Effect of Cocoa Products on Blood Pressure: Systematic Review and Meta-Analysis

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BACKGROUND
Cocoa products such as dark chocolate and cocoa beverages may have blood pressure (BP)–lowering properties due to their high content of plant-derived flavanols.

METHODS
We performed a meta-analysis of randomized controlled trials assessing the antihypertensive effects of flavanol-rich cocoa products. The primary outcome measure was the change in systolic and diastolic BP between intervention and control groups.

RESULTS
In total, 10 randomized controlled trials comprising 297 individuals were included in the analysis. The populations studied were either healthy normotensive adults or patients with prehypertension/stage 1 hypertension. Treatment duration ranged from 2 to 18 weeks. The mean BP change in the active treatment arms across all trials was −4.5 mm Hg (95% confidence interval (CI), −5.9 to −3.2, $P < 0.001$) for systolic BP and −2.5 mm Hg (95% CI, −3.9 to −1.2, $P < 0.001$) for diastolic BP.

CONCLUSIONS
The meta-analysis confirms the BP-lowering capacity of flavanol-rich cocoa products in a larger set of trials than previously reported. However, significant statistical heterogeneity across studies could be found, and questions such as the most appropriate dose and the long-term side effect profile warrant further investigation before cocoa products can be recommended as a treatment option in hypertension.

Keywords: *arterial hypertension; blood pressure; clinical trials; cocoa; hypertension; meta-analysis*

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Cocoa products such as dark chocolate and cocoa beverages may have blood pressure (BP)–lowering properties due to their high content of plant-derived flavanols.[1] Initial observations of the possible antihypertensive effects of cocoa-rich food came from the Kuna Indians, a native population living on islands off the Panama coast. Hypertension is very rare in the island Kuna Indians, and there is no age-dependent increase in BP. These effects are likely environmental because they are lost upon migration to urban Panama City. One striking dietary feature of the Kuna Indians living offshore is the consumption of large amounts of natural cocoa drinks rich in flavanols.[2] In contrast, Kuna Indians living in Panama City consume cocoa from grocery stores largely devoid of flavanols leading to the hypothesis that intake of flavanol-rich cocoa might be causally linked to the low prevalence of hypertension in island-dwelling Kuna Indians.

Further epidemiological evidence comes from a cohort of 470 men from the Dutch Zutphen Elderly Study. Habitual consumption of cocoa-containing food was inversely associated with BP.[3] Mean systolic and diastolic BP were 3.7 and 2.1 mm Hg lower in participants in the highest tertile of cocoa intake as compared to those in the lowest tertile. Furthermore, cocoa intake was inversely related to cardiovascular and all-cause mortality.

Sparked by these epidemiological observations, several randomized clinical trials examining the effect of cocoa-rich products on BP have been undertaken. In 2007, a meta-analysis of randomized studies examining the effect of cocoa- and flavanol-rich dark chocolate consumption on BP reported beneficial effects as compared to chocolate containing no or only negligible amounts of flavanols.[4] However, only five small trials were included in the analysis with a total of 96 participants. Several randomized controlled trials have been published since suggesting an updated meta-analysis with a more reliable assessment of the antihypertensive effects of flavanol-rich cocoa products.

METHODS

Literature search. We performed a search of MEDLINE via PubMed (1966 to June 2009), EMBASE (1980 to June 2009), CENTRAL (The Cochrane Controlled Clinical Trials Register) and the ClinicalTrials.gov Web site to identify randomized controlled trials examining the effect of dark chocolate or

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cocoa-containing beverages on arterial BP. Furthermore, we hand-searched bibliographic citations from the retrieved papers and from review articles. No language restrictions were applied.

MEDLINE and EMBASE were searched using the term "cacao" (major subject heading) OR the text words "cacao" OR "cocoa" OR "chocolate." The search was limited to the criteria "clinical trials" and "human." CENTRAL and the ClinicalTrials.gov Web site were searched with "chocolate OR cocoa OR cacao" as free terms without further restrictions applied to the search.

Two investigators (S.D. and J.S.) independently screened the titles and abstracts resulting from the search strategies. Articles were rejected on initial screening if titles or abstracts were clearly irrelevant. The full text of potentially relevant articles was reviewed to assess eligibility for the inclusion in the meta-analysis with any disagreement resolved by consensus.

Selection of studies. Study design had to meet the following criteria: (i) investigating flavanol-rich cocoa products such as dark chocolate and cocoa beverages; (ii) random allocation to treatment and control group; (iii) BP measurements at baseline and at a minimum of one more time point; (iv) because we wanted to study the effects of habitual intake of cocoa products on BP, single-dose trials were not included in the analysis, and a minimum of 2 weeks of treatment duration was required. No restrictions were made with regard to age, gender, medication, baseline BP, risk profile, or comorbidities. None of the individuals enrolled took any antihypertensive medication.

Data extraction. Data were independently extracted by two reviewers (S.D. and J.S.) using a standard form and cross-checked. When BP measurement data were available for both ambulatory BP monitoring and office BP, preference was given to values obtained by ABPM. The position of the patient during BP measurement may affect the BP-lowering effect. When BP measurement data were available in more than one position, data were extracted with the following order of preference: (i) sitting; (ii) standing; (iii) supine. If only one position was reported, data from that position were used.

Assessment of trial quality and risk of bias. Two independent reviewers (S.D. and J.S.) assessed the quality as well as the risk of bias of the trials included and created a risk of bias table according to recommendations by the Cochrane Collaboration.[5] We did not create funnel plots because the limited number of trials included and the lack of studies with large sample sizes preclude a meaningful interpretation.

Statistical analysis. The change in systolic and diastolic BP between the intervention and control groups was defined as the primary outcome measure. For parallel-group trials, the treatment effect was defined as the mean difference of the treatments (change from baseline in BP) between groups. None of the four parallel-group trials included in the meta-analysis directly reported standard deviations (SD) for the mean difference of the treatments. In one trial, the SD could be calculated from confidence intervals (CIs).[6] In the other three parallel-group trials, we estimated the SD based on the SD of BP at the end of treatment. For crossover trials, the treatment effect was defined as the mean within-subject difference of the treatments (change from baseline in BP) assuming no carry-over or period effect. To properly analyze crossover trials, it is necessary that the mean difference of the treatments and the corresponding standard error (which can be calculated from SD or CIs, and sample size) are available.[7–9] In one trial, the standard error could be calculated from the sample size and the SD of the mean difference of the treatments.[10] In another trial, the standard error was estimated from a P value for the mean difference of the treatments.[11] If the standard error for the within-person differences could not be extracted, correlation between treatment outcomes was approximated using a conservative estimate of the correlation coefficient ($r = 0.68$) derived from two trials in which individual pre- and post-treatment BP values were available.[4] Thereafter, the corresponding standard error was calculated as described in the *Cochrane Handbook for Systematic Reviews of Interventions*.[7] Statistical heterogeneity between the trials was tested using a standard χ^2 statistic with a P value set at 0.10. The I^2 statistic was used to examine inconsistencies across studies. To combine both parallel-group and crossover trials in the final analysis, the generic inverse variance method was used and a random effects model applied.[7] Sensitivity analyses were performed to test the robustness of the results. Subgroup analyses were carried out by comparing treatment effects (i) between the seven short-term trials[10–16] with a treatment duration of 2 weeks vs. the three medium-term trials[6,17,18] with a treatment duration between 4 and 18 weeks; (ii) between studies with lower[12,13,15,17,18] and higher[6,10,11,14,16] baseline BPs (groups divided by the median of baseline systolic BP); (iii) between studies with lower[6,12–15] and higher[10,11,16–18] flavanol content in the active arm (groups divided by the median of flavanol

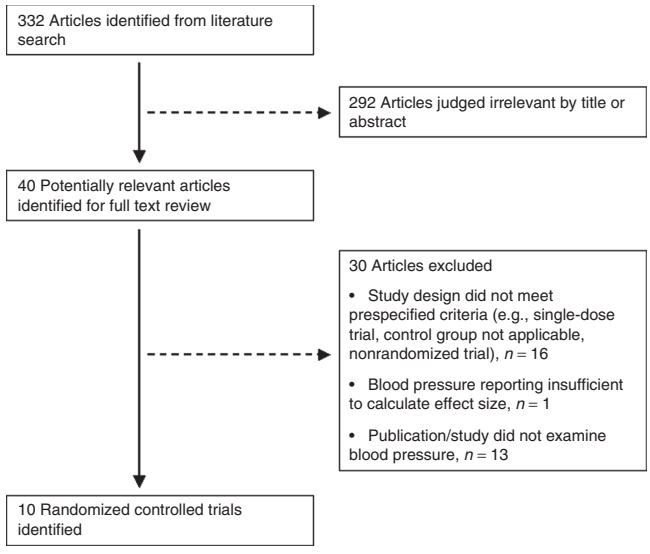

Figure 1 | Flowchart of the study selection process.

content). Data synthesis and statistical analyses were done using the Cochrane Collaboration Review Manager (RevMan, version 5.0.18; The Cochrane Collaboration, Copenhagen, Denmark). The study was performed in compliance with the Quality of Reporting of Meta-analyses guidelines.[19]

RESULTS

The study selection process is shown in **Figure 1**. Among the trials excluded from the analysis, two studies comparing low-flavanol vs. high-flavanol beverages could not be considered[20,21] because the amount of flavanols ingested in the low-flavanol control arm was significantly higher than those reported to possess significant BP-lowering capacity.[6] Another study reported mean pressures only and was therefore not included in the analysis.[22] In total, 10 randomized controlled trials examining the effect of cocoa products on BP were included in the analysis[6,10–18] (**Table 1**). A crossover design was used in six studies and a parallel-group design in four studies. Combining all studies, 297 individuals were analyzed.

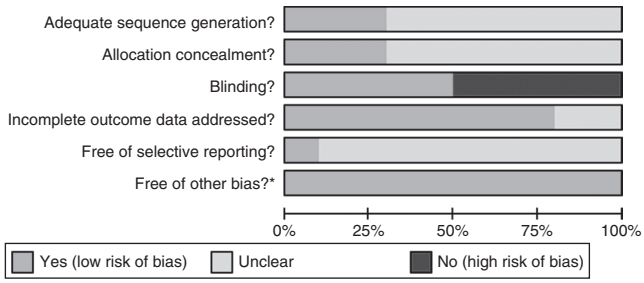

Figure 2 | Risk of bias graph. *e.g., the trial had extreme baseline imbalances; was stopped early; etc.

The populations studied were either healthy normotensive adults or patients with prehypertension/stage 1 hypertension without antihypertensive medication. The majority of studies used office BP to assess treatment effects. Treatment duration ranged from 2 to 18 weeks. Flavanol intake varied widely across studies, e.g., between 5 and 174 mg for the flavanol subcompound epicatechin (**Table 1**).

Results of the quality assessment are summarized in **Figure 2**. Among the trials using a "dark vs. white chocolate" design (as opposed to cocoa beverages or tablets), adequate blinding of participants was not possible due to the obvious differences in appearance and taste. However, investigators and end point assessment were blinded in most studies. Other minor sources of potential bias included the following: the majority of trials (i) did not describe the methods of sequence generation in the randomization process, (ii) did not provide sufficient data to permit judgment if participants or investigators could foresee the assignment to the treatment groups (allocation concealment), (iii) provided insufficient data to rule out selective reporting.

The mean BP reduction in the active treatment arms across all trials was −4.5 mm Hg (95% CI, −5.9 to −3.2, $P < 0.001$) for systolic BP and −2.5 mm Hg (95% CI, −3.9 to −1.2, $P < 0.001$) for diastolic BP (**Figure 3a,b**). Significant statistical heterogeneity across studies could be found in the initial analysis for both systolic BP ($\chi^2 = 84$, $P < 0.01$; $I^2 = 89\%$) and diastolic BP ($\chi^2 = 92$, $P < 0.01$; $I^2 = 90\%$). Sensitivity analyses revealed that three studies were partly responsible.[6,13,14] Two of these studies reported exceptionally large reductions in BP.[13,14] When excluding all three studies from the analysis, the I^2 statistic was reduced from 89 to 43% ($\chi^2 = 10$; $P = 0.11$) for systolic BP. The pooled reduction in systolic BP changed only slightly by

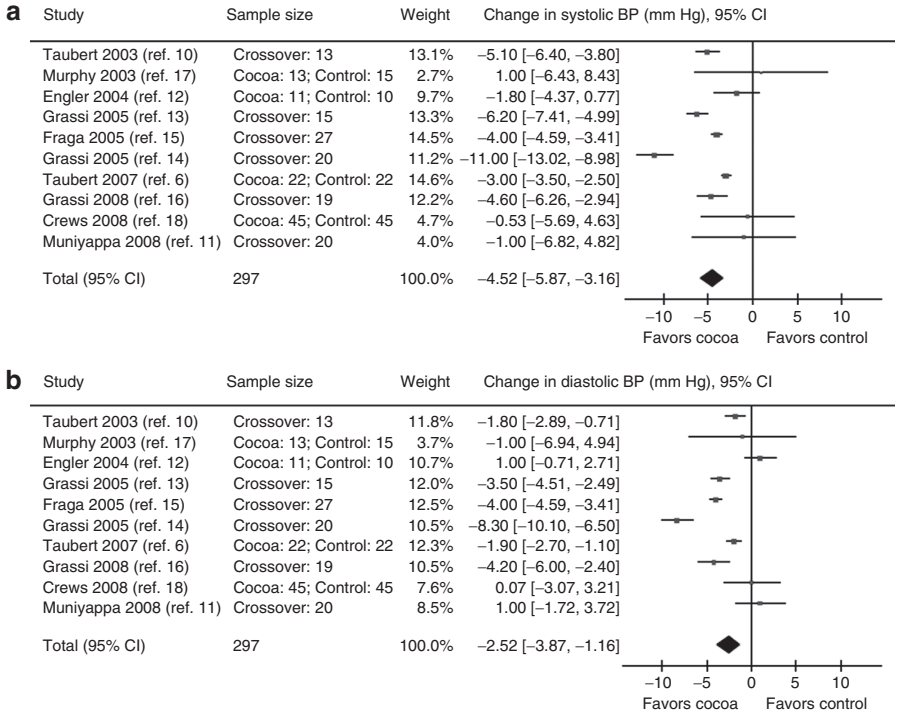

Figure 3 | Effect of cocoa product intake on (**a**) systolic blood pressure and (**b**) diastolic blood pressure. BP, blood pressure; CI, confidence interval.

Table 1 | Characteristics of trials included

Study	Taubert 2003 (ref. 10)	Murphy 2003 (ref. 17)	Engler 2004 (ref. 12)	Grassi 2005 (ref. 13)	Fraga 2005 (ref. 15)	Grassi 2005 (ref. 14)	Taubert 2007 (ref. 6)	Grassi 2008 (ref. 16)	Crews 2008 (ref. 18)	Muniyappa 2008 (ref. 11)
Intervention	Flavanol-rich dark chocolate vs. flavanol-free white chocolate	Flavanol-rich tablets vs. flavanol-poor tablets	Flavanol-rich dark chocolate vs. flavanol-free white chocolate	Flavanol-rich dark chocolate vs. flavanol-free white chocolate	Flavanol-rich milk chocolate vs. flavanol-poor chocolate	Flavanol-rich dark chocolate vs. flavanol-free white chocolate	Flavanol-rich dark chocolate vs. flavanol-free white chocolate	Flavanol-rich dark chocolate vs. flavanol-free white chocolate	Flavanol-rich dark chocolate and flavanol-rich cocoa beverage vs. matching placebo	Flavanol-rich cocoa drink vs. flavanol-poor cocoa drink
Flavanol intake in intervention group	Catechin 27 mg/d Epicatechin 81 mg/d	234 mg Cocoa, flavanols, and procyanidins (catechin and epicatechin values not stated)	46 mg Epicatechin/d 213 mg Procyanidins/d	168 mg Flavanols/d 22 mg Catechin 66 mg Epicatechin	168 mg Flavanols/d 39 mg Catechin and epicatechin 126 mg Procyanidins	168 mg Flavanols/d 22 mg Catechin 66 mg Epicatechin	Catechin 1.7 mg/d Epicatechin 5.1 mg/d	Catechin 36 mg/d Epicatechin 111 mg/d	754 mg Procyanidins/d (catechin and epicatechin values not stated)	902 mg Flavanols/d Catechin 62 mg/d Epicatechin 174 mg/d Procyanidins 676 mg/d
Flavanol intake in control group	Negligible	Negligible	Negligible	Negligible	Negligible	Negligible	Negligible	Negligible	Negligible	Negligible
Design	Randomized, crossover, 14 days	Randomized, parallel-group, 28 days	Randomized, parallel-group, controlled, 2 weeks	Randomized, crossover, 15 days	Randomized, crossover, 14 days	Randomized, crossover, 15 days	Randomized, parallel-group, 18 weeks	Randomized, crossover, 15 days	Randomized, parallel-group, 6 weeks	Randomized, crossover, 2 weeks
Population	Patients with isolated systolic hypertension (grade 1)	Healthy normotensive adults	Healthy normotensive adults	Healthy normotensive adults	Healthy normotensive young male adults	Patients with hypertension (grade 1)	Patients with prehypertension or hypertension (grade 1)	Patients with hypertension (grade 1) and impaired glucose tolerance	Healthy, older adults	Patients with hypertension (grade 1)
Number of participants	13	32 (28 analyzed)	22 (21 analyzed)	15	28 (27 analyzed)	20	44	19	101 (90 analyzed)	29 (20 analyzed)
Missing participants	0	4	1	0	1	0	0	0	11	9

Table 1 | Continued on next page

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Study	Taubert 2003 (ref. 10)	Murphy 2003 (ref. 17)	Engler 2004 (ref. 12)	Grassi 2005 (ref. 13)	Fraga 2005 (ref. 15)	Grassi 2005 (ref. 14)	Taubert 2007 (ref. 6)	Grassi 2008 (ref. 16)	Crews 2008 (ref. 18)	Muniyappa 2008 (ref. 11)
Men/women (*n*)	7/6	17/15	11/11	7/8	28/0	10/10	20/24	11/8	41/60	8/12
Age (years)	58.8 (mean), range 55–64	Active group: 40 ± 9 Placebo group: 47 ± 4 (means ± s.d.)	Range 21–55	33.9 ± 7.6 (mean ± s.d.)	Range 18–20	43.7 ± 7.8 (mean ± s.d.)	DC group: 63.4 ± 4.7 WC group: 63.7 ± 4.8 (means ± s.d.)	44.8 ± 8.0 (mean ± s.d.)	Chocolate and cocoa group: 68.8 ± 8.6 Placebo group: 68.7 ± 8.0 (means ± s.d.)	51 ± 1.5 (mean ± s.e.)
Baseline BP intervention group, systolic ± s.d./ diastolic ± s.d. (mm Hg)	153 ± 4/85 ± 5	118 ± 13/78 ± 12	121 ± 5/68 ± 3	109 ± 8/72 ± 5	123 ± 3/72 ± 2	136 ± 6/88 ± 4	148 ± 7/86 ± 4	135 ± 4/87 ± 4	127 ± 14/74 ± 8	141 ± 3/91 ± 3
Baseline BP control group, systolic ± s.d./ diastolic ± s.d. (mm Hg)	154 ± 4/84 ± 4	116 ± 9/76 ± 8	112 ± 8/66 ± 2	110 ± 8/72 ± 5	123 ± 3/71 ± 2	136 ± 6/88 ± 4	148 ± 8/87 ± 4	134 ± 4/87 ± 4	129 ± 14/75 ± 8	140 ± 2/87 ± 2
Antihypertensive medication	None	None	None	None	None	None	None	None	None	None
Details of BP measurement	Office BP (automated oscillometric device), seated position	Office BP (automated oscillometric device), no data on body position	Office BP (automated oscillometric device), seated position	Office BP, sphygmomanometer, seated position	Office BP (automated oscillometric device), no data on body position	ABPM	Office BP (automated oscillometric device), seated position	ABPM	Office BP (automated oscillometric device), seated position	Office BP, sphygmomanometer, seated position

ABPM, ambulatory blood pressure monitoring; BP, blood pressure.

Table 2 | Subgroup analyses by trial duration, baseline BP, and flavanol content

Subgroups	Mean difference in systolic BP (mm Hg, 95% CI)	Mean difference in diastolic BP (mm Hg, 95% CI)
Short-term trials[10–16]	−5.2 (−6.9 to −3.5)	−2.9 (−4.6 to −1.2)
Medium-term trials[6,17,18]	−3.0 (−3.5 to −2.5)	−1.8 (−2.5 to −1.0)
Lower baseline BP[12,13,15,17,18]	−3.6 (−5.5 to −1.8)	−3.6 (−5.5 to −1.8)
Higher baseline BP[6,10,11,14,16]	−5.3 (−7.9 to −2.6)	−5.3 (−7.9 to −2.6)
Lower flavanol content[6,12–15]	−5.2 (−7.0 to −3.3)	−5.2 (−7.0 to −3.3)
Higher flavanol content[10,11,16–18]	−4.0 (−5.6 to −2.3)	−4.0 (−5.6 to −2.3)

BP, blood pressure.

excluding the studies (−3.9 mm Hg, 95% CI, −4.9 to −2.9, $P <$ 0.001). However, for diastolic BP, significant heterogeneity was still present after removal of these studies from the analysis. Significant reductions in systolic and diastolic BP were noted in the active treatment arms for all subgroups analyzed (short- and medium-term trials, trials with lower and higher baseline BPs, and trials with higher vs. lower flavanol content). The results are displayed in **Table 2**.

DISCUSSION

The principal finding of this meta-analysis of randomized clinical trials examining the antihypertensive effects of cocoa products such as dark chocolate and cocoa beverages is a decrease of 4.5 mm Hg in systolic and 2.5 mm Hg in diastolic BP.

The precise mechanisms responsible for the presumed BP-lowering effect of cocoa-containing food are not fully explored. However, an increase in vasodilating nitric oxide bioavailability possibly caused, in part, by an enhanced nitric oxide synthase activity is considered a likely pathway.[6,23–25] Other mechanisms such as the inhibition of angiotensin-converting enzyme activity by flavanols[26] or theobromine[27] may also contribute to the antihypertensive effect.

The BP reductions seen in the current meta-analysis are similar to those observed in a previous review of five studies examining the effect of dark chocolate on BP that reported a mean pooled decrease of 4.7 mm Hg (95% CI, 7.6–1.8, $P =$ 0.002) in systolic BP and 2.8 mm Hg (95% CI, 4.8–0.8, $P =$ 0.006) in diastolic BP, respectively.[4] Our meta-analysis thus confirms the antihypertensive effect of cocoa products across a larger number of studies with more than three times as many participants compared to the previous report.

Several limitations must be addressed. The studies displayed a diverse spectrum of treatment regimens. Study duration ranged from 2 to 18 weeks. Estimated daily flavanol intake varied widely across studies. Most studies used doses of chocolate or cocoa beverages that must be considered too high for a potential long-term treatment. An obvious concern with the daily intake of high doses of cocoa products is the significant energy, fat, and sugar content potentially leading to adverse metabolic effects. Only one trial examined the effect of very low doses of dark chocolate (6.3 g/day relating to an energy intake of only 30 kcal/day).[6] The study found a significant reduction in systolic BP of 2.9 mm Hg (95% CI, 3.9–2.0, $P <$ 0.001) and diastolic BP of 1.9 mm Hg (95% CI, 2.7–1.1, $P <$ 0.001) compared to flavanol-free white chocolate. No adverse metabolic effects or weight gain were observed. Although these results are consistent with the overall BP reduction seen in this meta-analysis, further studies are needed to determine the optimal dose for the long-term ingestion of cocoa products. Furthermore, possible side effects such as weight gain or changes in metabolic parameters counteracting the BP-lowering effect might manifest themselves only with longer-term ingestion. All studies examined either healthy participants or patients with prehypertension/grade 1 hypertension. The statistical heterogeneity between the trials found in the analysis likely reflects the clinical diversity in treatment regimens. The overall results should therefore not be uncritically extrapolated to a potential chronic intake of cocoa products or applied to populations such as patients taking BP-lowering drugs, or those with multiple risk factors or cardiovascular end-organ damage.

Another limitation of clinical trials using dark chocolate is the lack of an adequate control substance. To date, there is no commercially available flavanol-free chocolate that offers the distinct bitter taste and dark color inherent to cocoa-rich chocolate. White chocolate has been used in most trials. However, informed consent requires that patients be instructed on the lack of beneficial health effects of white chocolate precluding the definition of a true placebo. For beverages, specifically manufactured cocoa and flavanol-poor placebo drinks similar in color and taste have been used.[11,18]

Our meta-analysis confirms the BP-lowering capacity of flavanol-rich cocoa products. However, several questions such as the most appropriate dose and the long-term side effect profile remain to be answered before cocoa products can be recommended as a treatment option in hypertension. A large-scale, well-controlled trial preferably with clinical end points seems warranted.

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1. Corti R, Flammer AJ, Hollenberg NK, Lüscher TF. Cocoa and cardiovascular health. *Circulation* 2009; 119:1433–1441.
2. McCullough ML, Chevaux K, Jackson L, Preston M, Martinez G, Schmitz HH, Coletti C, Campos H, Hollenberg NK. Hypertension, the Kuna, and the epidemiology of flavanols. *J Cardiovasc Pharmacol* 2006; 47(Suppl 2):S103–109; discussion 119.

3. Buijsse B, Feskens EJ, Kok FJ, Kromhout D. Cocoa intake, blood pressure, and cardiovascular mortality: the Zutphen Elderly Study. *Arch Intern Med* 2006; 166:411–417.
4. Taubert D, Roesen R, Schömig E. Effect of cocoa and tea intake on blood pressure: a meta-analysis. *Arch Intern Med* 2007; 167:626–634.
5. Higgins JPT, Altman DG (eds). Assessing risk of bias in included studies. In Higgins JPT, Green S (eds), *Cochrane Handbook for Systematic Reviews of Interventions*. Wiley: Chichester, UK, 2008, pp 187–241.
6. Taubert D, Roesen R, Lehmann C, Jung N, Schömig E. Effects of low habitual cocoa intake on blood pressure and bioactive nitric oxide: a randomized controlled trial. *JAMA* 2007; 298:49–60.
7. Higgins JPT, Deeks J, Altman DG (eds). Chapter 16: Special topics in statistics. In Higgins JPT, Green S (eds), *Cochrane Handbook for Systematic Reviews of Interventions*. Wiley: Chichester, UK, 2008, pp 481–529.
8. Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol* 2002; 31:140–149.
9. Curtin F, Altman DG, Elbourne D. Meta-analysis combining parallel and cross-over clinical trials. I: Continuous outcomes. *Stat Med* 2002; 21:2131–2144.
10. Taubert D, Berkels R, Roesen R, Klaus W. Chocolate and blood pressure in elderly individuals with isolated systolic hypertension. *JAMA* 2003; 290:1029–1030.
11. Muniyappa R, Hall G, Kolodziej TL, Karne RJ, Crandon SK, Quon MJ. Cocoa consumption for 2 wk enhances insulin-mediated vasodilatation without improving blood pressure or insulin resistance in essential hypertension. *Am J Clin Nutr* 2008; 88:1685–1696.
12. Engler MB, Engler MM, Chen CY, Malloy MJ, Browne A, Chiu EY, Kwak HK, Milbury P, Paul SM, Blumberg J, Mietus-Snyder ML. Flavonoid-rich dark chocolate improves endothelial function and increases plasma epicatechin concentrations in healthy adults. *J Am Coll Nutr* 2004; 23:197–204.
13. Grassi D, Lippi C, Necozione S, Desideri G, Ferri C. Short-term administration of dark chocolate is followed by a significant increase in insulin sensitivity and a decrease in blood pressure in healthy persons. *Am J Clin Nutr* 2005; 81:611–614.
14. Grassi D, Necozione S, Lippi C, Croce G, Valeri L, Pasqualetti P, Desideri G, Blumberg JB, Ferri C. Cocoa reduces blood pressure and insulin resistance and improves endothelium-dependent vasodilation in hypertensives. *Hypertension* 2005; 46:398–405.
15. Fraga CG, Actis-Goretta L, Ottaviani JI, Carrasquedo F, Lotito SB, Lazarus S, Schmitz HH, Keen CL. Regular consumption of a flavanol-rich chocolate can improve oxidant stress in young soccer players. *Clin Dev Immunol* 2005; 12:11–17.
16. Grassi D, Desideri G, Necozione S, Lippi C, Casale R, Properzi G, Blumberg JB, Ferri C. Blood pressure is reduced and insulin sensitivity increased in glucose-intolerant, hypertensive subjects after 15 days of consuming high-polyphenol dark chocolate. *J Nutr* 2008; 138:1671–1676.
17. Murphy KJ, Chronopoulos AK, Singh I, Francis MA, Moriarty H, Pike MJ, Turner AH, Mann NJ, Sinclair AJ. Dietary flavanols and procyanidin oligomers from cocoa (Theobroma cacao) inhibit platelet function. *Am J Clin Nutr* 2003; 77:1466–1473.
18. Crews WD Jr, Harrison DW, Wright JW. A double-blind, placebo-controlled, randomized trial of the effects of dark chocolate and cocoa on variables associated with neuropsychological functioning and cardiovascular health: clinical findings from a sample of healthy, cognitively intact older adults. *Am J Clin Nutr* 2008; 87:872–880.
19. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet* 1999; 354:1896–1900.
20. Wang-Polagruto JF, Villablanca AC, Polagruto JA, Lee L, Holt RR, Schrader HR, Ensunsa JL, Steinberg FM, Schmitz HH, Keen CL. Chronic consumption of flavanol-rich cocoa improves endothelial function and decreases vascular cell adhesion molecule in hypercholesterolemic postmenopausal women. *J Cardiovasc Pharmacol* 2006; 47(Suppl 2):S177–S186; discussion S206.
21. Sorond FA, Lipsitz LA, Hollenberg NK, Fisher ND. Cerebral blood flow response to flavanol-rich cocoa in healthy elderly humans. *Neuropsychiatr Dis Treat* 2008; 4:433–440.
22. Balzer J, Rassaf T, Heiss C, Kleinbongard P, Lauer T, Merx M, Heussen N, Gross HB, Keen CL, Schroeter H, Kelm M. Sustained benefits in vascular function through flavanol-containing cocoa in medicated diabetic patients a double-masked, randomized, controlled trial. *J Am Coll Cardiol* 2008; 51:2141–2149.
23. Heiss C, Kleinbongard P, Dejam A, Perré S, Schroeter H, Sies H, Kelm M. Acute consumption of flavanol-rich cocoa and the reversal of endothelial dysfunction in smokers. *J Am Coll Cardiol* 2005; 46:1276–1283.
24. Heiss C, Dejam A, Kleinbongard P, Schewe T, Sies H, Kelm M. Vascular effects of cocoa rich in flavan-3-ols. *JAMA* 2003; 290:1030–1031.
25. Fisher ND, Hughes M, Gerhard-Herman M, Hollenberg NK. Flavanol-rich cocoa induces nitric-oxide-dependent vasodilation in healthy humans. *J Hypertens* 2003; 21:2281–2286.
26. Actis-Goretta L, Ottaviani JI, Fraga CG. Inhibition of angiotensin converting enzyme activity by flavanol-rich foods. *J Agric Food Chem* 2006; 54:229–234.
27. Kelly CJ. Effects of theobromine should be considered in future studies. *Am J Clin Nutr* 2005; 82:486–487; author reply 487.