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Flavonoids, flavonoid-rich foods, and cardiovascular risk: a meta-analysis of randomized controlled trials[1,2]

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ABSTRACT

Background: The beneficial effects of flavonoid consumption on cardiovascular risk are supported by mechanistic and epidemiologic evidence.

Objective: We aimed to systematically review the effectiveness of different flavonoid subclasses and flavonoid-rich food sources on cardiovascular disease (CVD) and risk factors—ie, lipoproteins, blood pressure, and flow-mediated dilatation (FMD).

Design: Methods included a structured search strategy on MEDLINE, EMBASE, and Cochrane databases; formal inclusion or exclusion, data extraction, and validity assessment; and meta-analysis.

Results: One hundred thirty-three trials were included. No randomized controlled trial studied effects on CVD morbidity or mortality. Significant heterogeneity confirmed differential effects between flavonoid subclasses and foods. Chocolate increased FMD after acute (3.99%; 95% CI: 2.86, 5.12; 6 studies) and chronic (1.45%; 0.62, 2.28; 2 studies) intake and reduced systolic (−5.88 mm Hg; −9.55, −2.21; 5 studies) and diastolic (−3.30 mm Hg; −5.77, −0.83; 4 studies) blood pressure. Soy protein isolate (but not other soy products or components) significantly reduced diastolic blood pressure (−1.99 mm Hg; −2.86, −1.12; 9 studies) and LDL cholesterol (−0.19 mmol/L; −0.24, −0.14; 39 studies). Acute black tea consumption increased systolic (5.69 mm Hg; 1.52, 9.86; 4 studies) and diastolic (2.56 mm Hg; 1.03, 4.10; 4 studies) blood pressure. Green tea reduced LDL (−0.23 mmol/L; −0.34, −0.12; 4 studies). For many of the other flavonoids, there was insufficient evidence to draw conclusions about efficacy.

Conclusions: To date, the effects of flavonoids from soy and cocoa have been the main focus of attention. Future studies should focus on other commonly consumed subclasses (eg, anthocyanins and flavanones), examine dose-response effects, and be of long enough duration to allow assessment of clinically relevant endpoints. *Am J Clin Nutr* 2008;88:38–50.

INTRODUCTION

Dietary flavonoids represent a diverse range of polyphenolic compounds that occur naturally in plant foods. The range and structural complexity of flavonoids have led to their subclassification as flavonols, flavones, flavanones, flavan-3-ols (and their oligomers, proanthocyanidins), isoflavones, and anthocyanins. They are present in significant amounts in many commonly consumed fruits, vegetables, grains, herbs, and beverages. These structurally diverse compounds exhibit a range of biological activities in vitro that may explain their potential cardioprotective properties, including antioxidant and antiinflammatory effects and induction of apoptosis (1).

Epidemiologic evidence of the cardiovascular effects of diets rich in flavonoids is mixed, with some studies supporting (2–9) and some not supporting (10–13) positive effects. A large prospective study of postmenopausal women with 16 y of follow-up recently showed that dietary intakes of foods rich in anthocyanins and flavanones were associated with a lower risk of all-cause mortality, death due to coronary heart disease, and death due to cardiovascular disease (CVD) (14).

To date, a substantial number of studies have reported on the efficacy of individual plant foods or extracts in reducing biomarkers of CVD risk in acute and short-term interventions with healthy volunteers and at-risk population groups. However, these data have not been combined in a systematic examination of the relative effects of the different subclasses of flavonoids.

To examine the relative importance of the different flavonoid subclasses and flavonoid-rich foods, we undertook a systematic review of all published randomized controlled trials (RCTs) that fit our criteria for inclusion. The aims of this review were to determine optimal doses or food sources to reduce CVD risk and to identify priorities for future research.

MATERIALS AND METHODS

Search strategy

The Cochrane Library, MEDLINE, and EMBASE were searched by using soy and phytoestrogen terms to November 2006, flavonoid terms to July 2006, and flavonoid-related food terms to June 2007. The structured search strategies used indexing and text terms as well as truncation and sensitive RCT filters [ie, specific and sensitive strategies developed to ensure optimal collection of RCTs in electronic searches (15)] in the following

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format: [(flavonoid OR flavonoid-rich food text terms) OR (flavonoid OR flavonoid-rich food indexing terms)] AND human RCT filter. In addition, bibliographies of relevant reviews were checked, and experts were contacted in September 2007 for further studies. Non-English-language articles were translated when possible.

Study selection

Titles and abstracts and then full manuscripts were excluded if the studies reported were not randomized (with either a parallel or crossover design); had no flavonoid intervention; recruited children or pregnant or critically ill participants (although any degree of CVD was permissible); included a multifactorial intervention in which the effect of flavonoids could not be separated; or did not provide data on CVD or CVD risk factors. Flavonoid or flavonoid-containing food interventions had to provide, or advise on, a source of flavonoids that would be found as normal dietary constituents; that is, phytoestrogens from clover or bark products and chemically modified flavonoids were excluded. The intervention advised subjects either to eat more of or to take extracts (or purified versions) of flavonoids or foods rich in flavonoids from ≥1 of the following sources: flavonols, flavanols, anthocyanins, anthocynanidins, benzoflavones, biflavonoids, chalcones, flavanones, flavones, flavonolignans, and isoflavones or foods rich in these flavonoids, such as apples, onions, chocolate, tea, red grape juice, and soy (**Table 1** and **Table 2**). Studies were included only if a suitable control arm was available that allowed any observed effects to be reasonably ascribed to the flavonoids; for example, because alcohol itself alters CVD risk biomarkers (25, 26), a red wine intervention group had to be compared with a control group provided with a similar amount of alcohol.

We did not identify any studies reporting cardiovascular events (except, rarely, as adverse events). Therefore, we focused our primary outcomes on risk factors that have strong and consistent epidemiologic relations with CVD as well as evidence of causation [eg, LDL and HDL or systolic and diastolic blood pressure (BP) (27–29)]. Because endothelial dysfunction is an integral component of atherosclerosis, and because in vitro evidence suggests that at least some flavonoids exert their effects via the endothelium, endothelial function [measured as flow-mediated dilatation (FMD)], which is a predictor of cardiovascular events and which correlates with other CVD risk factors (29–33), was included as a primary outcome.

When a title and abstract could not be rejected with certainty, the full text of the article was obtained, and inclusion was assessed independently by 2 assessors using an inclusion-exclusion form. Disagreements were resolved by discussion among 3 of us (AC, PAK, and LH).

Data extraction and quality assessment

A data extraction form including quality characteristics was designed for the review and piloted by all of those involved in data extraction. Twenty percent of all data extraction and of the quality assessment was performed independently by 2 reviewers to ensure uniformity, and all data were entered by a single reviewer, who checked the extracted data and validity criteria against the original published report. Data were collected on participants, intervention, control, and outcomes and on potential effect modifiers, such as trial duration, flavonoid dose, type of intervention (purified supplement, extract, or food rich in the flavonoid), source of flavonoid, sex, and menopausal status.

Assessment of quality characteristics used a number of criteria. They included allocation concealment (lack of foreknowledge of treatment assignment: coded as adequate, unclear, or inadequate), participant masking, researcher masking, outcome assessor masking, reported industry funding, and a determination of whether saturated fat intake in the intervention and control arms was similar (within 2% of total energy intake: coded as yes, unclear, or no).

Data synthesis

For dichotomous outcomes, the numbers of participants experiencing an outcome and the total numbers of participants randomly assigned were extracted for each study arm from parallel randomized studies only. For continuous outcomes in parallel studies, the number of participants was assessed, and the means and SDs of changes in the variables between baseline and the end of the intervention period (for the intervention and the control groups) were extracted. When these data were not available, the means and SDs of the outcome measurement in the intervention and control arms were used. If the differences between intervention and control arms at baseline were greater than the changes occurring in ≥1 of the arms, the data were not included in the meta-analyses.

In crossover studies, it was intended that we would extract paired *t* test data that evaluated whether the measurement on intervention minus the measurement on control for each subject was different from zero (34). However, because these data were rarely provided in practice, we resorted to using means and SDs separately on intervention and on control. This step provides a conservative estimate of effect and reduces the power of crossover studies to show real effects of interventions (35). For all data, SDs were calculated, when necessary, from SEs or CIs, and data not provided in numerical form were estimated from figures.

Given the range of flavonoid subclasses found in individual foods, it was decided to group studies by food sources when feasible [eg, red wine and grape, chocolate and cocoa, black tea, green tea, soyfoods, and soy protein isolate (SPI) and isoflavone extracts]. When the number of studies was very small, studies were grouped by the major flavonoid represented in the intervention. The main analyses were performed for each food or flavonoid group, and all trials with relevant outcome data were included. Meta-analysis was performed with REVMAN software (version 4.2.8; The Cochrane Collaboration, Oxford, United Kingdom) by using the DerSimonian and Laird random-effects model (34). The results of meta-analyses were considered for further data analysis only when data from ≥3 studies were available. To explore the effects of factors on the primary outcomes, subgrouping was used when data from ≥5 studies were included. These factors were the type of control or placebo group, the type of intervention, the dose, the duration, the participants' sex and menopausal status, and the participants' baseline risk of CVD (comparing hypertensive and normotensive participants for assessment of BP and comparing dyslipidemic and normolipidemic participants for assessment of serum lipids).

Meta-regression was planned, but not conducted, because there were insufficient numbers of studies (or insufficient data on

TABLE 1
Flavonoid subclasses, structures, food sources, and intakes

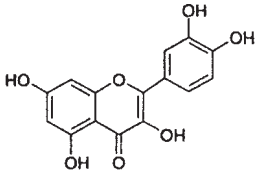
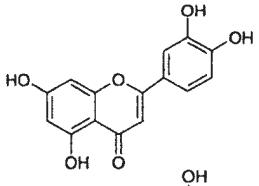
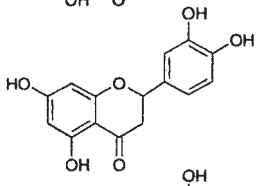
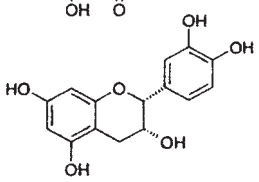
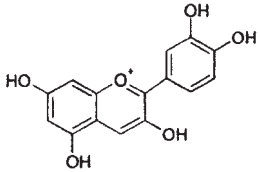
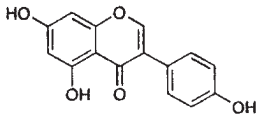
Flavonoid subclass	Structure	Synonyms	Example compounds	Major dietary sources	Estimated daily intakes (16)
					mg/d
Flavonols			Quercetin, kaempferol, myricetin, and isorhamnetin Important glycosides include rutin (quercetin rutinoside).	Onions, broccoli, tea, and various fruits	12.9
Flavones			Apigenin, luteolin, and tangeretin	Herbs (especially parsley), celery, and chamomile tea Tangeretin is present in tangerines and some other citrus.	1.6
Flavanones			Naringenin and hesperetin Dietary forms are glycosides such as hesperidin and narirutin.	Citrus fruit including oranges and grapefruit	14.4
Flavan-3-ols		Flavanols Polymeric forms are called proanthocyanidins (eg, procyanidins and prodelphinidins). Catechins Green tea catechins	(+)-Catechin, (−)-epicatechin, and their polymers (eg, procyanidins-B1, -C1) Tea catechins such as epigallocatechin gallate	Cocoa or dark chocolate, apples, grapes, red wine, and green tea Green tea and black tea to a lesser extent	156.9
Anthocyanidins		Anthocyanins (=glycosylated forms)	Cyanidin, delphinidin, pelargonidin, and malvidin Glycosylated derivatives known as anthocyanins	Colored berries and other fruit, especially cranberries, black currants, and blueberries	3.1
Isoflavones		Phytoestrogens	Daidzein, genistein, and glycitein Glycosylated forms are daidzin, genistin, and glycitin, respectively.	Soy products including fermented products, eg, tofu, tempeh, miso, and soy protein isolate	1.2 (US and Netherlands) 25–50 (Asia) (17)

TABLE 2
Flavonoid composition of commonly consumed flavonoid-rich foods and dietary supplements

Food, beverage, or supplement	Major flavonoids present	Typical content
Cocoa or dark chocolate, mg/g (18)	(−)-Epicatechin	0.07–1.94
	(+)-Catechin	0.04–0.52
	Procyanidin B2	0.04–1.17
	Procyanidin B5	0.00–0.24
Black tea, mg/g dry tea (19)[1]	Various monomeric catechins	41.8
	Theaflavins (products of catechin oxidation)	5.9
	Thearubigens (products of catechin oxidation)	124.9
Green tea, mg/d dry tea (20, 21)	Epigallocatechin-3-gallate	898
	Epigallocatechin	17.1
	Epicatechin-3-gallate	17.6
	Epicatechin	7.93
	Total catechins	136
Soy products, mg/g (22)	Isoflavones	Soybeans: 0.56–3.81
	Unfermented soy contains daidzin and genistin (ie, glycosides)	Soy protein isolate: 0.47–0.62
	Fermented soy products contain daidzein and genistein (aglycones)	
Red wine, mg/L (23, 24)	Flavan-3-ols	
	Monomers	20
	Dimers	40
	Trimers	27
	4–6mers	67
	7–10mers	50
	>10mers	110
	Total flavan-3-ols	313
	Anthocyanins	85
	Quercetin	4.83–31.7
	Total polyphenols (maturation results in the formation of many new compounds)	1000–3000

[1] Hot water extracts ≈85% of the flavonoids extracted by solvents (19), and a typical cup of tea is made with ≈3 g tea solids (ie, one tea bag = 3 g dry wt tea).

relevant subgroups) within each flavonoid group for each outcome. Sensitivity analysis was used to assess the robustness of statistically significant results to trial quality, and funnel plots were used to assess for evidence of bias (36). Cochran's test for heterogeneity was used to determine whether the studies included in the meta-analysis were evaluating the same underlying sizes of effect. A threshold of $P < 0.1$ was used to decide whether heterogeneity (genuine variation in effect sizes) was present. I^2 (an estimate of the proportion of total observed variability that is due to genuine variation rather than random error within studies) was used to quantify the degree of inconsistency among studies; it was considered substantial when it was >50% (34, 37).

RESULTS

We screened 6393 titles or abstracts, of which 582 were ordered in full text. The review flow diagram is shown in **Figure 1**. One hundred seventy RCTs (reported in a total of 242 published articles) fulfilled all inclusion criteria, and the main characteristics of included studies are shown in **Table 3**.

These 170 RCTs, which included 6557 participants, assessed the effects of a flavonoid source compared with a control on a risk factor for CVD included in our primary outcome measures. Of the 133 trials that assessed the effect of flavonoids on ≥1 of our primary outcomes (See Table S1 under "Supplemental data" in the current online issue), 74 (56%) assessed the effects of soy- or soy isoflavone–containing products. Of the remainder, most (n = 49; 37%) examined the effects of flavanols (16 assessed the effect of red wine or grape, 11 assessed chocolate or cocoa, 8 assessed black tea, 7 assessed green tea, and 7 assessed other flavanols). To date, few studies (n = 4) have determined the effects of anthocyanins; flavonols, flavanones, or other flavonoids (n = 2 each); or anthocyanidins, benzoflavones, biflavonoids, chalcones, flavones, or flavonolignans (no studies) on the major CVD risk markers.

Another 13 studies reported that they had assessed effects on a primary outcome, but data were not presented in a way that was usable for the present meta-analysis. Study duration ranged from acute (hours) to 52 wk; only 5 studies conducted an intervention for a year, and 4 of those 5 studies assessed the effects of soy or isoflavones. Fifty-four percent of studies used a crossover design, and many included only a small number of participants (the median number of participants was as low as 14 and as high as 27 in different subclasses).

The quality of included studies varied, and attempts to mask participants were reported in 76 studies, but masking of researchers and outcome assessors was less well reported (in 22 and 33 trials, respectively). Allocation concealment (ie, the person who is recruiting is not aware of the study arm to which a participant will be allocated until recruitment is complete) was clearly adequate in only a few studies (13 of 170 trials). In 36 intervention studies, the difference between intervention and control arms in saturated fat intake was <2% of total energy intake, but the difference was unclear in the remaining 134 studies (studies with a greater difference were excluded). Dropouts were clearly reported in 101 studies, and some form of industry funding was reported in 98 trials (58%) (**Table 4**).

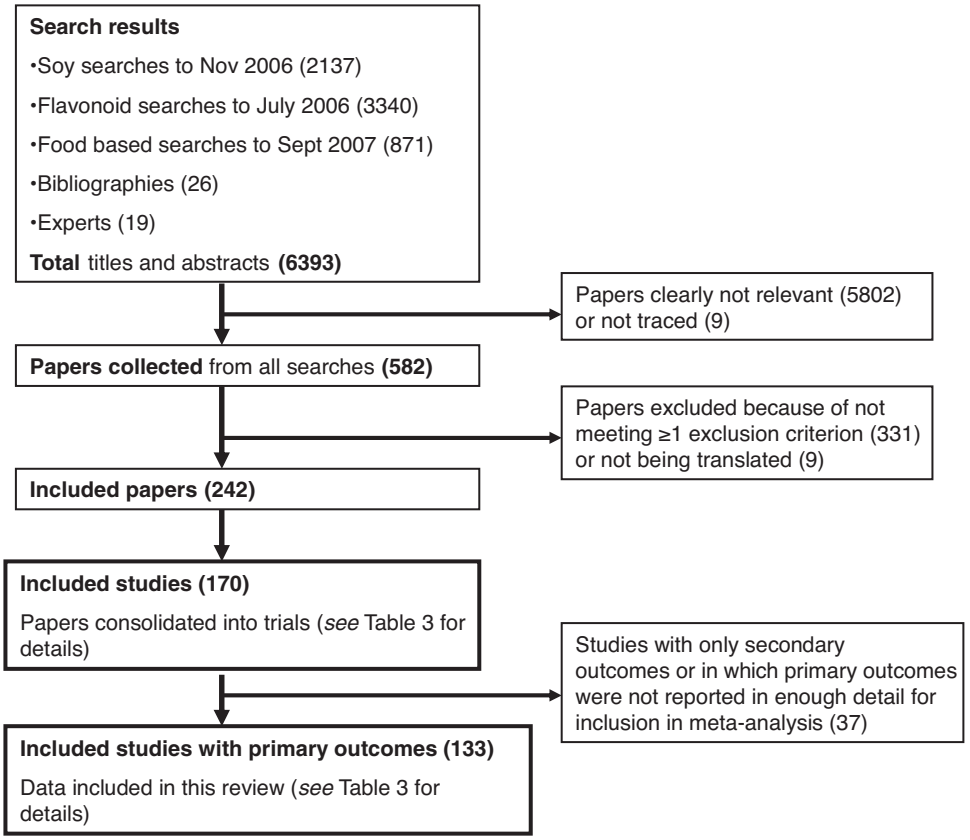


FIGURE 1. Systematic review flow diagram. Numbers in parentheses represent *n*.

Flow-mediated dilatation

Fifteen trials provided information on FMD after chronic (≥2 wk) flavonoid intake (**Figure 2**A), and 14 did so after acute (up to 6 h) intake (Figure 2B). As expected, given the differences in chemical structures and range of doses, we observed significant heterogeneity between different flavonoid subgroups (P for heterogeneity < 0.01, $I^2 = \approx 80\%$ in both acute and chronic studies), which confirmed that different flavonoid groups have different effects on FMD.

Only the SPI and isoflavone extract groups included ≥3 studies assessing chronic effects on FMD, and neither group showed statistically significant effects: SPI increased FMD by 1.77% (95% CI: −0.23%, 3.77%; 4 studies), and isoflavone extract increased FMD by 0.94% (95% CI: −0.39%, 2.27%; 4 studies). The few studies on the chronic effects of red wine or grape and other flavanols also do not suggest significant effects. The data suggested a beneficial effect of black tea and chocolate or cocoa—black tea increased FMD by 3.40% (95% CI: 1.85%, 4.95%; 1 study), and chocolate or cocoa increased FMD by 1.45% (95% CI: 0.62%, 2.28%; 2 studies)—and also suggested that flavonols caused a reduction in FMD (1.4%; 95% CI: −2.66, −0.14; 1 study). None of the meta-analyses suggested significant heterogeneity.

When data were available from ≥3 acute studies, only chocolate or cocoa significantly improved FMD (3.99%; 95% CI: 2.86, 5.12; 6 studies, P for heterogeneity = 0.1, I^2 = 46%; 70–177 mg epicatechin/d, at 90–149 min). In addition, studies of red wine or grape and black tea suggested a modest benefit, although neither was statistically significant and both were significantly heterogeneous (red wine 1.25%; 95% CI: −0.12, 2.62; 4 studies; black tea 1.70%; 95% CI: −0.17, 3.57; 3 studies). For many of the subclasses, including anthocyanins, flavanones, green tea, and soyfoods, no published data on potential FMD effects were available.

Chocolate or cocoa was the only group to show significant effects, both acutely and chronically, on FMD. The time-course suggests a peak effect at ≈2 h (**Figure 3**A), but subgrouping by epicatechin dose (as stated within each study) does not suggest a strong epicatechin dose effect (Figure 3B); however, this finding does not rule out a dose-dependent effect of another component of chocolate. Further chronic intake data would be necessary to confirm a clinically significant effect. A funnel plot of the acute effects of chocolate or cocoa (although including only 6 data points) suggests reporting bias—ie, studies finding smaller FMD effects may not have been reported, which would have inflated the observed effects in the present meta-analysis (data not shown). Because there was only a limited number of studies, and because those studies were of varied validity, sensitivity analyses (which removed studies with a greater risk of bias) tended to result in a loss of the significant effects of cocoa and chocolate on FMD. Removing studies that did not report attempted blinding of participants did not alter the significantly positive effect of an acute dose of chocolate or cocoa on FMD (4.9%; 95% CI: 3.1, 6.7; 4 studies), but the significant effect of chronic intake was lost (3.6%; 95% CI: −1.7, 8.9; 1 study). Removing studies on the basis of allocation concealment, blinding of researchers or outcomes assessors, funding, or similarity of saturated fat intake in the 2 arms or periods removed all studies, so results were not robust to sensitivity analysis. The validity of chocolate or cocoa studies is of importance. Two studies that contributed data to

TABLE 3
Characteristics of included studies

Type of flavonoid	Studies included	Participants analyzed[1]	Total participants in studies	Studies providing primary outcomes	Participants for primary outcomes	Additional studies with unusable primary outcome data	Duration	Crossover studies	Participants in intervention arm
	n	*n*	*n (%)*	*n*	*n*	*n*	*wk*	*n*	*n*
Flavonol	4	102/98[2]	158 (2)	2	48/49		4 (1–12)[3]	2 (1)[4]	27 (13–40)
Flavanols									
Black tea	12	281/274	304 (5)	8	214/208	2	2 (0–4)	10 (7)	18 (10–65)
Chocolate or cocoa	13	226/226	277 (4)	11	190/190		2 (0–18)	10 (8)	19 (5–27)
Green tea	12	326/320	515 (8)	7	258/252	3	3.5 (0–12)	7 (3)	14.5 (9–114)
Red wine or grape	24	385/385	546 (8)	16	264/264		2 (0–6)	15 (9)	14 (6–44)
Other	9	210/204	290 (4)	7	174/174	1	4 (1–16)	5 (4)	22 (10–42)
Anthocyanins	5	83/73	156 (2)	4	64/54	1	3 (2–52)	0 (0)	17 (10–26)
Flavanones	4	94/94	176 (3)	2	31/29		6.5 (3–8)	1 (1)	19.5 (12–43)
Flavonoid mixtures	4	103/102	163 (2)	2	61/60		3 (2–6)	2 (0)	20 (10–32)
Whole soy	15	347/362	436 (7)	14	343/359	1	4 (2.5–26)	10 (10)	23 (4–48)
Soy protein isolate	48	1554/1570	2593 (40)	43	1206/1222	4	6 (0–52)	23 (21)	25 (7–139)
Isoflavone extract	20	653/644	943 (14)	18	627/619	1	12 (2–52)	7 (7)	20.5 (8–117)
Total	170		6557	133		13		92 (71)	

[1] Counted twice for crossover studies.
[2] Intervention/control (all such values).
[3] Median; range in parentheses (all such values).
[4] Primary outcomes in parentheses (all such values).

chronic effects of chocolate on FMD were excluded because of a large difference in the quantity of saturated fat provided in the intervention and control groups (a difference between the 2 groups of >2% in the energy from saturated fat). It is also worth noting that a high proportion of studies (62%) in this group reported that they were funded by the chocolate industry.

To date, few studies have looked at the effects of the different flavonoids on glyceryl tri-nitrate (GTN)–mediated FMD, a measure of endothelium-independent dilatation, but there were 3 studies each for the chronic effects of isoflavone extract (showing no effect: 0.35%; 95% CI: −3.04, 3.74) and the acute effects of black tea intake (also showing no effect: −0.2%; 95% CI: −1.5, 1.1). None of the flavonoid subgroups showed any significant effect on GTN-mediated FMD.

Blood pressure

Chronic intake of chocolate and cocoa also had beneficial effects on systolic and diastolic BP. Forty-four and 43 studies

TABLE 4
Validity of included studies[1]

Type of flavonoid	Allocation concealment[2]	Masking of participants[3]	Masking of researchers[3]	Masking of outcome assessors[3]	Dropouts reported clearly?[3]	Studies reporting industry funding[3]	Saturated fat intake in intervention arm within 2% of control group?[4]
Flavonol	0/4	3/1	0/4	0/4	2/2	1/3	0/4
Black tea	1/11	2/10	2/10	4/8	10/2	8/4	1/11
Chocolate or cocoa	1/12	5/8	1/12	3/10	7/6	8/5	2/11
Green tea	0/12	3/9	1/11	2/10	6/6	6/6	3/9
Red wine or grape	0/24	2/22	0/24	4/20	16/8	5/19	4/20
Other	2/7	4/5	2/7	3/6	4/5	8/1	0/9
Anthocyanins	1/4	1/4	0/5	1/4	4/1	3/2	0/5
Flavanones	0/4	3/1	0/4	0/4	3/1	3/1	0/4
Flavonoid mixtures	0/4	1/3	1/3	1/3	2/2	1/3	2/2
Soy, SPI, and isoflavone	8/75	52/31	15/68	15/68	47/36	55/28	24/59
Total	13/157	76/94	22/148	33/137	101/69	98/72	36/134

[1] SPI, soy protein isolate.
[2] Values in this column are adequate/unclear or inadequate.
[3] Values in this column are yes/unclear or no.
[4] Values in this column are yes/unclear.

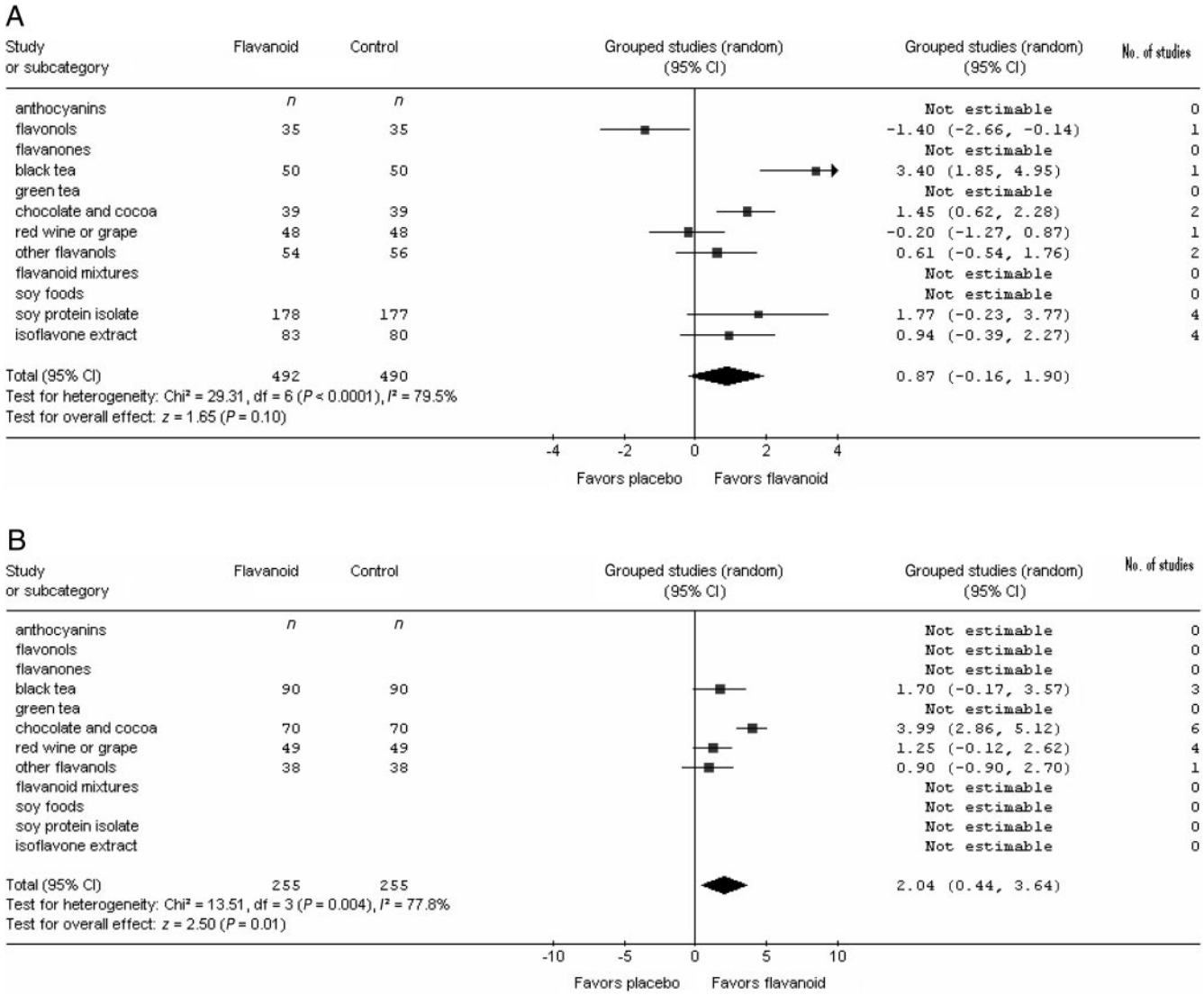


FIGURE 2. Effect of chronic (A) and acute (B) intakes of flavonoids on the percentage of flow-mediated dilatation (%FMD). Meta-analysis used the weighted mean difference in the DerSimonian and Laird random-effects model. A: There was no significant heterogeneity within any of the flavonoid subclasses shown in this figure (values for heterogeneity were $P = 0.43$ for chocolate or cocoa; 0.66 for red wine or grape; 0.86 for other flavanols; 0.22 for soy protein isolate; and 0.69 for isoflavone extract). B: There was significant heterogeneity in the black tea and red wine or grape subclasses shown in this figure. Values for heterogeneity were $P = 0.0006$ for black tea, $P = 0.10$ for chocolate or cocoa, and $P = 0.05$ for red wine or grape.

assessed the effect of chronic intake of flavonoids on systolic and diastolic BP, respectively, and 7 assessed the effect of acute intake. Chronic consumption of black tea, red wine or grape, and other flavanols (all with ≥3 included studies) did not show significant effects on systolic or diastolic BP, but chocolate and cocoa reduced both systolic (by 5.88 mm Hg; 95% CI: −9.55, −2.21; 5 studies; P for heterogeneity = 0.0003, $I^2 = 81\%$) and diastolic (by 3.30 mm Hg; 95% CI: −5.77, −0.83; 4 studies; P for heterogeneity = 0.009, $I^2 = 70\%$).

For the chocolate data, the clear heterogeneity in these analyses is partly explained by dose and duration, so that subgrouping by dose or duration reduces apparent levels of heterogeneity (effects appear greater in studies with higher doses and shorter duration; data not shown). There are only 5 data points, but the funnel plot suggests that small studies showing large systolic BP reductions may be overrepresented (funnel plots not shown).

The effect of the different soy sources on BP varied. SPI significantly reduced diastolic BP (by 1.99 mm Hg; 95% CI: −2.86, −1.12; 9 studies; P for heterogeneity = 0.4, $I^2 = 6\%$ over 4–24 wk), although the effect on systolic BP was not significant (−1.60 mm Hg; 95% CI: −3.62, 0.42; 9 studies; P for heterogeneity = 0.2, $I^2 = 27\%$ over 4–24 wk). No other soy groups showed significant reduction in systolic or diastolic BP, but soyfoods were close to significance for both systolic and diastolic BP (with smaller numbers of participants than for the other soy groups). The data for isoflavone extracts suggest a reduction in systolic BP (close to significance; **Figure 4**) but no effect on diastolic BP.

The ingestion of black tea resulted in an acute increase in systolic BP (5.69 mm Hg; 95% CI: 1.52, 9.86; 4 studies; P for heterogeneity = 0.13, $I^2 = 44\%$) and diastolic BP (2.56 mm Hg; 95% CI: 1.03, 4.10; 4 studies; P for heterogeneity = 0.57, $I^2 =$

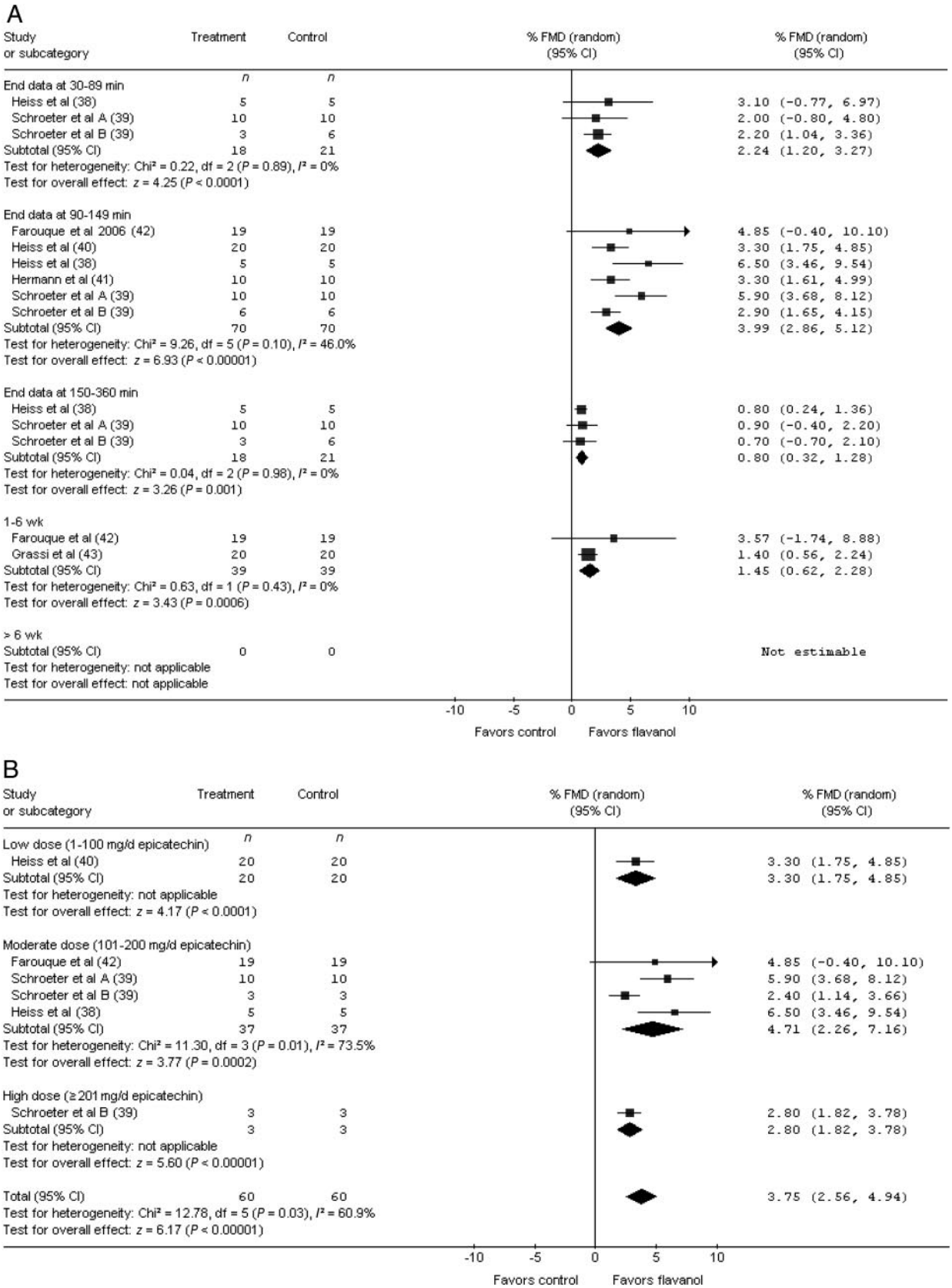


FIGURE 3. A: Effect of chocolate or cocoa on the percentage of flow-mediated dilatation (%FMD), subgrouped to show the time-course. B: Acute effect of chocolate or cocoa on %FMD, subgrouped by epicatechin dose (at 90–149 min). In both parts of the figure, meta-analysis used the weighted mean difference in the DerSimonian and Laird random-effects model. The report by Schroeter et al (39) contains details of 2 distinct studies, labeled "A" and "B."

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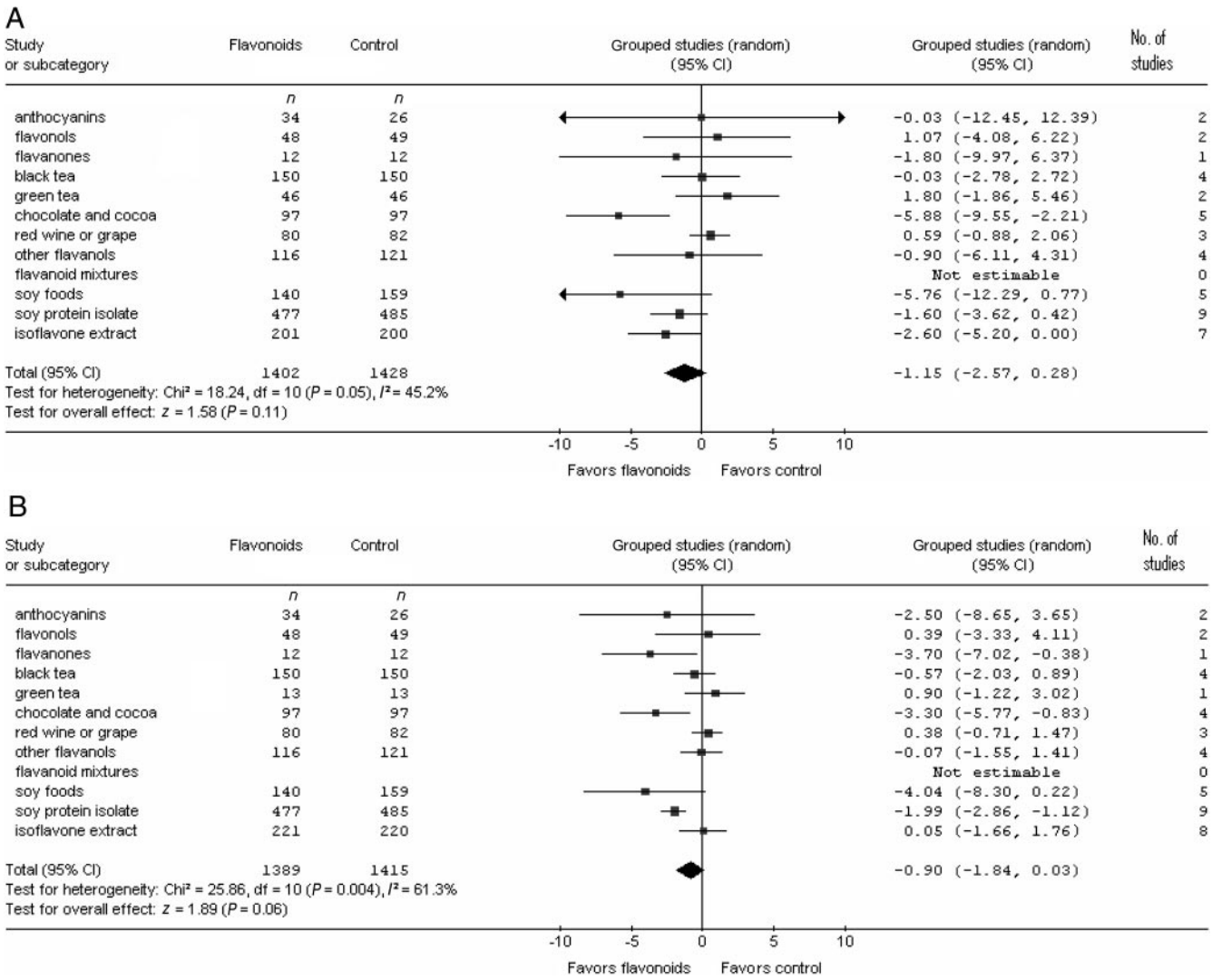

FIGURE 4. Effect of chronic intake of flavonoids on systolic (A) and diastolic (B) blood pressure. Meta-analysis used the weighted mean difference in the DerSimonian and Laird random-effects model. A: There was significant heterogeneity in the chocolate or cocoa, other flavanols, and soy food subclasses shown in this figure. Values for heterogeneity were $P = 0.29$ for anthocyanins, $P = 0.96$ for flavonols, $P = 0.99$ for black tea, $P = 0.90$ for green tea, $P = 0.00003$ for chocolate or cocoa, $P = 0.65$ for red wine or grape, $P < 0.00001$ for other flavonols, $P = 0.002$ for soyfoods, $P = 0.19$ for soy protein isolate, and $P = 0.71$ for isoflavone extracts. B: There was significant heterogeneity in the chocolate or cocoa, other flavanols, isoflavone extracts, and soy food subclasses shown in this figure. Values for heterogeneity were $P = 0.78$ for anthocyanins, $P = 0.71$ for flavonols, $P = 0.96$ for black tea, $P = 0.009$ for chocolate or cocoa, $P = 0.94$ for red wine or grape, $P = 0.07$ for other flavonols, $P = 0.006$ for soyfoods, $P = 0.39$ for soy protein isolate, and $P = 0.06$ for isoflavone extracts.

0%). These increases may be due to the known effects of caffeine on BP, as was seen in a meta-analysis (44), but the 2 studies that controlled for caffeine intake (tea versus water plus caffeine) still suggested a rise in diastolic BP (4.42 mm Hg; 95% CI: 1.38, 7.46; no evidence of heterogeneity, $I^2 = 0\%$), as did studies without control for caffeine (tea versus water only; 1.93 mm Hg; 95% CI: 0.15, 3.71; 2 studies; no evidence of heterogeneity, $I^2 = 0\%$). Theabromine is unlikely to be the cause of this effect because it is also a component of chocolate, and chocolate consumption was not associated with an acute increase in BP.

High- and low-density lipoproteins

One hundred two trials reported HDL outcomes, and 92 reported LDL outcomes. As expected, given the diverse nature of the subclasses, there was evidence of heterogeneity between the flavonoid classes for LDL (P for heterogeneity $= 0.002$, $I^2 = 64\%$), although not for HDL, on which the effects were minimal (**Figure 5**). The available evidence indicates that anthocyanins, black tea, chocolate and cocoa, red wine or grape, other flavanols, flavonoid mixtures, soyfoods, and isoflavone extracts had no effect on LDL concentrations (Figure 5A). Both SPI (−0.19 mmol/L; 95% CI: −0.24, −0.14; 39 studies; P for heterogeneity $= 0.03$, $I^2 = 29\%$) and green tea (−0.23 mmol/L; 95% CI: −0.34, −0.12; 4 studies; P for heterogeneity $= 0.62$, $I^2 = 0\%$) significantly reduced LDL.

DISCUSSION

One hundred thirty-three trials of the effects of flavonoids on CVD risk factors were included in this review. Significant heterogeneity confirmed differential effects between flavonoid

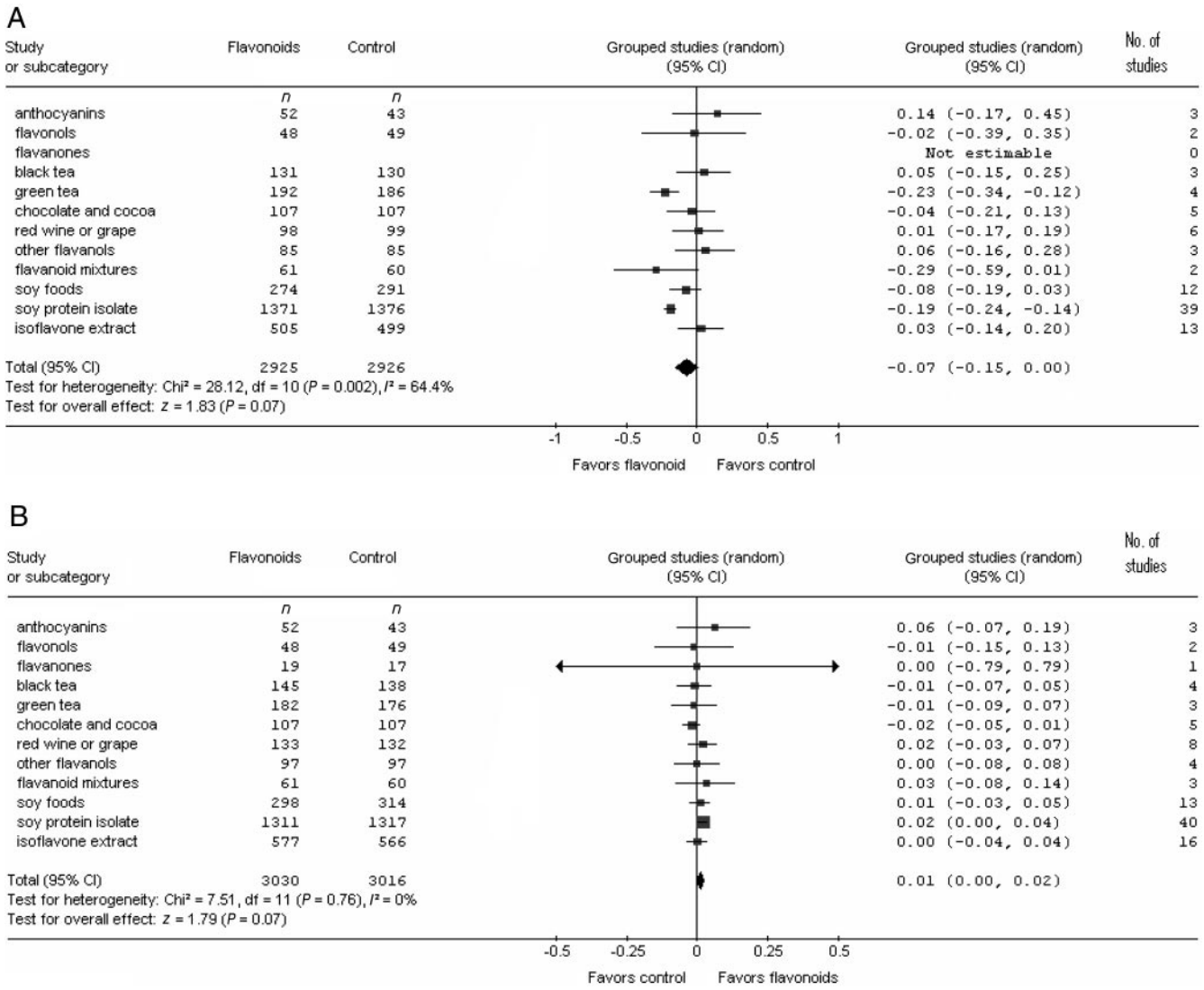

FIGURE 5. Effect of flavonoids on LDL (A) and HDL (B) cholesterol, measured in mmol/L. Meta-analysis used the weighted mean difference in the DerSimonian and Laird random effects model. A: There was significant heterogeneity in the chocolate or cocoa, isolated soy protein, and isoflavone extract subclasses shown in this figure. Values for heterogeneity were $P = 0.44$ for anthocyanins, $P = 0.76$ for flavonols, $P = 0.71$ for black tea, $P = 0.62$ for green tea, $P = 0.06$ for chocolate or cocoa, $P = 0.81$ for red wine or grape, $P = 0.79$ for other flavonols, $P = 0.10$ for flavanoid mixtures, $P = 0.90$ for soyfoods, $P = 0.03$ for soy protein isolate, and $P < 0.00001$ for isoflavone extracts. B: There was significant heterogeneity in the flavanoid mixtures subclasses shown in this figure. Values for heterogeneity were $P = 0.90$ for anthocyanins, $P = 0.77$ for flavonols, $P = 0.81$ for black tea, $P = 0.12$ for green tea, $P = 0.94$ for chocolate or cocoa, $P = 0.96$ for red wine or grape, $P = 0.76$ for other flavonols, $P = 0.02$ for flavanoid mixtures, $P = 0.98$ for soyfoods, $P = 0.62$ for soy protein isolate, and $P = 0.67$ for isoflavone extracts.

subclasses. Chocolate increased FMD and reduced systolic and diastolic BP after acute and chronic intakes. SPI (but not other soy groups) significantly reduced diastolic BP and LDL cholesterol. Acute consumption of black tea increased systolic and diastolic BP, whereas that of green tea reduced LDL. For many other flavonoid subclasses or flavonoid-rich foods, there was insufficient evidence to draw conclusions about efficacy.

To our knowledge, this report is the first systematic review assessing the effectiveness of the range of flavonoid subclasses and flavonoid-rich food sources on CVD risk factors within RCTs. Epidemiologic studies support the protective effect of foods rich in flavonoids or total flavonoid intake on CVD, but only some have examined the relative effectiveness of the subclasses (3, 5, 8–14, 45–51). However, a recent prospective study reported that anthocyanidins, flavanones, and foods rich in flavonoids (including apples, pears, strawberries, red wine, chocolate, and bran) were associated with lower CVD mortality (14).

Shortcomings in the ability of this systematic review to quantify the effects of flavonoid-rich foods and extracts on CVD risk factors include the absence of studies powered to assess effects on CVD and an absence or shortage of well-designed studies of risk factors for most flavonoids. This review highlights areas in which limited data exist, but this feature should not be interpreted as lack of effectiveness.

The weaknesses of the available data include few and very small studies; parallel studies with baseline levels of specific outcomes differing widely between intervention and control arms; crossover studies in which a paired *t* test is not reported;

and a large number of studies in which data on at least some outcomes are missing or poorly reported. Problems with methodologic validity—including lack of evidence of adequate allocation concealment, blinding, similarity of intervention and control arms in terms of saturated fat intake, predominance of industry funding, and suggested reporting bias—may all lead to exaggerated suggestions of effectiveness (52). In addition, when there is evidence of effectiveness of foods rich in flavonoids, it is not clear that the flavonoids themselves (rather than other bioactive components) are solely or partially responsible for the observed effects.

Given these reservations, this review provides evidence that some flavonoids or foods rich in flavonoids, such as chocolate or cocoa, and black tea, may modulate important risk factors. Chocolate and cocoa appear to reduce FMD acutely and reduce both systolic and diastolic BP after chronic intake (although the effect may be reduced over periods >6 wk); data from studies of longer duration would be valuable to examinations of the sustainability of these effects. There is evidence that black tea leads to acute rises in systolic and diastolic BP independent of caffeine content; the mechanism for, and clinical consequences of, this effect should be further explored. Chronic green tea intake may reduce LDL concentrations significantly, and SPI (although not whole soy or soy extracts) may reduce both LDL and diastolic BP after chronic intake.

There is sufficient evidence (eg, ≥3 studies contributing data, ≥100 participants per arm, and statistical significance) to suggest that chronic intakes of black tea have no overall effect on systolic or diastolic BP or LDL or HDL cholesterol; those of chocolate or cocoa have no effect on LDL or HDL cholesterol; those of green tea, red wine or grape, and soyfoods have no effect on HDL cholesterol; those of other flavanols (flavanols other than those in studies of chocolate, tea, or red wine) have no effect on systolic or diastolic BP; those on SPI have no effect on systolic BP; and those of isoflavone extracts have no effect on diastolic BP or LDL or HDL cholesterol.

The reduction in BP associated with chocolate or cocoa reported here is similar to that identified in a review by Taubert et al (53), although they included one study with very large between-arm differences in saturated fat intake (which we excluded), and our analysis included a more recent trial. Their review did not identify significant effects of black tea on BP, probably because they combined data on green and black tea and did not include several more-recent trials. Our results for soy products are similar to those seen in previously published systematic reviews examining the effects of soy and isoflavones on CVD risk factors—SPI appears to reduce LDL but generally has no effect on HDL, and soyfoods and isoflavone extracts do not show effects on lipids (54–58). Soyfoods were close to significance for both systolic and diastolic BP, and isoflavone extract data suggested a reduction in systolic BP but no effect on diastolic BP (previous reviews also suggested no effect). Effects on FMD were mixed, as reported in a previous review (56); we showed that SPI has a positive but not significantly positive effect, but no effect was observed for isoflavone extracts (59). The review also examined effects on other CVD outcomes (our secondary outcomes, including inflammatory markers), which will be reported separately.

Because of the wide range of flavonoid structures, it is not surprising that we observed wide variability in the effects on biomarkers of CVD risk. This heterogeneity of results also reflects wide variation in the bioavailability of the subclasses (1, 60). The most abundant flavonoid compounds may not necessarily lead to the highest concentrations of biologically active metabolites in target tissues, nor may they be the most biologically active in relation to specific health outcomes. Some subclasses are rather well absorbed; for example, after ingestion of isoflavones (in amounts that are achievable by diet; *see* Tables 1 and 2), the flavanol epicatechin, the flavanones, and their metabolites can reach micromolar concentrations in plasma (60). In contrast, even large oral doses of anthocyanins result in only nanomolar plasma concentrations (61). Flavonoids are thought to influence FMD through effects on the acute response cell–signaling pathways that increase nitric oxide production. In addition, numerous in vitro effects have been ascribed to the flavonoids, including antioxidant and antiinflammatory effects and effects on platelet aggregation (62–64). However, many in vitro studies have not taken bioavailability or metabolism into account, and the effects observed may not reflect the in vivo situation (65). The range of concentrations required to elicit effects in vitro ranges from <0.1 μmol/L to >100 μmol/L, whereas physiologic concentrations will rarely reach 10 μmol/L (61).

Together the data included in this meta-analysis suggest that there may be clinically relevant effects of some flavonoid subclasses or flavonoid-rich foods on CVD risk factors; however, for many subclasses, there are limited data from intervention trials with which to examine potential efficacy. For example, anthocyanins and flavanones are commonly consumed as part of a normal diet, and a future focus on these subclasses is needed to determine their specific CVD effects.

The changes in risk factors observed after flavonoid intake are clinically significant. In persons at low risk of coronary heart disease, an FMD increase of 1.4% decreases Framingham risk by 1% (29). Our summary suggests that daily consumption of 50 g dark chocolate increases FMD by 4% acutely and by 1.4% chronically. The reduction of systolic BP by 5.9 mm Hg after chronic intake of chocolate or cocoa, as found in this review, would, on a population level, be expected to reduce stroke risk by 8%, coronary artery disease mortality by 5%, and all-cause mortality by 4% (66). Both green tea and SPI appear to reduce LDL cholesterol by ≈0.2 mmol/L, which would be estimated to result in a 3% reduction in all-cause mortality and a 6% reduction in both CHD-related mortality and total CHD events (67). These are profound effects and must be considered seriously in terms of the potential for dietary phytochemicals to modulate CVD risk. As with any intervention, potential risks also must to be considered, eg, the acute rises in BP after black tea ingestion. Fifty g chocolate (doses typically used in reported trials were in the range of 50 to 100 g/d) provides ≈15 g fat and ≈230 kcal, >10% of daily energy intake, and 25% of recommended fat intake (68); this addition to the diet may adversely affect weight and overall dietary quality, counteracting observed CVD benefits. To achieve the clinically important LDL reductions discussed above, 2–5 mugs green tea/d (up to one-half of the usual fluid intake) or 20-56 g SPI powder/d (up to 75% of the usual protein intake) would be required, and hence the side-effects and effectiveness of dietary regimens in reducing CVD risk should be considered carefully.

In this systematic review, we assessed the effectiveness of flavonoid subclasses and flavonoid-rich food sources in relation to CVD risk factors by reviewing available published intervention trials. The synthesis of the data from those trials provides an important snapshot of the current state of the art and facilitates the

identification of future research priorities. Future studies should assess dose-response effects, be of adequate duration, and report all outcomes assessed, particularly risk factors known to relate causally to CVD incidence.

The authors' contributions were as follows—AC and LH: developed the study concept; AC, LH, PK, EBR, and JC: designed the study; LH: wrote the protocol and developed and conducted the electronic searches; PK, JC, IH, KLC, JR, WH, and AC: assessed studies for inclusion, extracted data, and assessed validity; LH: duplicated inclusion, conducted data extraction and validity assessment, conducted meta-analyses, and tabulated data; AC, PK, and LH: wrote the first draft of the manuscript; JC and EBR provided critical review of the manuscript; and all other authors: contributed to writing the manuscript and approved the final version. None of the authors had a personal or financial conflict of interest.

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