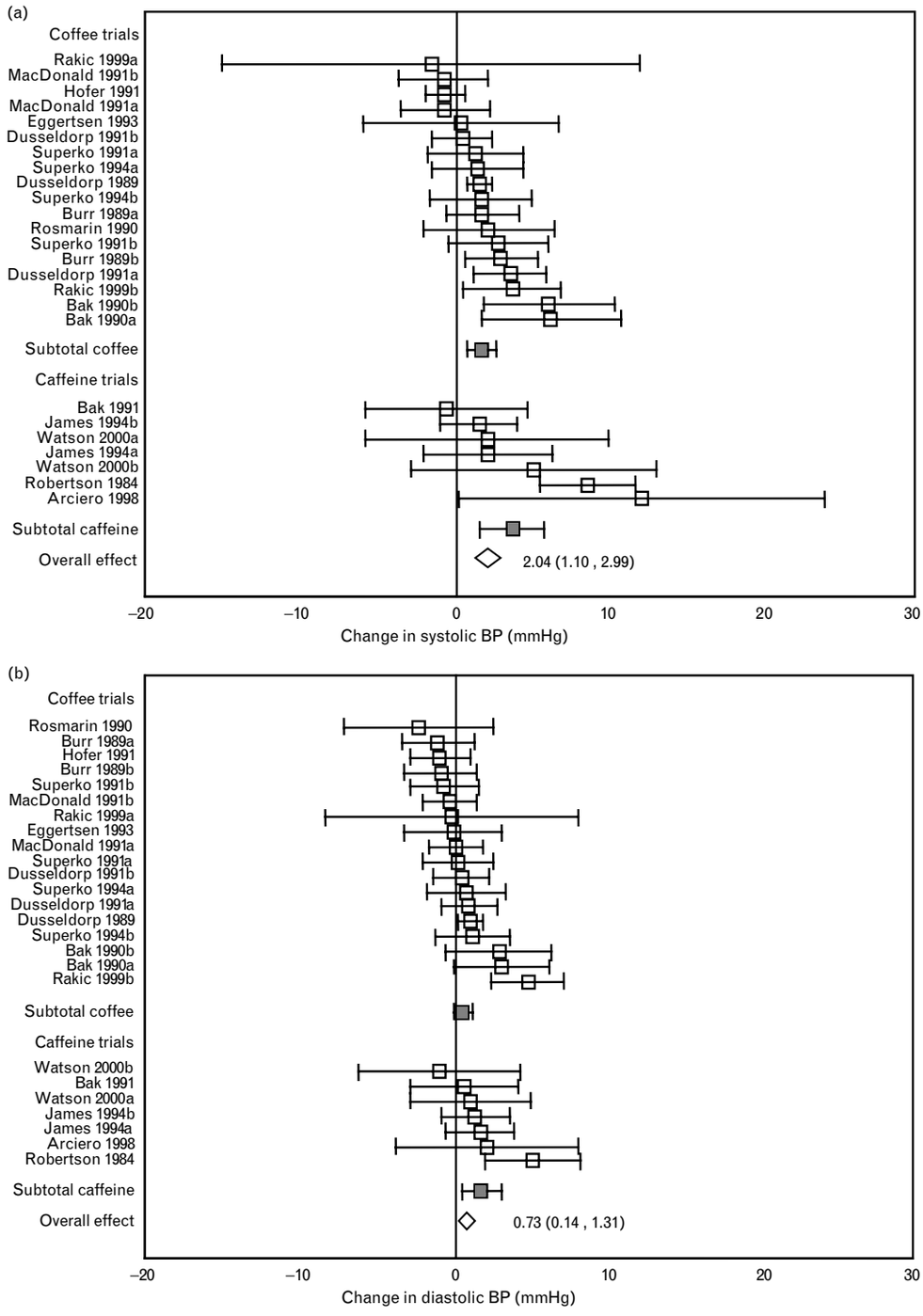
Table 3 additionally presents findings from stratified multivariate meta-analysis, in which adjustments were made for age, gender, baseline BP, type of intervention, baseline caffeine intake and caffeine dose (except when used as a stratification factor). The increased BP response for caffeine compared to coffee treatment found in univariate analysis became more pronounced after adjustment for potential confounders, both for systolic BP ($P = 0.006$) and diastolic BP ($P = 0.084$). In trials with a high caffeine dose of $\geq$ 410 mg/day, a larger response in systolic ($P < 0.001$) and diastolic ($P = 0.002$) BP was observed than in trials with a lower dose. The effect of coffee and caffeine on diastolic BP was significantly larger in trials that included > 50% women, compared to trials that mainly included men ($P = 0.011$). Age, BP level and other population characteristics were not significantly associated with BP response in multivariate analysis.

BP estimates were also obtained for different brewing methods in coffee trials (data not in table). After adjustment for confounders, the strongest effect was found for boiled coffee [systolic BP: 4.75 mmHg (2.33–7.17) and diastolic BP: 1.85 mmHg (−0.10–3.80)]. Filtered coffee caused a moderate elevation of BP [systolic BP: 2.07 mmHg (0.95–3.18) and diastolic BP: 0.44 mmHg (−0.52–1.38)], whereas only a small, non-significant elevation of BP was found for instant coffee [1.07 mmHg (−0.68–2.82) and 0.19 mmHg (−1.04–1.41), respectively]. BP estimates for coffee were larger if control subjects received no coffee [systolic BP: 2.80 mmHg (1.72–3.89) and diastolic BP: 1.10 mmHg (0.25–1.96)] when compared to decaffeinated coffee [systolic BP: 0.92 mmHg (−0.33–2.16) and diastolic BP: −0.15 mmHg −1.39–1.10)].

Publication bias

A funnel plot for systolic BP is shown in Figure 3. A funnel-shaped pattern with a broader spread of net change in BP for trials with a small weight factor was observed, and a decreasing spread as the size of the weight factor increases. From visual examination of the plot, it can be concluded that small studies in which BP showed a relatively large

Fig. 2



Net changes in systolic and diastolic blood pressure (BP) in coffee and caffeine trials. BP effects in trials of coffee and caffeine intake were calculated as the difference in BP change from baseline between the intervention and control group (for parallel trials) or the difference in BP levels at the end of the intervention and control periods (for crossover trials). BP effects in individual trials are depicted as open squares with 95% confidence intervals, for systolic BP (Forest plot a) and diastolic BP (Forest plot b), respectively. Meta-analysis yielded pooled estimates of 2.04 mmHg (1.10–2.99) for systolic BP and 0.73 mmHg (0.14–1.31) for diastolic BP, which are depicted as open diamonds with 95% confidence intervals.

Table 3 Blood pressure (BP) response to coffee and caffeine in strata of study population characteristics and caffeine dose

		Systolic BP		Diastolic BP	
	Strata (*n*)	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Intervention					
Coffee	18	1.64 (0.68,2.61)	1.22 (0.52,1.92)	0.51 (−0.08,1.10)	0.49 (−0.06,1.04)
Caffeine	7	3.64 (1.57,5.71)	4.16 (2.13,6.20)	1.72 (0.44,3.00)	2.41 (0.98,3.84)
P		0.087	0.006	0.091	0.084
Age					
< 40 years	15	2.40 (1.25,3.55)	2.41 (1.43,3.38)	0.77 (0.03,1.51)	0.73 (0.01,1.44)
≥ 40 years	10	1.34 (−0.26,2.93)	1.24 (−0.23,2.72)	0.66 (−0.28,1.61)	1.09 (−0.08,2.25)
P		0.28	0.25	0.87	0.65
Baseline BP					
< 130/85 mmHg	19	2.24 (1.22,3.25)	2.09 (0.79,3.40)	0.65 (−0.02,1.32)	1.13 (0.38,1.89)
≥ 130/85 mmHg	6	1.05 (−1.16,3.26)	2.06 (−1.09,5.20)	1.00 (−0.24,2.23)	0.75 (−1.05,2.55)
P		0.34	0.98	0.63	0.74
Gender					
< 50% males	8	2.15 (0.53,3.78)	2.61 (1.75,3.46)	1.28 (0.40,2.16)	1.86 (1.10,2.62)
≥ 50% males	17	1.99 (0.83,3.14)	1.53 (0.51,2.55)	0.36 (−0.34,1.07)	0.42 (−0.32,1.16)
P		0.87	0.10	0.11	0.011
Baseline caffeine intake[b]					
< 400 mg/day	12	1.50 (0.12,2.87)	1.90 (0.76,3.04)	0.28 (−0.54,1.11)	0.56 (−0.22,1.34)
≥ 400 mg/day	13	2.48 (1.23,3.74)	2.26 (1.17,3.36)	1.17 (0.35,2.00)	1.46 (0.62,2.29)
P		0.30	0.64	0.14	0.13
Caffeine dose[c]					
< 410 mg/day	12	0.76 (−0.62,2.13)	0.72 (−0.35,1.78)	0.52 (−0.42,1.50)	−0.52 (−1.62,0.57)
≥ 410 mg/day	13	2.68 (1.63,3.72)	2.98 (2.15,3.80)	0.85 (0.12,1.59)	1.96 (1.19,2.73)
P		0.029	< 0.001	0.59	0.002
Study duration					
< 6 weeks	12	1.83 (0.49,3.18)	0.72 (−0.12,1.57)	1.92 (0.88,2.96)	0.65 (−0.14,1.45)
≥ 6 weeks	13	2.23 (0.93,3.54)	0.73 (−0.08,1.54)	2.18 (1.10,3.27)	1.36 (0.65,2.08)
P		0.68	0.99	0.72	0.21

Values are mean BP effects (mmHg) with 95% confidence intervals and *P* value for difference in BP response between strata. For some trials, different treatments using the same control group have been included in stratified analysis. *P* values for differences between strata have not been adjusted for use of the same control group. [a]Adjusted for the following variables (except when used as stratification factor): type of intervention (coffee or caffeine), age, proportion of males, baseline BP, baseline caffeine intake and caffeine dose; [b]From the diet, including coffee consumption; [c]From coffee or caffeine tablets, depending on the trial.

decrease during coffee or caffeine treatment (i.e. > 2 mmHg) may not have been published.

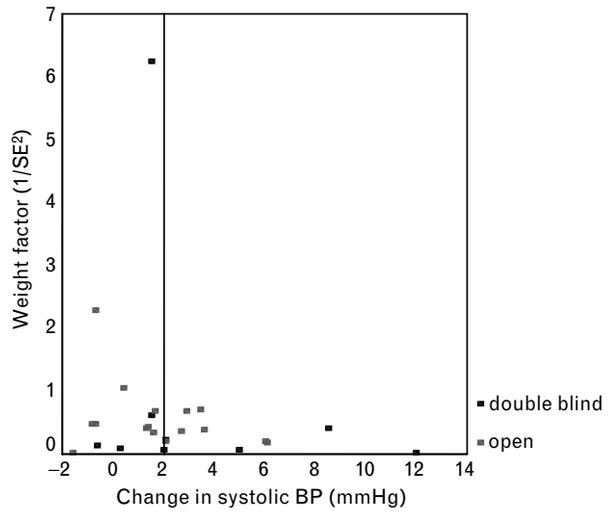
Discussion

This meta-analysis of 16 randomized controlled trials, comprising 1010 subjects, yielded an overall BP increase of 2.0/0.7 mmHg for regular coffee or caffeine intake. BP elevations appeared to be 2–3 times larger for caffeine tablets than for caffeinated coffee despite equal average doses of caffeine. Effects on HR were negligible and not statistically significant.

The present meta-analysis was based on a comprehensive, systematic literature search of randomized controlled trials, which have high internal validity, and analyses were performed using an advanced statistical approach that takes into account both *within* and *between* study variation [24]. Furthermore, the inclusion of caffeine trials allowed comparison of the BP effect of pure caffeine with caffeinated coffee. Finally, we could examine whether the method of coffee preparation had an effect on BP.

However, certain limitations need to be considered. First, nine out of 11 coffee trials were not blinded and this may have influenced the observed effects on BP. The habit of drinking coffee may cause physical or mental relaxation or, conversely, abstinence may induce a level of discomfort, which could both influence BP. In this meta-analysis we could not distinguish these 'side effects' from the BP effect of compounds in coffee. Caffeine trials, on the other hand, were all double blind and BP changes in these studies can truly be attributed to caffeine. Secondly, we could not sufficiently explore the BP effect of chronic coffee and caffeine intake in hypertensive subjects, as the subgroup analysis for elevated BP (i.e. ≥ 135/85 mmHg) included only six strata. However, our data do not suggest that hypertension is an important modifying factor in the relationship between caffeine and BP. Furthermore, we cannot exclude the possibility that significant differences among subgroups are based on coincidence due to multiple testing. Stratified analyses were intended to be exploratory, rather than conclusive. Subgroup comparisons may provide clues to underlying biological mechanisms and indicate directions for further research, but we emphasize that findings should be interpreted with caution. Pooling of original trial databases would have been a better approach to study heterogeneity with more statistical power, but this appeared not feasible in the present

Fig. 3



Funnel plot of change in systolic blood pressure (BP) against weight factor. Systolic BP effects in trials are depicted as black (double-blind strata) and grey (open strata) squares, scattered around the pooled BP estimate of 2.04 mmHg. Visual examination of the funnel plot for publication bias suggests that small trials with reductions in systolic BP > 2 mmHg may be under-represented.

study. Finally, we found some evidence for publication bias, but this had little influence on the pooled BP estimates, since studies that were overrepresented had small weight factors.

The BP effects that we found are smaller than the estimates of 2.4 mmHg for systolic BP and 1.2 mmHg for diastolic BP in a meta-analysis of 11 coffee trials (total of 522 subjects) by Jee *et al.* [2]. This discrepancy can be explained by the fact that we excluded trials with a duration of less than 7 days. Also, the present meta-analysis comprised twice as many subjects and included five caffeine trials that had not been examined by Jee *et al.* [2].

Coffee is a widely consumed beverage, and even small effects on BP could impact public health. To illustrate, a 2 mmHg average reduction in population BP may result in an annual reduction in stroke, coronary heart disease and all-cause mortality of about 6, 4 and 3%, respectively [25]. In a prospective cohort study of 1017 young white US males with a median follow-up of 33 years, drinking coffee was positively associated with BP and risk of hypertension, although findings were weak [26].

Despite its potential BP-raising effect, coffee drinking appeared not to be associated with coronary events and stroke in a prospective study that included over 45 000 US men [27]. Several explanations may be given for this paradoxical finding. First, coffee contains other substances (e.g. potassium, magnesium and chlorogenic acid) [28] that could exert a protective effect in the cardiovascular system. In addition, a number of epidemiological studies have recently shown an inverse association of coffee drinking with risk of diabetes mellitus type 2, which is a strong risk factor for cardiovascular disease [29,30]. Moreover, although we excluded short-term trials, we cannot exclude the possibility that the BP rise associated with coffee or caffeine is transient and eventually not leading to cardiovascular damage.

Coffee drinking is often related to cigarette smoking and these habits acted synergistically on BP in patients with malignant hypertension [31]. In our meta-analysis, only eight strata (on a total of 25 strata) included smokers. Since the majority of trials were conducted in non-smokers, and the proportion of smokers in other trials was generally low, this will not have had a large effect on our BP estimates.

Caffeine intake had larger effects on BP than coffee intake, which could not be explained by differences in frequency and timing of intake over the day, since these were roughly similar in both types of trials. However, bioavailability of caffeine may differ between coffee and tablets. Possibly, ingestion of caffeine tablets is more harmful to BP than coffee drinking because it is not associated with favourable 'side effects', such as physical or mental relaxation. Furthermore, caffeine tablets lack substances that could possibly exert a beneficial effect in the cardiovascular system.

Finally, alcohol intake may have contributed to the difference in BP effects that we observed for coffee and caffeine. Coffee and alcohol seem to have contrasting effects on gamma-glutamyl transpeptidase, which is a marker for alcohol-related hypertension, with coffee, but not caffeine, protecting liver cells from the effect of alcohol [32]. Regrettably, for the majority of studies included in the present meta-analysis the concurrent level of alcohol consumption was not reported.

BP effects tended to be related to coffee brewing method in this study, although findings must be interpreted with caution because of limited statistical power in this stratified analysis. Strongest BP effects were found for boiled coffee, whereas instant coffee caused only a small elevation of BP. Boiled, unfiltered coffee contains the diterpene lipids cafestol and kahweol [28,33] but these affect blood cholesterol rather than BP [33]. Therefore, if anything, BP effects related to brewing method are probably attributable to different amounts of caffeine in the various types of coffee.

Caffeine-induced pressor effects may involve several mechanisms, of which the most plausible is antagonism of endogenous adenosine, leading to vasoconstriction and

increased total peripheral resistance [1]. Habitual use of caffeine has been reported to lead to haemodynamic tolerance after 1–4 days [34] and we therefore excluded from our meta-analysis studies of duration less than 1 week. However, Lovallo *et al.* [35] recently reported lack of tolerance after acute dosing in half of the subjects that had been exposed to a caffeine intake as high as 600 mg/day for 5 days.

This meta-analysis shows that regular caffeine intake increases BP, although the pressure effect of caffeine was only small if ingested through coffee. More research is needed on the cardiovascular effects of caffeine and caffeinated foods and beverages other than coffee, such as cola and sport drinks.

References

1 James JE. Is habitual caffeine use a preventable cardiovascular risk factor? *Lancet* 1997; **349**:279–281.
2 Jee SH, He J, Whelton PK, Suh I, Klag MJ. The effect of chronic coffee drinking on blood pressure: a meta-analysis of controlled clinical trials. *Hypertension* 1999; **33**:647–652.
3 Nurminen ML, Niittynen L, Korpela R, Vapaatalo H. Coffee, caffeine and blood pressure: a critical review. *Eur J Clin Nutr* 1999; **53**:831–839.
4 LaCroix AZ, Mead LA, Liang KY, Thomas CB, Pearson TA. Coffee consumption and the incidence of coronary heart disease. *N Engl J Med* 1986; **315**:977–982.
5 Tverdal A, Stensvold I, Solvoll K, Foss OP, Lund-Larsen P, Bjartveit K. Coffee consumption and death from coronary heart disease in middle aged Norwegian men and women. *BMJ* 1990; **300**:566–569.
6 Arciero PJ, Gardner AW, Benowitz NL, Poehlman ET. Relationship of blood pressure, heart rate and behavioral mood state to norepinephrine kinetics in younger and older men following caffeine ingestion. *Eur J Clin Nutr* 1998; **52**:805–812.
7 Bak AA, Grobbee DE. A randomized study on coffee and blood pressure. *J Hum Hypertens* 1990; **4**:259–264.
8 Bak AA, Grobbee DE. Caffeine, blood pressure and serum lipids. *Am J Clin Nutr* 1991; **53**:971–975.
9 Burr ML, Gallacher JEJ, Butland BK, Bolton CH, Downs LG. Coffee, blood pressure and plasma lipids: a randomized controlled trial. *Eur J Clin Nutr* 1989; **43**:477–483.
10 Dusseldorp M van, Smits P, Thien T, Katan MB. Effect of decaffeinated *vs.* regular coffee on blood pressure. A 12-week, double blind trial. *Hypertension* 1989; **14**:563–569.
11 Dusseldorp M van, Smits P, Lenders JW, Thien T, Katan MB. Boiled coffee and blood pressure. A 14-week controlled trial. *Hypertension* 1991; **18**:607–613.
12 Eggertsen R, Andreasson A, Hedner T, Karlberg BE, Hanson L. Effect of coffee on ambulatory blood pressure in patients with treated hypertension. *J Intern Med* 1993; **233**:351–355.
13 Höfer I, Bättig K. Cardiovascular, behavioral, and subjective effects of caffeine under field conditions. *Pharmacol Biochem Behav* 1994; **48**:899–908.
14 James JE. Chronic effects of habitual caffeine consumption on laboratory blood pressure levels. *J Cardiovasc Risk* 1994; **1**:159–164.
15 MacDonald TM, Sharpe K, Fowler G, Lyons D, Freestone S, Lovell HG, *et al.* Caffeine restriction: effect on mild hypertension. *BMJ* 1991; **303**:1235–1238.
16 Rakic V, Burke V, Beilin LJ. Effects of coffee on ambulatory blood pressure in older men and women: a randomized controlled trial. *Hypertension* 1999; **33**:869–873.
17 Robertson D, Hollister AS, Kincaid D, Workman R, Goldberg MR, Tung C, Smith B. Caffeine and hypertension. *Am J Med* 1984; **77**:54–60.
18 Rosmarin PC, Applegate WB, Somes GW. Coffee consumption and blood pressure: a randomized, crossover clinical trial. *J Gen Intern Med* 1990; **5**:211–213.
19 Superko HR, Bortz W, Williams PT, Albers JJ, Wood PD. Caffeinated and decaffeinated coffee effects on plasma lipoprotein cholesterol, apolipoproteins, and lipase activity: a controlled, randomized trial. *Am J Clin Nutr* 1991; **54**:599–605.
20 Superko HR, Myll J, DiRicco C, Williams PT, Bortz WM, Wood PD. Effects of cessation of caffeinated-coffee consumption on ambulatory and resting blood pressure in men. *Am J Cardiol* 1994; **73**:780–784.
21 Watson JM, Jenkins EJ, Hamilton P, Lunt MJ, Kerr D. Influence of caffeine on the frequency and perception of hypoglycemia in free-living patients with type 1 diabetes. *Diabetes Care* 2000; **23**:455–459.
22 Follmann D, Elliott P, Suh I, Cutler J. Variance imputation for overviews of clinical trials with continuous response. *J Clin Epidemiol* 1992; **45**:769–773.
23 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**:177–188.
24 Houwelingen HC van, Arends LR, Stijnen T. Tutorial in biostatistics. Advanced methods in meta-analysis: multivariate approach and meta-regression. *Stat Med* 2002; **21**:589–624.
25 Whelton PK. Epidemiology of hypertension. *Lancet* 1994; **344**:101–106.
26 Klag MJ, Wang NY, Meoni LA, Brancati FL, Cooper LA, Liang KY, *et al.* Coffee intake and risk of hypertension: the Johns Hopkins precursors study. *Arch Intern Med* 2002; **162**:657–662.
27 Grobbee DE, Rimm EB, Giovannucci E, Golditz G, Stampfer M, Willett W. Coffee, caffeine and cardiovascular disease in men. *N Engl J Med* 1990; **323**:1026–1032.
28 Viani R. The composition of coffee. In: Garattini S (editor): *Caffeine, coffee and health*. New York: Raven Press; 1993, pp. 17–41.
29 Dam RM van, Feskens EJ. Coffee consumption and risk of type 2 diabetes mellitus. *Lancet* 2002; **360**:1477–1478.
30 Tuomilehto J, Hu G, Bidel S, Lindstrom J, Jousilahti P. Coffee consumption and risk of type 2 diabetes mellitus among middle-aged Finnish men and women. *JAMA* 2004; **291**:1213–1219.
31 Freestone S, Yeo WW, Ramsay LE. Effect of coffee and cigarette smoking on the blood pressure of patients with accelerated (malignant) hypertension. *J Hum Hypertens* 1995; **9**:89–91.
32 Aubin HJ, Laureaux C, Zerah F, Tilekete S, Vervier F, Vallat B, Barrucand D. Joint influence of alcohol, tobacco, and coffee on biological markers of heavy drinking in alcoholics. *Biol Psychiatry* 1998; **44**:638–643.
33 Urgert R, Katan MB. The cholesterol-raising factor from coffee beans. *Annu Rev Nutr* 1997; **17**:305–324.
34 Robertson D, Wade D, Workman R, Woosley RL, Oates JA. Tolerance to the humoral and hemodynamic effects of caffeine in man. *J Clin Invest* 1981; **67**:1111–1117.
35 Lovallo WR, Wilson MF, Vincent AS, Sung BH, McKey BS, Whitsett TL. Blood pressure response to caffeine shows incomplete tolerance after short-term regular consumption. *Hypertension* 2004; **43**:760–765.