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GUIDELINES/CLINICAL TRIALS/META-ANALYSIS (WJ KOSTIS, SECTION EDITOR)

Cocoa Consumption and Blood Pressure in Middle-Aged and Elderly Subjects: a Meta-Analysis

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Abstract

Purpose of Review The effect of cocoa consumption on blood pressure (BP) has been investigated in previous studies; however, to date, no meta-analysis has been conducted specific to middle-aged and elderly subjects. Thus, the aim of the present study was to evaluate the effect of cocoa consumption on indices of blood pressure, in middle-aged and elderly subjects.

Recent Findings Pubmed/Medline™, Cochrane Library™, Google Scholar™, and Scopus™ were searched until March 2019. The quantitative Jadad scale was used as the systematic assessment of bias in the included trials. We used a random effects model to estimate the pooled weighted mean differences (WMDs) with 95% confidence intervals (CIs). We further conducted sensitivity analysis and stratified analysis by baseline blood pressure, follow-up duration, and mean age. Thirteen studies with 758 total participants were included in the present meta-analysis. A significant reduction in SBP by 2.77 (95% CI − 5.28, − 0.27, $P = 0.03$, $I^2 = 89\%$) and DBP by 1.47 mm/Hg (− 95% CI − 2.40, − 0.55, $P = 0.001$, $I^2 = 45\%$) were observed after cocoa consumption. Stratified analyses showed BP-lowering effects of cocoa consumption in longer-term duration and hypertensive subgroups.

Summary Our meta-analysis showed a significant inverse association between cocoa consumption and SBP/DBP. However, the analysis could not conclude any beneficial effect of cocoa consumption on blood pressure in normotensive/elevated blood pressure subjects. Therefore, further studies are warranted to affirm the efficacy of cocoa consumption for the improvement of blood pressure in elderly subjects.

Keywords Cocoa · Blood pressure · Middle-aged · Elderly · Meta-analysis

Introduction

High blood pressure, or hypertension, is an inarguably important risk factor for cardiovascular disease and purported to be attributable for nearly 50% of ischemic heart disease and over 50% of cerebrovascular events globally [1]. More than a third of cardiovascular deaths are attributable to hypertension in Western populations [2], in addition to 13.5% worldwide [1]. Furthermore, the prevalence of hypertension is known to increase concurrently with aging. In fact, the, now seminal, Framingham study demonstrated that almost two-thirds of males and three quarter of females will develop hypertension by the age of 70 years [3–5].

The association between cardiovascular risk and blood pressure levels is believed to be continuous [6], where the risk of ischemic heart disease, stroke, and other comorbidities is shown to be reduced, by nearly half, for every 20-mmHg reduction in systolic blood pressure (SBP), and 10-mmHg diastolic blood pressure (DBP), respectively [7•]. While managing blood pressure is often difficult in older populations, not only because of comorbidities but also due to vascular remodeling and the changes in renal and endocrine physiology [5], it is evident that even small or modest reductions in blood pressure may protect against cardiovascular events at a population level.

Hypertension is typically treated using various pharmacotherapies. However, complementary medicine such as dietary supplements and foods could be considered as an effective treatment for various situations [8–10] including hypertension [11, 12]. Chocolate and flavanol-rich cocoa-based products

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have attracted attention as an alternate treatment [13••, 14••, 15••, 16••]. Numerous randomized clinical trials examining the effect of cocoa-rich products on BP have been undertaken and have reported beneficial effects as compared with chocolate containing no or negligible amounts of flavanols [13••, 14••, 15••, 16••]. The blood pressure-lowering properties of cocoa have been putatively attributed to the formation of endothelial nitric oxide (NO), which may facilitate vasodilation, and subsequently reduces blood pressure. Increased NO production may conceivably be triggered by upregulation of NO synthase via the insulin-mediated signaling pathway [17]. Further, cocoa flavanols have been shown to inhibit angiotensin converting enzyme activity, and therein reduce blood pressure [18, 19]. Recently, numerous clinical trials have investigated the effect of chocolate and cocoa-based products on blood pressure. Although, there are several meta-analysis which investigated the blood pressure-lowering effect of cocoa consumption [13••, 14••, 16••]; however, to date, no meta-analysis has been conducted specific to middle-aged and elderly subjects, and given the marked benefits associated with blood pressure reduction in this population, and the prediction that by the year 2050, one-fifth of the world population will surpass 80 years of age [20••], the aim of the present study was to investigate the effect of cocoa consumption on indices of blood pressure, in middle-aged and elderly subjects, manifest in randomized controlled trials (RCTs).

Methods

Literature Search

The current systematic review and meta-analysis was conducted according to the PRISMA guidelines [21•] and Cochrane Handbook for Systematic Reviews [22•]. Pubmed/Medline™, Cochrane Library™, Google Scholar™, and Scopus™ were searched until March 2019. We comprehensively searched for RCTs that investigated the efficacy of cocoa consumption on blood pressure in middle-aged and elderly subjects. Moreover, the reference lists of pertinent studies were manually investigated to explore additional potentially relevant studies. Both free text and MeSH items were used in titles and abstracts as follow: ("cacao" [MeSh] OR "cocoa" OR "chocolate") AND ("Blood Pressure" [MeSh] OR "Blood Pressure" OR "Hypertension" [MeSh] OR "Prehypertension" [MeSh] OR "SBP" OR "DBP". The searches were not restricted based on the language and the searches were limited to human studies.

Study Selection

We selected the original studies if they met the following inclusion criteria: (1) consumption of any cocoa products including chocolate (as bar, powder) or drink, cocoa, or refined cocoa flavan-3-ols compared with a control group, (2) random allocation to intervention and control group, (3) studies with blood pressure measurements at the baseline and end of the trial (reported mean changes and standard deviations or necessary data for calculating in the case of unavailable value), (4) participants with the mean age of ≥ 45 years as the middle-aged and ≥ 65 years as the elderly subjects. We did not restrict the studies according to participant's gender, clinical condition, and baseline blood pressure. The raw data were extracted independently by two reviewers, and discrepancies were subsequently adjudicated by the third reviewer. We tried to contact the authors of publications in which necessary measurements were insufficient to obtain additional study data.

Data Extraction

The following data were extracted by using a standard form and cross-checked (Table 1). The first author of the publication, year of publication, location of study, age and gender of subjects, the sample size of intervention/control groups, follow-up duration, intervention/control treatments and dosages, clinical condition of participants, design of trials, baseline blood pressure, and significant reported outcomes.

Quality Assessment

We used the quantitative Jadad scale as the systematic assessment of bias in the included trials with the score ranges from 0 to 5. Higher scores suggest higher quality. The scale includes three main parameters: randomization, blinding, and monitoring of subject drop outs with the following scoring system: one point for stating random allocation and one additional point if the method of randomization was suitable. One point was given for stating the blinding and one more point if the method of blinding was appropriate. One point was deducted in the case of inappropriate method of randomization or blinding. Finally, another extra point was given for stating the withdrawals with the reasons [23•].

Statistical Analysis

The data synthesis was conducted using Review Manager Software (Review Manager 5.3; Cochrane Collaboration, Oxford, England) and Comprehensive Meta-Analysis (version 3.2; Biostat). The change and standard deviation (SD) in SBP and DBP between intervention and control groups were presumed as the outcomes. We estimated the SD by [SD = SEM × sqrt (n); n = number of subjects] when standard error of mean (SEM) was reported in the trials. In the case or reported data as median/mean and variation range or interquartile range, the method of Hozo et al. were calculated to estimate the SDs [24•]. The statistical heterogeneity was

Table 1 Descriptions of all included trials

Study name	Year	Country	Age (mean)	Gender	Intervention sample size	Placebo sample size	Follow-up duration (week)	Intervention dosage	Control dosage	Clinical condition	Design	Baseline BP intervention	Significant outcome
Crews	2008	USA	68.7	F/M	45	43	6	Flavanoid and procyanidin--rich dark chocolate bars and artificially sweetened cocoa beverage mix products for	Low-polyphenol placebo	Healthy	Parallel	126.83/74.22	SBP and DBP had not changed significantly.
Davison	2008	Australia	45.3	F/M	12	11	12	High-flavanol cocoa	Low-flavanol cocoa	Sedentary	Parallel	124/76	Diastolic BP reduced by 1.6 mmHg, independent of exercise.
Davison (a)	2010	Australia	56.2	F/M	12	14	6	372 mg cocoa flavanol	Low-flavanol cocoa	High-normal BP or untreated mild hypertension	Parallel	133.1/81.3	SBP and DBP had not changed significantly
Davison (b)	2010	Australia	60.2	F/M	13	14	6	712 mg cocoa flavanol	Low-flavanol cocoa	High-normal BP or untreated mild hypertension	Parallel	127.4/78.3	SBP and DBP had not changed significantly
Davison (c)	2010	Australia	56.8	F/M	13	14	6	1052 mg cocoa flavanol	Low-flavanol cocoa	high-normal BP or untreated mild hypertension	Parallel	127.8/76.3	There were significant reductions in 24-h systolic (5.3 ± 5.1 mmHg) and diastolic (3 ± 3.2 mmHg) blood pressure.
Desideri (a)	2012	Italy	Elderly (> 6-5)	F/M	30	30	8	High-flavanol cocoa	Low-flavanol cocoa	MCI (mild cognitive impairment)	Parallel	141.1/84.5	Systolic and diastolic blood pressure levels were significantly lower at the end of follow-up.
Desideri (b)	2012	Italy	Elderly (> 6-5)	F/M	30	30	8	Intermediate flavanol cocoa	Low-flavanol cocoa	MCI (mild cognitive impairment)	Parallel	142.4/86.4	Systolic and diastolic blood pressure levels were significantly lower at the end of follow-up.
Flammer	2011	Switzerland	60.3	F/M	10	10	4	Flavanol-rich chocolate	Cocoa-liquor-free control chocolate	Stable congestive heart failure (CHF) (NYHA ≥ II) and ejection fraction < 50%	Parallel	109.5/65.8	Systolic and diastolic BP were not affected
Haghighat	2013	Iran	58.7	F/M	32	28	8	Dark chocolate	White chocolate	Type 2 diabetes	Parallel	137/85.1	

Table 1 (continued)

Study name	Year	Country	Age (mean)	Gender	Intervention sample size	Placebo sample size	Follow-up duration (week)	Intervention dosage	Control dosage	Clinical condition	Design	Baseline BP intervention	Significant outcome
													Systolic and diastolic blood pressure significantly reduced.
Ibero-Baraibar	2016	Spain	NS	F/M	23	24	4	Ready-to-eat meals with cocoa	Ready-to-eat meals without cocoa	Obese	Parallel	NS	NS
Mastroiacovo (a)	2014	Italy	68.76	F/M	30	30	8	Intermediate flavanol cocoa (IF)	Low-flavanol cocoa (LF)	Unconcerned about their own memory functions	Parallel	137/83.5	Systolic and diastolic blood pressure at the end of follow-up were significantly lower in the IF group. A significant reduction in diastolic blood pressure was also observed in the LF group, but this decrease was lower in magnitude than the changes observed in the IF group.
Mastroiacovo (b)	2014	Italy	70	F/M	30	30	8	High-flavanol cocoa (HF)	Low-flavanol cocoa (LF)	Unconcerned about their own memory functions	Parallel	138/83.5	Systolic and diastolic blood pressure at the end of follow-up were significantly lower in the HF group. A significant reduction in diastolic blood pressure was also observed in subjects assigned to the LF group, but this decrease was lower in magnitude than the changes observed in the HF group.
Mellor	2010	UK	NS	F/M	12	12	8	High-polyphenol content chocolate	Low-polyphenol content chocolate	Type 2 diabetes	Crossover	132/80	NS
Neufinger (a)	2013	Netherlands	55.3	F/M	10	10	4	Cocoa powder naturally has theobromine and flavanoids	Neither cocoa nor theobromine	Healthy	Parallel	117/75.3	Systolic and diastolic blood pressure did not significantly changed.
Neufinger (b)	2013	Netherlands	55.9	F/M	9	10	4	Cocoa powder naturally has flavanoids with added	Neither cocoa nor theobromine	Healthy	Parallel	119.2/75.2	Systolic and diastolic blood pressure did not significantly changed.

Table 1 (continued)

Study name	Year	Country	Age (mean)	Gender	Intervention sample size	Placebo sample size	Follow-up duration (week)	Intervention dosage	Control dosage	Clinical condition	Design	Baseline BP intervention	Significant outcome
								pure theobromine					
Rassaf	2016	Germany	65	F/M	24	25	30 days	Cocoa flavanol (CF)	Cocoa flavanol-free placebo	Patients on hemodialysis with ESRD	Parallel	138.26/73.02	CF intake was associated with reductions in systolic BP (SBP) during hemodialysis (HD) and DBP after HD.
Sorond	2013	USA	NS	F/M	29	29	30 days	Flavanol-rich cocoa	Flavanol-poor cocoa	Hypertension and/or well--controlled diabetes mellitus type2	Parallel	124/69	Among all subjects, blood pressure decreased after 1 day of cocoa. However, after 1 month of cocoa, blood pressures were not significantly different from baseline.
Taubert	2007	Germany	63.4	F/M	22	22	18	Dark chocolate	White chocolate	Good general health except for upper-range pre--hypertension or stage 1 hypertension	Parallel	147.7/86.4	Systolic and diastolic blood pressure significantly reduced by dark chocolate.

quantitatively estimated using I^2 statistic test and χ^2 on Cochrane's Q statistic test. According to the observed heterogeneity among trials and Cochrane Handbook Guideline [22•], random effects were used in the meta-analysis.

Pre-specified subgroup analyses were conducted by comparing different treatment characteristics: (i) duration of treatment: shorter-term trials (treatment duration of less than 6 weeks) [25–29] vs. longer-term trials (treatment duration ≥ 6 weeks) [30–37]; (ii) mean age of participants in intervention group: 9 trials with middle-aged participants (between 45 and 65 years old) [25, 27, 31, 32, 34, 37] and 6 trials with elderly subjects (≥ 65 years old) [28, 30, 33, 35] and 3 trials with unknown mean age in the intervention group [26, 29, 36]; (iii) baseline BP level: 3 trials with normotensive subjects [25, 27], 5 trials with elevated blood pressure subjects [29–32], and 10 trials with hypertensive patients [26, 28, 31, 33–37]. Different subgroups based on follow-up duration and baseline BP level divided by their medians. Additionally, the influence of single studies on the pooled weighted mean difference was executed by conducting sensitivity analyses according to the Cochrane guidelines [38•].

The potential publication bias was investigated by multiple analysis including Egger's weighted regression test, Begg's rank correlation method, and funnel plots test. The asymmetric shape of funnel plot is considered as a positive indicator of a publication bias. A P value of less than 0.05 was considered as statistically significant in the analyses.

Results

Results of the Literature Search

We initially identified a total number of 438 potentially eligible articles. Of these, 381 articles were excluded because they were duplicated studies, were irrelevant to the purpose of the present meta-analysis, and were excluded after title and abstract assessment because they were review, editorial, and letter studies. Finally, full-text screening of the 57 potentially relevant articles resulted in 13 eligible studies [25–37]. The main reasons for exclusion were as follows: cocoa was not given as the primary or secondary intervention; the designs of the studies were not randomized placebo controlled; studies which did not report sufficient detail for being included in the present meta-analysis and trials which did not have the appropriate placebo/control arm or appropriate design. Four included studies [27, 31, 33, 35] used different arms investigated different dosages of cocoa and/or participants with different clinical conditions; therefore, according to Cochrane guidelines, all of these arms are considered as dependent trials. Finally, 13 studies with 18 trials with 758 total participants were included in the present meta-analysis. A flow diagram detailing the number of records retrieved by individual searches and the number of included trials of the present meta-analysis is presented in Fig. 1.

Study Characteristics

The characteristics of the 18 included trials with 379 participants in the intervention group and 379 participants in control group are shown in Table 1. Different forms of cocoa were administered in the included trials including cocoa drink or powder of dark chocolate. The sample size of the trials varied from 9 to 45 participants. As for the 18 trials that evaluated hemodynamic parameters, 4 trials investigated the effect of cocoa on healthy adults [27, 30, 32]. The other studies investigated the beneficial effects of cocoa consumption in patients with type 2 diabetes ($n = 3$) [29, 34, 36], overweight and obesity ($n = 1$) [26], cognitive function disorders ($n = 4$) [33, 35], pre-hypertension and hypertension ($n = 4$) [29, 31, 37], hemodialysis [28], and congestive heart failure (CHF) ($n = 1$) [25].

All included trials were published between 2007 and 2016. Of these, 2 trials were conducted in USA [29, 30], 4 in Australia [31, 32], Italy [33, 35], 2 in Netherlands [27], Germany [28, 37], and the remaining 4 trials were carried out in Iran [34], Spain [26], Switzerland [25], and UK [36].

All of the included trials reported the types of consumed cocoa products. Additionally, all included studies reported the doses of functional ingredients of the cocoa products. Different types of cocoa used in the trials varied in their functional compounds including flavanols, proanthocyanidin, and theobromine. The duration of treatment varied from 4 to 18 weeks. Seventeen of the included trials used parallel [25–35, 37] and the remaining one trial used a crossover design [36]. The mean age of participants in intervention varied between 45.3 ± 4.4 and 70.0 ± 0.88 years. According to the recent American College of Cardiology/American Heart Association (ACC/AHA) updated guidelines; 3 included trials have been conducted in normotensive subjects [25, 27], another 5 trials in participants with elevated blood pressure [29–32], and 10 remaining trials were enrolled in the hypertensive patients [26, 28, 31, 33–37] with the ranges of 109.5 to 147.7 and 65.8 to 86.4 for mean baseline SBP and DBP in the intervention groups, respectively.

Quality Assessment

The quality of studies was assessed by using the Jadad scale. According to the previous studies, the trials with Jadad score of equal or more than 3 are considered as high quality. Otherwise, they will be categorized as low-quality trials. As detailed in Table 2, 15 trials were identified as high-quality trials [25–30, 32–37]. Other 3 trials are categorized as low-quality studies [31].

Of all included trials, 10 [25–28, 30, 31, 37], 12 [25, 27, 28, 30, 33–37], and 14 [25–30, 32, 33, 35–37] trials obtained full

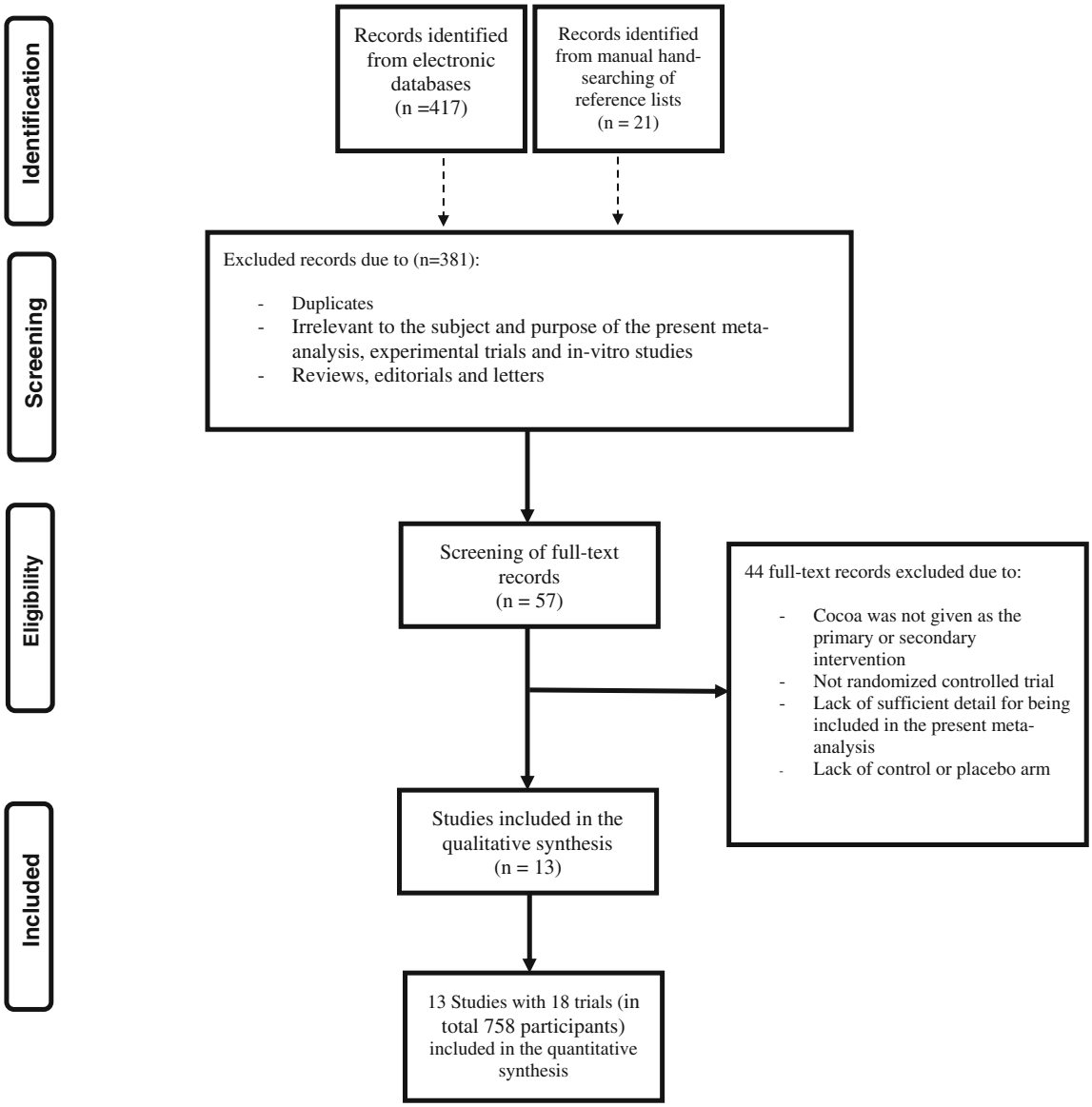

Fig. 1 Flowchart of study selection process

points of randomizations, blinding, and withdrawal domains, respectively.

The Effects of Cocoa Product Consumption on Blood Pressure

Of the 18 included trials, 12 with 577 participants [25, 28, 30–35, 37] and 10 with 440 participants [27, 31–35, 37] revealed an inverse association between cocoa consumption with SBP and DBP, respectively. The results from the meta-analyses revealed a significant reduction in SBP by 2.77 (95% CI − 5.28, − 0.27, $P = 0.03$, $I^2 = 89\%$, P value for heterogeneity < 0. 001) and DBP by 1.47 mm/Hg (− 95% CI − 2.40, − 0.55, $P = 0.001$, $I^2 = 45\%$, P value for heterogeneity = 0.02) after cocoa consumption (Fig. 2). The meta-analysis was performed using a random effects model and to explore the potential source of heterogeneity, we conducted subgroup analysis.

Subgroup Analysis

Subgroup analyses were conducted to explore the effect of cocoa consumption on SBP and DBP, according to the different characteristics of trials including mean age of participants in intervention groups, follow-up duration, and baseline BP levels of subjects (Table 3).

Subgrouping by mean age (middle age vs. elderly) showed significant changes in both SBP and DBP. However, the analysis suggested greater and significant effects for SBP (WMD − 5.26, 95% CI − 7.58, − 2.94, $P < 0.001$, $I^2 = 34\%$, P value for heterogeneity = 0.18) and DBP (WMD − 2.01, 95% CI −

Table 2 Quality of the included studies according to the Jadad scale tool

Study; year	Blinding	Randomization	Withdrawals and dropouts descriptions	Score
Crews 2008	2	2	1	5
Davison 2008	1	1	1	3
Davison 2010	0	2	0	2
Desideri 2012	2	1	1	4
Flammer 2011	2	2	1	5
Haghighat 2013	2	1	0	3
Ibero-Baraibar 2016	1	2	1	4
Mastroiacovo 2014	2	1	1	4
Mellor 2010	2	1	1	4
Neufinger 2013	2	2	1	5
Rassaf 2015	2	2	1	5
Sorond 2013	1	1	1	3
Taubert 2007	2	2	1	5

3.35, − 0.68, $P < 0.001$, $I^2 = 0\%$, P value for heterogeneity = 0.46) in elderly subgroup with no significant heterogeneity.

When we stratified by follow-up duration, studies of longer-term cocoa consumption improved both SBP by 4.00 mm/Hg (95% CI − 5.49, − 2.52, $P < 0.001$, $I^2 = 41\%$, P value for heterogeneity = 0.07) and DBP by 2.04 (95% CI − 2.95, − 1.13, $P < 0.001$, $I^2 = 24\%$, P value for heterogeneity = 0.20), whereas the shorter-term subgroup did not indicate any beneficial effects of cocoa consumption on SBP and DBP.

When we subgrouped studies comparing different levels of baseline BP, no significant differences in efficacy was observed in normotensive subjects and patients with elevated blood pressure. There were differences in efficacy of cocoa consumption on improving SBP (WMD − 4.60, 95% CI − 6.26, − 2.94, $P < 0.001$, $I^2 = 38\%$, P value for heterogeneity = 0.12) and DBP (WMD − 2.16, 95% CI − 2.95, − 1.38, $P < 0.001$, $I^2 = 3\%$, P value for heterogeneity = 0.41) in subgroups of hypertensive subjects.

Sensitivity Analysis

The pooled weighted mean difference after sensitivity analysis ranged from − 2.37 (95% CI = − 4.9, 0.17) to − 3.62 (95% CI = − 5.01, − 2.23) in SBP and from − 1.22 (95% CI = − 2.05, − 0.38) to − 1.75 (95% CI = − 2.62, − 0.88) in DBP (Fig. 3).

Publication Bias

The symmetric vision of funnel plots and the data of Egger tests suggested no significant publication bias in the meta-analyses of both SBP (Egger test: intercept, − 1.37; standard error: 0.96; 95% CI − 3.41, 0.66; $t = 1.42$, df = 16; two-tailed $P = 0.17$) and DBP (Egger test: intercept, − 0.33; standard error: 0.50; 95% CI − 1.40, 0.72; $t = 0.67$, df = 16; two-tailed $P = 0.50$) (Fig. 4).

Discussion

Our meta-analysis, including 18 trials, showed that a significant inverse association between cocoa consumption and SBP and DBP in middle-aged or elderly subjects. There are several meta-analysis studies that have investigated the effect of cocoa consumption on blood pressure [13••, 14••, 15••, 16••]. However, to our knowledge, the current study is the first analysis from trials on the efficacy of cocoa consumption on blood pressure in middle-aged and elderly subjects.

Although the significant SBP- and DBP-lowering effects of cocoa in the middle-aged and elderly subjects was observed, the overall effect size was relatively small and could not be considered as clinically relevant in middle-aged participants. In contrast, the clinical importance of SBP- and DBP-lowering effects of cocoa in elderly subjects must be taken into account. For instance, it has been shown that a decline of 5 mmHg in systolic blood pressure may decrease the risk of cardiovascular diseases by about 20% over a period of 5 years [2]. The Framingham Heart Study demonstrated that a reduction of 2 mmHg in DBP was associated with a 6% reduction in the risk of CHD [3]. With respect to lifestyle changes, it has been shown that structured exercise longer than 150 min/week was associated with reductions in SBP by about 3 mmHg and DBP by about 1.5 mmHg [4]. Furthermore, the DASH dietary pattern, as an approach for improving the hypertension complications, reduced SBP by 5.5 mmHg and DBP by 3 mmHg overall [5].

Previous meta-analyses showed significant reductions of SBP and DBP after cocoa consumption [13••, 14••, 15••, 16••]. Desch et al. revealed a mean blood pressure change of − 4.5 and − 2.5 for SBP and DBP, respectively [13••].

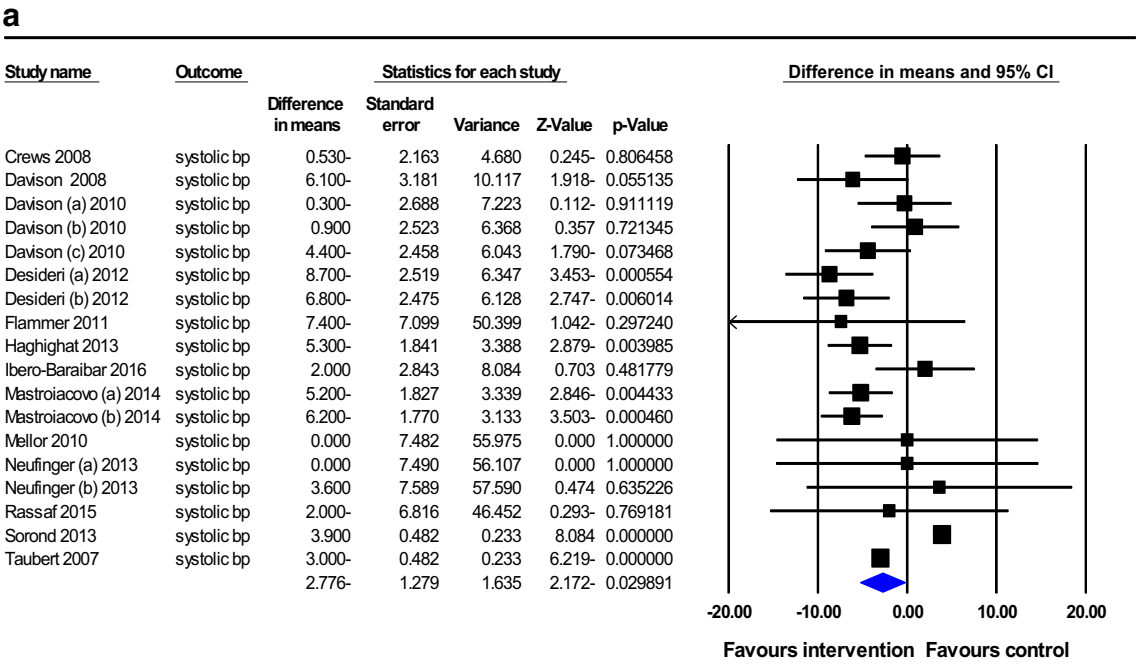

Fig. 2 Forest plot of mean differences in **a** systolic blood pressure (mmHg) and **b** diastolic blood pressure (mmHg) by using a random effects model

Similarly, Ried et al. showed a reduction of 1.76 mmHg in both SBP and DBP after cocoa consumption [16••]. All of previous meta-analysis emphasized on the blood pressure-lowering effects of cocoa consumption in line with our study which could detect a significant effect of cocoa consumption and blood pressure in elderly or middle-aged subjects. Our pooled mean differences and effect sizes are bigger in compared with the previous studies which prove promising effects of cocoa consumption on blood pressure indices in middle-aged and elderly subjects. This could be because the previous reports pooled all trials with different age ranges. In this situation, it would be possible that the trials with lower mean age of participants show different patterns of effect sizes in blood pressure in compared with middle-aged/elderly subjects. Therefore, that could be the possible reason of relatively large effect sizes of our study in compared with previous meta-

Table 3 Stratified analysis examining the effect of cocoa consumption on systolic and diastolic blood pressure compared with controls

Subgroup			WMD (95% CI)	Test for overall effect	Test for heterogeneity	I^2 (%)
Stage						
	Normal	SBP	− 1.52 (− 9.86, 6.83)	$P = 0.72$	$P = 0.55$	0
		DBP	0.40 (− 5.36, 6.16)	$P = 0.89$	$P = 0.99$	0
	Elevated	SBP	− 0.77 (− 4.89, 3.35)	$P = 0.71$	$P < 0.001$	81
		DBP	− 0.78 (− 2.17, 0.62)	$P = 0.28$	$P = 0.13$	44
	Hypertension	SBP	− 4.60 (− 6.26, − 2.94)	$P < 0.001$	$P = 0.12$	38
		DBP	− 2.16 (− 2.95, − 1.38)	$P < 0.001$	$P = 0.41$	3
Follow-up duration, weeks						
	< 6	SBP	3.75 (2.83, 4.68)	$P < 0.001$	$P = 0.56$	0
		DBP	0.11 (− 0.71, 0.93)	$P = 0.79$	$P = 0.96$	0
	≥ 6	SBP	− 4.00 (− 5.49, − 2.52)	$P < 0.001$	$P = 0.07$	41
		DBP	− 2.04 (− 2.95, − 1.13)	$P < 0.001$	$P = 0.20$	24
Age						
	Middle-aged	SBP	− 3.02 (− 3.88, − 2.16)	$P < 0.001$	$P = 0.48$	0
		DBP	− 1.95 (− 3.15, − 0.75)	$P = 0.001$	$P = 0.22$	25
	Elderly	SBP	− 5.26 (− 7.58, − 2.94)	$P < 0.001$	$P = 0.18$	34
		DBP	− 2.01 (− 3.35, − 0.68)	$P < 0.001$	$P = 0.46$	0

SBP, systolic blood pressure; *DBP*, diastolic blood pressure

analysis, as they analysed all trials disregard to mean age of subjects. On the other hand, subgrouping the subjects according to their mean ages could lead to more homogenous results with more specific effect sizes.

Our study showed a reduction of 2.77 mmHg in SBP and 1.47 mmHg in DBP after cocoa consumption in middle-aged and elderly subjects. Nevertheless, due to the observed significant heterogeneity explored between the included trials in SBP and DBP analyses and the potential influence of the heterogeneity on the accuracy of the final results, we tried to conduct a stratified analysis on the basis of stated moderators to find the possible source of heterogeneity.

The stratified analyses revealed that cocoa consumption in middle-aged groups significantly decreased both SBP and DBP. Moreover, we could confirm the SBP- and DBP-lowering effect of cocoa consumption on elderly subjects with a low heterogeneity among trials which make the findings more reliable. The observed effect size in elderly subjects (SBP − 5.26 mmHg and DBP − 2.01 mmHg) was considerable and comparable with the effects of other lifestyle modifications on blood pressure. Additionally, it was evident that longer-term consumption of cocoa improved both SBP and DBP, whereas the shorter-term consumption did not show any beneficial effects on either SBP or DBP. Interestingly, the mean changes in longer-term cocoa consumption (SBP − 4.00 mmHg and DBP −2.04) were comparable with clinically relevant values. Moreover, unlike the normotensive and elevated blood pressure subjects, there were beneficial effects of cocoa consumption on SBP and DBP in subgroups consisting of those who had existing hypertensive.

Some previous studies [13••] suggested that the mean differences in outcome is not dependent on baseline blood pressure, which is in contrast with the present meta-analysis, whereas another meta-analysis study revealed that flavanol-rich cocoa products did not reduce the blood pressure significantly in the normotensive subgroups [15••]. Moreover, in a recent meta-analysis, Ried et al. showed that baseline blood pressure may have a potential role in the efficacy of cocoa consumption on improving blood pressure, which is in agreement with the present meta-analysis [16••].

The observed heterogeneity was reduced statistically in the normotensive and hypertensive subjects, suggesting that the effect size based on the subgroup analysis is highly comparable and can be interpreted with relative confidence. However, heterogeneity did not reduce in the elevated blood pressure subgroups, which may be influenced by varying, pre-existing conditions of patients, and administered drugs. These results are in agreement with studies investigating the effect of various supplements on hemodynamic parameters, which similarly showed that blood pressure is dependent on baseline blood pressure, and hypertensive subgroups revealed diminished effects on blood pressure, as compared with normotensive subjects [39, 40].

Contrary to our study, the meta-regression analysis performed by Ried et al. did not suggest any association between duration of cocoa consumption and blood pressure outcomes [15••], while the subgroup analysis in our study demonstrated both SBP- and DBP-lowering effects of longer-term (≥ 6 weeks) cocoa consumption in middle-aged and elderly subjects.

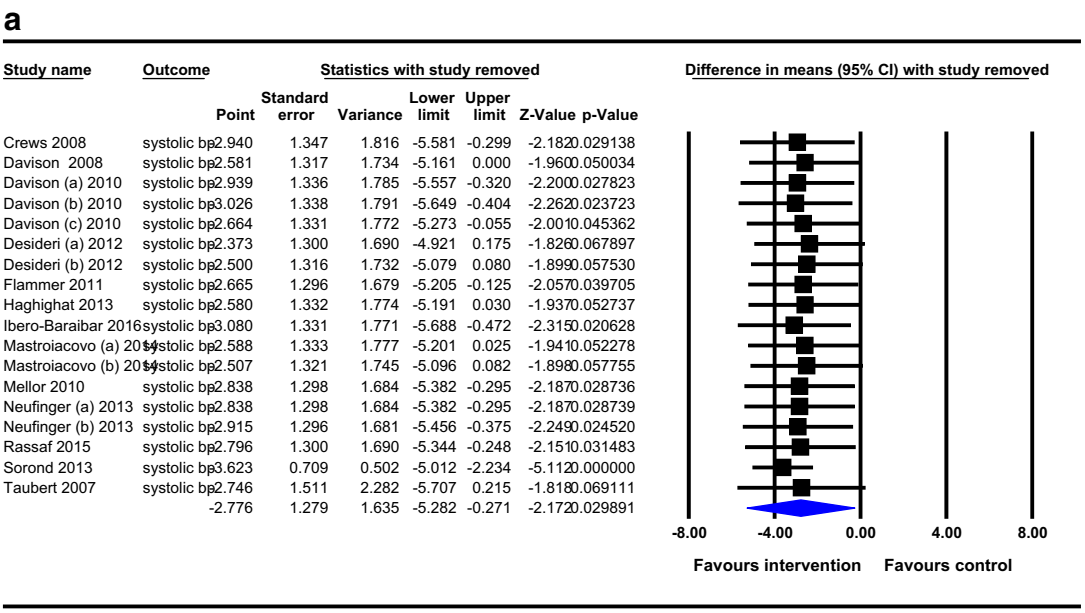

Fig. 3 Sensitivity analysis for **a** systolic blood pressure and **b** diastolic blood pressure

In a recent meta-analysis study [16••], the authors concluded that the age of subjects may have a decisive role in the effect of cocoa on blood pressure, with younger subjects responding with greater, and indeed significant, reductions of blood pressure; notwithstanding, this needs to be further investigated in order to establish a plausible mechanism [16••]. Thus, it is pragmatic to respect that the age of participants may conceivably result in varying responses in blood pressure, following cocoa consumption. There are hemodynamic mechanisms which can justify the age-related hypertension and the effect of intervention on hypertension. In a recent study, it was shown that an increased DBP is a strong risk factor for developing hypertension in younger subjects (< 50 years), while in the older subjects (≥ 50 years), increased SBP was purportedly the predominant risk factor [41]. The mechanisms underlying the explanation of the differences between younger and older patient responses with respect of BP elevation are equivocal. However, a putative reason is the close association between elevation of DBP and increased vascular resistance, which decreases with age due to sympathetic nervous activation [41]. Increased vascular stiffness develops an elevated BP in elderly subjects, which is mainly due to an increase in stiffness of the large arteries. This results in a considerable augmentation of central SBP in late systole and

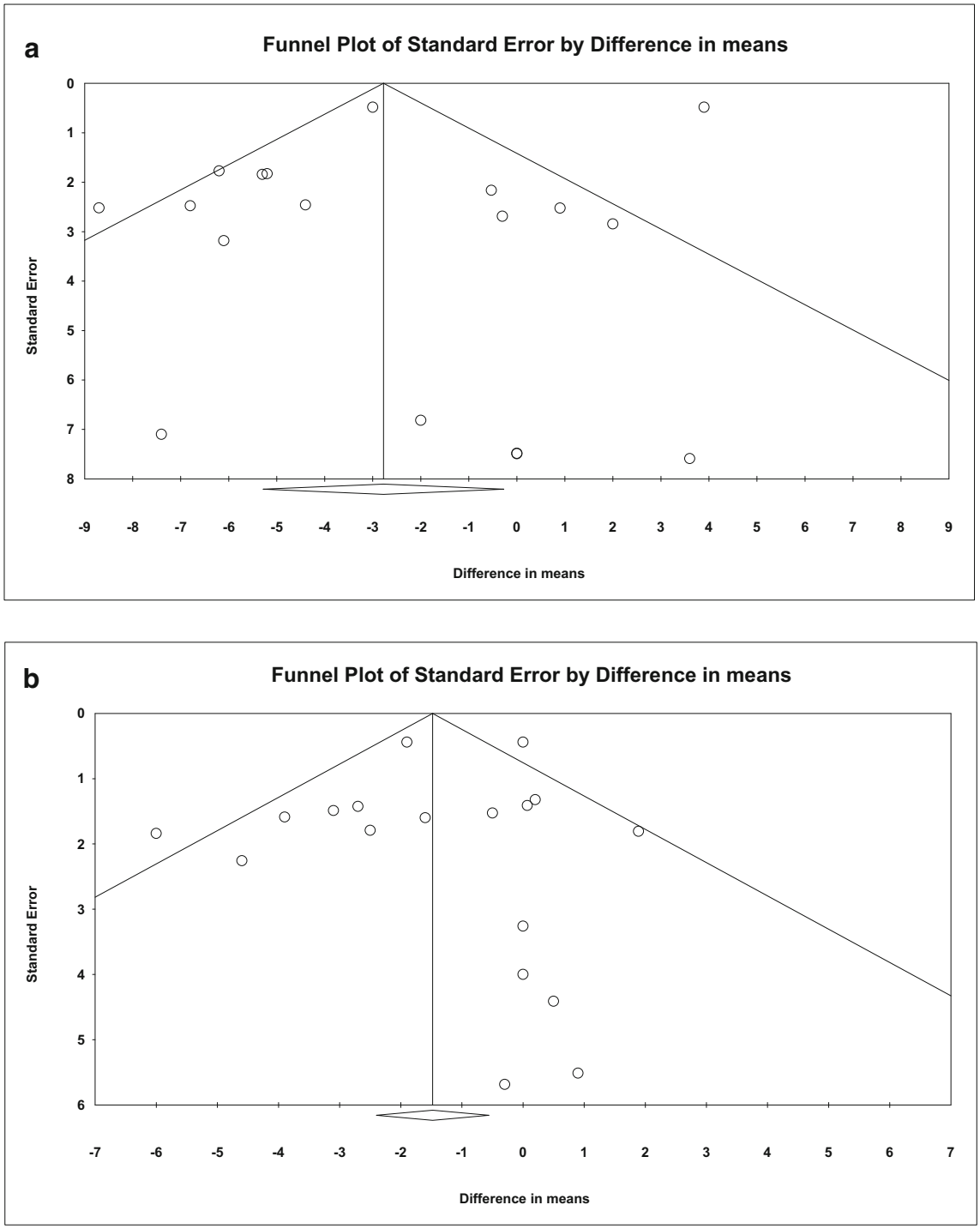

Fig. 4 Funnel plot of meta-analysis of **a** systolic blood pressure and **b** diastolic blood pressure

cardiac afterload [41] and is considered a putative mechanism that explains the increase in SBP and decrease in DBP in an aged population [42]. Additionally, recent studies have shown that elevated SBP variability was related to age and is dependent upon vascular stiffness [43, 44], whereas DBP variability did not show any interaction with age [45, 46].

In general, it has been shown that pulse pressure increases significantly after the age of 50 years which could be as a result of arterial wall stiffening leads to associated increment in SBP and fall in DBP [47]. The findings derived from the Framingham Heart Study, demonstrated a continuous increase of SBP between the ages of 30 and 84 years, whereas DBP showed a varying pattern of increasing until the fifth decade and decreasing from the sixth decade to at least 84 years of age [48].

Whereas both SBP and DBP are independently considered as important predictors of CVD in younger people, SBP

should be considered as the selected predictor for elderly subjects, especially those with more than 50 years of age. Additionally, according to previous studies [49, 50], the DBP was reduced to < 90 mmHg in 90% of subjects, whereas the SBP was reduced to < 140 mmHg in just 60% of elderly subjects. Therefore, it seems that DBP is more responsible to anti-hypertensive agents in compared with the SBP in elderly persons.

As it has been shown in the present meta-analysis, cocoa consumption influenced the SBP and DBP regarding either the overall results or the subgroups (except for shorter-term consumption of cocoa and normotensive/elevated blood pressure subjects). Therefore, it can be assumed that the anti-hypertensive effect of cocoa products in middle-aged subjects and elderly is likely limited to hypertensive subjects.

Strengths and Limitations

While there are previous meta-analytical reports explicating that cocoa consumption can significantly lower blood pressure, the current meta-analysis was first to investigate the effect of cocoa consumption in middle-aged or elderly subjects. The observed heterogeneity decreased in a number of subgroups, such as normotensive and hypertensive subjects, thereby enabling us to assert our findings as a firm evidence that cocoa consumption may have elicit beneficial effects on blood pressure in middle-aged or elderly subjects with hypertension. Another strength of the present meta-analysis is that we were able to analyse a large number of trials. Moreover, the sample sizes included in the present meta-analysis were adequate. Further, we endeavoured to focus on a specific population in an effort to ameliorate heterogeneity between studies. Notwithstanding, the current study has several limitations, which must be addressed. The intervention used in the studies included a wide spectrum of treatments with different forms of cocoa, various polyphenol content, and different dietary intakes which means dietary intakes of flavanol across all including subjects was incongruent. A further limitation of the present study was the variation of daily calorie consumption and dietary macronutrients which may potentially influence the metabolic response.

The lack of an adequate control arm in such trials using the dark chocolate is considered as another limitation of the study. One more important limitation of the present study is related to placebo interventions: there are multiple placebo interventions in the study including white chocolate and poor or low content polyphenol chocolates or drinks. However, the lack of beneficial health effects of consumption of white chocolate may justify the considering of white chocolate as placebo. One more limitation of the study is the observed statistical heterogeneity among the trials found in the meta-analysis even after conducting subgroup analyses with 14 comparisons, which seems to reflect the different clinical conditions of participants which may result in different patterns of drugs and supplement use. Thus, the authors strongly recommend that high-quality, randomized controlled trials, with placebo, control, and intervention arms must be conducted, so that veracity may be asserted in the findings of this, and indeed all previous analyses.

Conclusion

Our meta-analysis showed a significant inverse association between cocoa consumption and SBP/DBP. However, the analysis could not conclude any beneficial effect of cocoa consumption on SBP/DBP in normotensive or middle-aged subjects. Moreover, consumption of cocoa in durations of more than 6 weeks improved both SBP and DBP. Our work elucidated promising effects of cocoa consumption on improving blood pressure in hypertensive subjects compared with other subjects. However, further studies are warranted to affirm the efficacy of cocoa consumption for the improvement of blood pressure in elderly subjects. Additionally, more large-scale and high-quality studies are needed to verify the beneficial effects of longer-term consumption of cocoa on blood pressure.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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

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- • Of importance
- •• Of major importance

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