Dietary intakes of flavan-3-ols and cardiometabolic health: systematic review and meta-analysis of randomized trials and prospective cohort studies

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ABSTRACT

Background: Although available data suggest that some dietary flavan-3-ol sources reduce cardiometabolic risk, to our knowledge no review has systematically synthesized their specific contribution.

Objective: We aimed to examine, for the first time, if there is consistent evidence that higher flavan-3-ol intake, irrespective of dietary source, reduces cardiometabolic risk.

Methods: MEDLINE, Cochrane Central, and Commonwealth Agricultural Bureau abstracts were searched for prospective cohorts and randomized controlled trials (RCTs) published from 1946 to March 2019 on flavan-3-ol intake and cardiovascular disease (CVD) risk. Random-effects models meta-analysis was used. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach assessed the strength of evidence.

Results: Of 15 prospective cohorts (23 publications), 4 found highest compared with lowest habitual intakes of flavan-3-ols were associated with a 13% reduction in risk of CVD mortality and 2 found a 19% reduction in risk of chronic heart disease (CHD) incidence. Highest compared with lowest habitual intakes of monomers were associated with a reduction in risk of type 2 diabetes mellitus (T2DM) ($n = 5$) and stroke ($n = 4$) (10% and 18%, respectively). No association was found for hypertension. Of 156 RCTs, flavan-3-ol intervention resulted in significant improvements in acute/chronic flow-mediated dilation (FMD), systolic (SBP) and diastolic blood pressure (DBP), total cholesterol (TC), LDL and HDL cholesterol, triglycerides (TGs), hemoglobin A1c (HbA1c), and homeostasis model assessment of insulin resistance (HOMA-IR). All analyses, except HbA1c, were associated with moderate/high heterogeneity. When analyses were limited to good methodological quality studies, improvements in TC, HDL cholesterol, SBP, DBP, HOMA-IR, and acute/chronic FMD remained significant. In GRADE evaluations, there was moderate evidence in cohort studies that flavan-3-ol and monomer intakes were associated with reduced risk of CVD mortality, CHD, stroke, and T2DM, whereas RCTs reported improved TC, HDL cholesterol, SBP, and HOMA-IR.

Conclusions: Available evidence supports a beneficial effect of flavan-3-ol intake on cardiometabolic outcomes, but there was considerable heterogeneity in the meta-analysis. Future research should focus on an integrated intake/biomarker approach in cohorts and high-quality dose–response RCTs. This review was registered at www.crd.york.ac.uk/PROSPERO/ as CRD42018035782. *Am J Clin Nutr* 2019;110:1067–1078.

Keywords: flavan-3-ols, flavonoids, cardiovascular, diabetes, blood pressure

Introduction

Interest in the role of dietary flavonoids (naturally occurring plant bioactives) in reducing the risk of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) stems from findings

from a range of interdisciplinary sources (prospective studies, clinical trials, and mechanistic studies in animal and in vitro) (1–4). However, to date, the majority of the data has focused on specific flavonoid-rich food sources like tea, cocoa, fruits, and soy, all of which contain a range of bioactive constituents beyond flavonoids (5–7). Although a number of systematic reviews have collated the available data for these individual flavonoid-rich food sources (5–13), to our knowledge no review has systematically examined the specific contribution of the flavonoid content of the foods in relation to cardiometabolic health.

One subclass of dietary flavonoids that is of significant interest is the flavan-3-ols, although to date both population-based studies and clinical trials have mainly focused on their 2 main food sources, tea and cocoa, with a number of systematic reviews and meta-analyses published for these individual foods (5–13). Because these foods contain a range of other potentially bioactive constituents, we recently undertook a comprehensive and systematic evidence-mapping exercise which provided the evidence base to suggest that sufficient evidence is now available to conduct a systematic review and meta-analysis on the potential cardiometabolic health effects of flavan-3-ols per se (irrespective of source) (14).

Our aim, using a combination of evidence from both randomized controlled trials (RCTs) and prospective cohort data, was to examine if there was consistent evidence that a higher intake of flavan-3-ols reduced the risk of CVD. We also examined if there was a dose–response relation, a minimum intake for a vascular benefit, if food source or form (food compared with supplement/pure compound) affected the magnitude of the health effect, and if any individual flavan-3-ol components were driving the cardiometabolic health effects.

Methods

This study is a systematic review of published literature evaluating the effects of flavan-3-ol intake on CVD outcomes and risk factors. The review was conducted in 2 phases: a first phase of evidence mapping (14) followed by a full systematic review. A technical expert panel was convened that served as key informants to identify issues relevant to flavan-3-ols, refine key questions, identify interventions of interest, define eligibility criteria, and develop the analytic framework (14). A standard protocol was developed and registered in the PROSPERO database (https://www.crd.york.ac.uk/PROSPERO) as CRD42018035782. This review was conducted using standard methodology and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (15).

Data sources and study eligibility

A comprehensive search of the scientific literature was conducted in MEDLINE, the Cochrane Central databases, and the Commonwealth Agricultural Bureau from inception through 26 April, 2016 for evidence mapping (14) and this search was further updated until 9 March, 2019. The reference lists of any previously published systematic reviews on flavan-3-ols and health outcomes were screened to identify additional studies. Search key terms for monomer, proanthocyanidin, and foods and beverages (i.e., tea, red wine) rich in flavan-3-ols were combined with the outcomes of interest and limited by terms for study designs of interest (i.e., randomized trials and prospective cohort studies) and by studies conducted in humans. No language restriction was applied. The detailed search strategy is reported elsewhere (14). Citations were screened in duplicate using predefined eligibility criteria and any disagreements regarding study inclusion or exclusion were resolved in group meetings.

Study inclusion criteria.

We included RCTs and prospective cohort studies conducted in adults (≥18 y) that quantified the amount of flavan-3-ols consumed per day or per week. Studies that provided sufficient serving size data were also included, provided estimation of total flavan-3-ol consumption was possible using the USDA (16, 17) or Phenol Explorer databases (www.phenol-explorer.eu) (18). Interventions included monomers, proanthocyanidins, and foods and beverages rich in flavan-3-ol content such as fruits (i.e., apples, berries, and grapes), dark chocolate, cocoa, teas, and red wine. Comparators included low flavan-3-ol content or no flavan-3-ols or placebos. The primary outcomes of interest included CVD clinical outcomes [e.g., CVD mortality, chronic heart disease (CHD), stroke, diabetes, and hypertension]; secondary outcomes included risk factors [serum lipids, blood pressures, glucose metabolism, and flow-mediated dilation (FMD)] and biomarkers [high-sensitivity CRP (hsCRP), IL-6, and TNF-α]. The full study eligibility criteria are described elsewhere (14).

Study exclusion criteria.

We excluded retrospective studies, cross-sectional studies, case series, case reports, and narrative reviews. Studies evaluating interventions that were not clearly specified, including in relation to type of wine (i.e., red or white), type of tea (i.e., black or green), type of chocolate (i.e., dark or white), and cinnamon, were excluded.

In addition to the aforementioned common eligibility criteria, we specified the following additional criteria according to study design. We included prospective cohort studies that reported multivariable results adjusting for any potential confounders and had ≥6 mo of follow-up time.

We included RCTs that recruited participants who were healthy, at an increased risk of CVD, or had existing CVD. Minimum intervention duration was applied according to outcomes of interest. For studies with eligible interventions such as extracts that reported insufficient data on flavan-3-ol content, study authors or product manufacturers were contacted to obtain additional information on flavan-3-ols expressed as mg/d.

Data extraction

A standardized, prepiloted data extraction form was created for extracting data in the Systematic Review Data Repository (https://srdr.ahrq.gov). The forms were designed to capture all relevant elements from the descriptions on study population characteristics, enrolled and analyzed sample sizes, study design features, interventions and comparators, relevant outcomes, results, and risk of bias assessment. Data from each study were

extracted independently by 1 of 6 investigators and confirmed by ≥1 other. Data discrepancies were identified and resolved through group discussion.

Risk of bias/quality assessment

Two reviewers independently assessed the risk of bias for each included study. For RCTs, we used the Cochrane risk-of-bias tool for clinical trials along with nutrition-specific items from a critical appraisal of micronutrient systematic reviews (19, 20). For prospective cohort studies, we assessed the following domains: risk of selection, performance, attrition, detection, and selective outcome reporting biases (21). Each methodological quality item was rated as Yes, No, or Unclear.

Data synthesis

All included studies were summarized in narrative form and in summary tables that tabulated important features of the study populations, design, intervention, outcomes, and results.

Summary tables were organized by key questions and by outcome of interest. We performed meta-analyses where there were ≥3 unique studies deemed to be sufficiently similar in population and outcomes (22). The results from RCTs and prospective cohort studies were meta-analyzed separately.

For categorical outcomes, we conducted meta-analysis using a random-effects model and reported the results as summary RRs, comparing the extreme categories of flavan-3-ols (highest compared with lowest, as defined within each study). When ≥3 studies reported their results stratified by age or sex, we performed subgroup meta-analyses for age and sex categories.

For continuous outcomes, we extracted the mean baseline levels in both intervention and control arms and measures of variance (SD or SE). We estimated the within-cohort changes (i.e., intervention final − intervention initial, or control final − control initial). We calculated the SE for within-cohort change. We then calculated net differences for continuous outcomes using the following equation: net change = (intervention final − intervention initial) − (control final − control initial).

When studies reported sufficient information, we conducted stratified analysis by monomers, proanthocyanidins, types of interventions, and quartiles of median flavan-3-ol intake. The types of interventions were categorized into cocoa, extract, fruit, pure form, tea, and wine. To evaluate possible dose effects and heterogeneity in results, we also performed several meta-regression analyses with continuous flavan-3-ol dosage (in milligrams per day) and outcomes of interest.

We tested between-study heterogeneity with the Q statistic (significant when $P < 0.10$) and quantified its extent with the I^2 statistic (23). I^2 statistics were further classified in terms of heterogeneity as follows: >25% as low; >50% as moderate; and >75% as high. Analyses were performed in Stata version 13 (StataCorp) with the metan, metareg, and metabias functions.

Grading overall strength of evidence

A structured approach modeled after the GRADE (Grading of Recommendations Assessment, Development and Evaluation) was employed to grade the quality of overall evidence for each outcome as 1 of the following 4 grades: High, Moderate, Low, or Very Low (24).

Results

The database searches identified 4047 abstracts. After title and abstract screening, 365 articles (108 articles from the updated search and 257 articles identified from the evidence map) were retrieved for full-text review. An additional 9 articles were identified by the expert. A total of 23 prospective cohort articles and 157 RCTs (156 publications) met the eligibility criteria. The study flow diagram is depicted in **Figure 1**.

Cohort studies

Fifteen different cohorts [in 23 publications (25–47)] reported the following outcomes: CVD mortality (25, 26, 29, 32, 35–37, 39, 47), incident CHD (31, 38, 39, 41), stroke (25, 31, 37–39, 41), hypertension (27, 34, 39, 43), and T2DM (33, 40, 42, 44–46). One RCT was analyzed as an observational cohort study (38, 44). Details about baseline characteristics are available in **Table 1**. Four studies included only postmenopausal women (26, 32, 35, 36). All studies assessed flavan-3-ol intake by semiquantitative FFQ administered at baseline, but only a few also assessed flavan-3-ol intake at follow-up time points (25, 27, 29, 40). All adjusted for variables including participant characteristics such as age or CVD risk factors such as T2DM or hypertension. All cohorts except 4 did not adjust for diet factors (26, 32, 34, 36). The methodological quality of the eligible cohort studies was rated good, reflecting low risk of bias (**Supplemental Table 1**). A summary of the overall effects across the meta-analysis of all eligible outcomes from the cohort studies can be found in **Figure 2**.

CVD mortality.

Seven cohorts in 9 publications (25, 26, 29, 32, 35–37, 39, 47) reported an association between flavan-3-ol intake and risk of CVD mortality (196,148 participants who were followed for 5–25 y) (Table 1). Four cohorts reported data on total flavan-3-ol intake (32, 35, 36, 39) and 5 cohorts [in 6 studies (25, 26, 29, 35, 37, 47)] reported data on monomers; of these, 1 reported data on components of monomers [gallated compared with nongallated forms (29)]. Ascertainment of CVD mortality was by examination of hospital records (25, 29), national death index or registry (26, 32, 35–37), or death certificates (39, 47).

Higher flavan-3-ol intake was significantly associated with a reduction in risk of CVD mortality in 4 cohorts (summary RR: 0.87; 95% CI: 0.77, 0.98; $I^2 = 43.2\%$). In subgroup analysis, a higher flavan-3-ol intake was significantly associated with a reduction in risk of CVD mortality among women, but no similar association was found in men (**Supplemental Table 2**). Higher monomer intake was significantly associated with lower risk of CVD mortality among women, but no similar association was found in men (Supplemental Table 2).
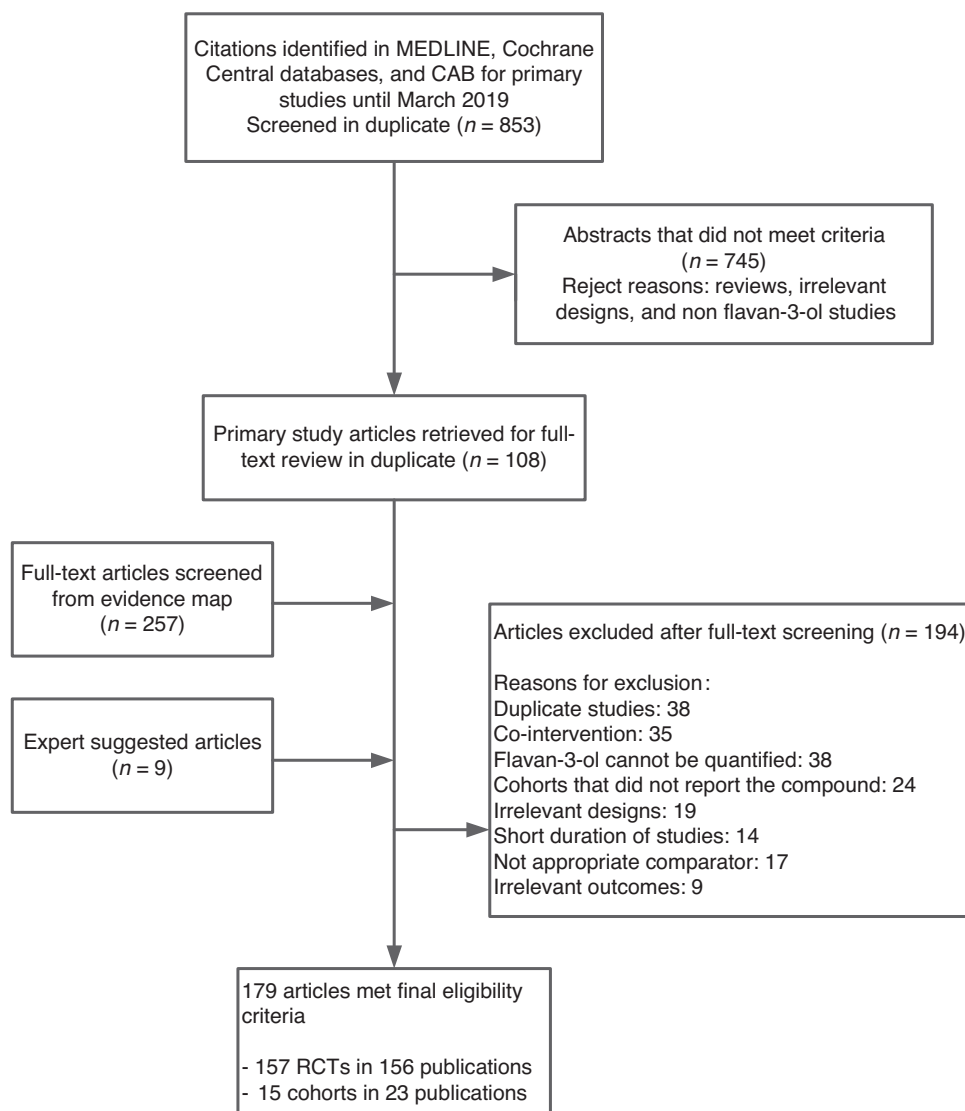
FIGURE 1 Study flow diagram depicting the review process. CAB, Commonwealth Agricultural Bureau; RCT, randomized controlled trial.

CHD incidence.

Three cohorts (31, 38, 39) reported an association between flavan-3-ol intake and risk of incident CHD (Table 1). The studies included 48,735 participants who were followed for 4–11 y. All studies included both sexes. Two studies reported total flavan-3-ol intake (38, 39) and 1 study reported data for monomers and proanthocyanidins (31). Ascertainment of incident CHD in all studies was either by examination of hospital records or through adjudication.

A higher habitual flavan-3-ol intake was also significantly associated with a reduction in risk of CHD incidence in 2 cohorts that reported data stratified by sexes (summary RR: 0.81; 95% CI: 0.66, 0.99; $I^2 = 60.8\%$). In subgroup analysis, higher flavan-3-ol intake was significantly associated with lower CHD incidence among men, but no similar association was found in women. There was no association between monomer intake and CHD incidence in the whole population or by sex (Supplemental Table 2).

Stroke.

Six cohorts (25, 31, 37–39, 41) reported the association between flavan-3-ol intake and risk of stroke (Table 1). The studies included 173,487 participants who were followed for 4–18 y. Two studies included all men (25, 37), whereas the others included both sexes. Four studies reported data on the association between monomer intake and risk of stroke (25, 30, 37, 41). Ascertainment of stroke in all studies was either by examination of hospital records or through adjudication, but only 1 cohort reported stroke outcome adjudication by a neurologist (37).

There was no association between higher flavan-3-ol intake and incidence of stroke in 2 cohorts that reported data stratified by sexes (summary RR: 0.95; 95% CI: 0.80, 1.12; $I^2 = 0.0\%$). Insufficient data precluded additional sex-specific subgroup analyses. Higher monomer intake was associated with a significant reduction in risk of stroke in 4 cohorts (summary RR: 0.82; 95% CI: 0.68, 0.99; $I^2 = 0.0\%$).

TABLE 1 Study characteristics of included cohorts[1]

Authors	Country	Cohort name	Follow-up years	*n* enrolled (*n* analyzed)	Male, %	Mean age,[2] y	BMI,[3] kg/m^2	Funding source	Comorbidities
Adriouch et al. (41)	France	NutriNet-Santé	18	84,158 (84,158)	21.3	44.1 ± 14.5	NR	Government, academia	Diabetes, hypertension, hypercholesterolemia
Arts et al. (25)	Netherlands	The Zutphen Elderly Study	10	939 (806)	100	71 (65–84)	25.5 (NR)	Government	Hypertension, hypercholesterolemia
Arts et al. (26)	United States	Iowa Women's Health Study	12	34,492 (32,857)	0	61.5 (55–69)	26.9 (NR)	Government	Diabetes, hypertension, CVD
Cassidy et al. (27)	United States	NHS, NHS II, HPFS	14	156,957 (156,957)	14.7	44.6 (25–75)	24.6 (NR)	Government	Hypertension
Cassidy et al. (28)	United States	NHS	18	93,600 (93,600)	0	36.6 (25–42)	24.6 (NR)	Government	Diabetes, hypertension, hypercholesterolemia
Dower et al. (29)	Netherlands	The Zutphen Elderly Study	25	774 (774)	100	71.9 (65–84)	25.6 (NR)	Government, industry	Diabetes, CVD, hypertension, hypercholesterolemia
Goetz et al. (30)	United States	REGARDS	6.5	30,239 (20,024)	44	64.6 (NR)	29.1 (NR)	Government	Diabetes, hypertension
Goetz et al. (31)	United States	REGARDS	6	16,678 (16,678)	41.2	64.3 (NR)	29 (NR)	Government	NR
Grosso et al. (42)	Poland	HAPIEE subcohort	4	10,728 (5806)	47	57.4 (45–69)	27.7 (NR)	Government, foundation	NR
Grosso et al. (43)	Poland	HAPIEE subcohort	4	2725 (2725)	42.2	55.6 (45–69)	26.4 (NR)	Government, foundation	Hypertension
Ivey et al. (32)	Australia	Calcium Intake Fracture Outcome Study	5	1063 (1063)	0	80.1 (NR)	27.1 (NR)	Government, foundation, hospital	Diabetes, hypertension
Jacques et al. (33)	United States	Framingham Heart Study Offspring cohort	11.9	2915 (2915)	45.5	54.2 (28–62)	26.7 (NR)	Government, foundation	Diabetes, CVD
Lajous et al. (34)	France	EPIC	13.8	40,574 (40,574)	0	51.6 (NR)	22.2 (NR)	Government, foundation	Diabetes, CVD, hypertension, hypercholesterolemia
McCullough et al. (35)	United States	American Cancer Society's CPS-II Nutrition Cohort	7	98,469 (98,469)	38.77	69.1 (NR)	NR	Government	Diabetes, CVD, hypertension, hypercholesterolemia
Mink et al. (36)	United States	Iowa Women's Health Study	12	34,492 (34,492)	0	61 (55–69)	26.9 (NR)	Foundation	Diabetes, CVD, hypertension
Mursu et al. (37)	Finland	The Kuopio Ischaemic Heart Disease Risk Factor Study	15.2	2682 (1950)	100	52.4 (42–60)	26.7 (NR)	Foundation	Diabetes, CVD
Ponzo et al. (47)	Italy	NR	12	1658 (1658)	47	54.6 (45–64)	26.6 (NR)	Government	CVD, diabetes, hypercholesterolemia, hypertension
Tresserra-Rimbau et al. (38)	Spain	PREDIMED	4.3	7447 (7172)	42.65	67 (NR)	30 (NR)	Government	Diabetes, CVD, hypertension
Tresserra-Rimbau et al. (44)	Spain	PREDIMED	5.51	3430 (3430)	38.3	66.6 (NR)	29.9 (NR)	Government, industry	Hypercholesterolemia, hypertension
Vogiatzoglou et al. (39)	United Kingdom	EPIC-Norfolk	11.1	25,639 (24,885)	34	60 (40–75)	27 (NR)	Government, industry	Diabetes, CVD, hypertension, hypercholesterolemia
Wedick et al. (40)	United States	NHS, NHS II, HPFS	12–18	289,900 (199,980)	20.6 (0, 0, 100)	44.3 (25–75)	24.9 (NR)	Government	Diabetes, CVD, hypercholesterolemia, hypertension
Zamora-Ros et al. (45, 46)	Eight European countries	EPIC-Interact subcohort	NR	16,154 (15,268)	37.8	52.4 (NR)	26.0 (NR)	Government	CVD, diabetes, hypercholesterolemia, hypertension

[1]CPS, Cancer Prevention Study; CVD, cardiovascular disease; EPIC, European Prospective Investigation into Cancer and Nutrition; HAPIEE, Health, Alcohol and Psychosocial factors in Eastern Europe; HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; NR, not reported; PREDIMED, Prevención con Dieta Mediterránea study; REGARDS, REasons for Geographic and Racial Differences in Stroke.

[2]Mean ± SD or mean (range).

[3]Mean ± SD.

Hypertension.

Six cohorts [Nurses' Health Study (NHS), NHS II, Health Professionals Follow-Up Study (HPFS), French-European Prospective Investigation into Cancer and Nutrition (EPIC); EPIC-Norfolk; Health, Alcohol and Psychosocial factors in Eastern Europe (HAPIEE)] in 4 studies (27, 34, 39, 43) reported on the association between monomer or polymer intake and risk

of hypertension (Table 1). Only 1 cohort reported data on total flavan-3-ol intake and blood pressure [systolic (SBP) and diastolic blood pressure (DBP)] as a continuous outcome (39). The remaining 5 cohorts reported data on the association between monomer or proanthocyanidin intake and incident hypertension. The studies included 225,141 participants who were followed for 11–14 y. Three cohorts included only women (French-EPIC; NHS; NHS II), 1 cohort included only men (HPFS), and 2 cohorts
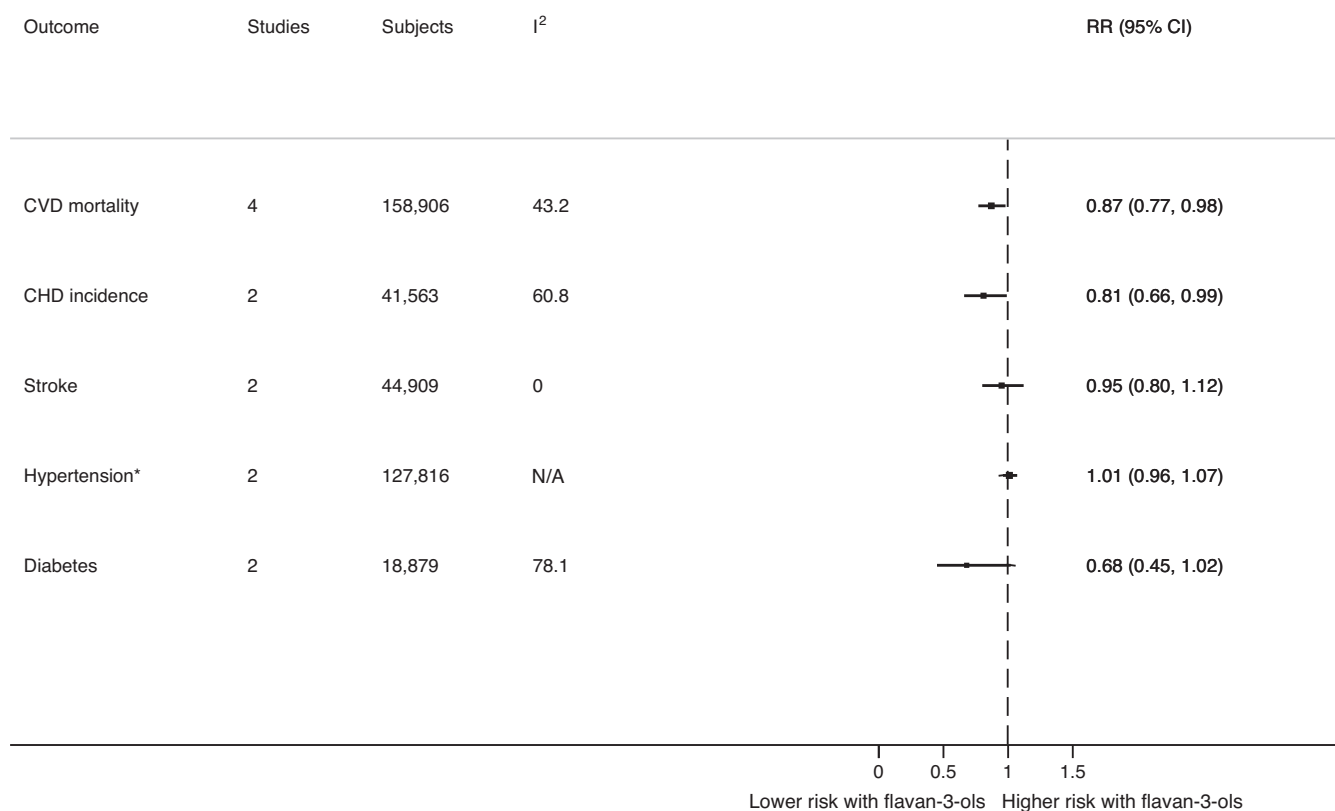
Outcome	Studies	Subjects	I^2		RR (95% CI)
CVD mortality	4	158,906	43.2		0.87 (0.77, 0.98)
CHD incidence	2	41,563	60.8		0.81 (0.66, 0.99)
Stroke	2	44,909	0		0.95 (0.80, 1.12)
Hypertension*	2	127,816	N/A		1.01 (0.96, 1.07)
Diabetes	2	18,879	78.1		0.68 (0.45, 1.02)

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            0      0.5      1      1.5
   Lower risk with flavan-3-ols   Higher risk with flavan-3-ols
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FIGURE 2 The effect of flavan-3-ols on cardiometabolic health outcomes from prospective cohort studies. Data reported are RRs and 95% CIs for a fully adjusted random-effects meta-analysis model for each outcome. *Hypertension outcome included men and women subpopulations from the same cohort from 1 article that reported total flavan-3-ol intake and blood pressure. CHD, chronic heart disease; CVD, cardiovascular disease.

included both sexes (EPIC-Norfolk; HAPIEE). Ascertainment of hypertension was by self-reported data (27, 34) or done at the time of the baseline visit (43); but this was not reported in 1 cohort (39).

There was no association between higher monomer intake (summary RR: 1.01; 95% CI: 0.96, 1.07; $I^2 = 65.8\%$) or between proanthocyanidin intake (summary RR: 0.98; 95% CI: 0.93, 1.04; $I^2 = 70.4\%$) and incident hypertension. Insufficient data precluded additional sex-specific subgroup analyses.

T2DM.

Two cohorts (HAPIEE and EPIC-Interact) reported an association between total flavan-3-ol intake and risk of T2DM. Six cohorts (NHS, NHS II, HPFS, Framingham Offspring, EPIC-Interact, Prevención con Dieta Mediterránea) in 5 studies reported on the association between monomer intake and risk of T2DM (Table 1). Of these, 1 study reported on the association between subclasses of monomers or proanthocyanidins and risk of T2DM (46). The studies included 233,207 participants who were followed for 5–18 y. Ascertainment of T2DM was by using multiple data sources including questionnaire evaluation of symptoms, diagnostic tests, hospital admissions, and hypoglycemic therapy in most of the studies (40, 42, 44–46), or via confirmation by a physician at each study examination (33).

There was no association between total flavan-3-ol intake and T2DM in 2 studies (summary RR: 0.68; 95% CI: 0.45,

1.02; $I^2 = 78.1\%$). Higher monomer intake was significantly associated with a reduction in risk of T2DM in 5 studies (summary RR: 0.90; 95% CI: 0.83, 0.97; $I^2 = 52.8\%$). Insufficient data precluded additional sex-specific subgroup analyses. Higher proanthocyanidin intake was significantly associated with a reduction in risk of T2DM in 3 studies (summary RR: 0.89; 95% CI: 0.81, 0.98; $I^2 = 0.0\%$).

Overall strength of evidence among cohort outcomes.

We then graded the overall strength of evidence for the outcomes reported in cohort studies. There was moderate strength of evidence that higher habitual intake of flavan-3-ols is associated with a reduction in risk of CVD mortality (total flavan-3-ol and monomer intake), CHD incidence (total flavan-3-ol intake), and stroke (monomer intake), and high strength of evidence for an association of higher monomer and proanthocyanidin intake with a reduction in risk of T2DM incidence (**Supplemental Table 3**). No difference in outcomes was observed for hypertension (data not shown; graded low strength of evidence).

RCTs

Only 1 long-term RCT (48) among 157 eligible RCTs (from 156 publications) reported clinical outcomes that evaluated flavan-3-ol intervention and CVD risk factors (references of the

TABLE 2 Description of study-level characteristics of eligible RCTs[1]

	Total	RCT parallel	RCT crossover
Publications	157 (100.00)	92 (58.6)	65 (41.4)
Blinding			
Double-blind	95 (60.5)	59 (64.1)	36 (55.4)
Single-blind	26 (16.6)	10 (10.8)	16 (24.6)
Not blinded	17 (10.8)	11 (12.0)	6 (9.2)
Unclear	19 (12.1)	12 (13.0)	7 (10.7)
Mean age			
<50 y	54 (34.4)	28 (30.4)	26 (40.0)
≥50 y	79 (50.3)	43 (46.7)	36 (55.4)
Baseline health			
Healthy	53 (33.8)	23 (25.0)	30 (46.2)
At risk of CVD	86 (54.8)	62 (67.4)	24 (36.9)
Existing CVD	8 (5.1)	2 (2.2)	6 (9.2)
Mixed	10 (6.4)	5 (5.4)	5 (7.7)
Study region			
Africa	3 (1.9)	2 (2.2)	1 (1.5)
Asia	20 (12.7)	17 (18.5)	3 (4.6)
Australia	7 (4.5)	4 (4.3)	3 (4.6)
Eastern Europe	6 (3.8)	4 (4.3)	2 (3.1)
Western Europe	60 (38.2)	24 (26.1)	36 (55.4)
Middle East	12 (7.6)	12 (13.0)	0 (0.0)
North America	47 (29.9)	27 (29.3)	20 (30.8)
South America	2 (1.3)	2 (2.2)	0 (0.0)
Diabetes			
100%	20 (12.7)	17 (18.5)	3 (4.6)
None	87 (55.4)	38 (41.3)	49 (75.4)
Mixed	16 (10.2)	8 (8.7)	8 (12.3)
Not reported	34 (21.7)	29 (31.5)	5 (7.7)
Hypertension			
100%	14 (8.9)	6 (6.5)	8 (12.3)
None	50 (31.8)	20 (21.7)	30 (46.2)
Mixed	22 (14.0)	13 (14.1)	9 (13.8)
Not reported	71 (45.2)	53 (57.6)	18 (27.7)
Hypercholesterolemia			
100%	9 (5.7)	7 (7.6)	2 (3.1)
None	37 (23.5)	12 (13.0)	25 (38.5)
Mixed	13 (8.3)	8 (8.7)	5 (7.7)
Not reported	98 (62.4)	65 (70.6)	33 (50.7)
CVD			
100%	9 (6.0)	2 (2.2)	7 (10.8)
None	91 (60.3)	52 (56.5)	45 (69.2)
Mixed	2 (1.3)	1 (1.1)	1 (1.5)
Not reported	49 (32.4)	37 (41.6)	12 (18.5)
Intervention			
Cocoa	50 (31.9)	24 (26.1)	26 (40.0)
Extract	26 (16.5)	20 (21.7)	6 (9.2)
Fruit	40 (25.5)	21 (22.8)	19 (29.2)
Pure form	5 (3.2)	2 (2.2)	3 (4.6)
Tea	27 (17.2)	20 (21.7)	7 (10.7)
Wine	9 (5.7)	5 (5.4)	4 (6.2)

[1]Values are numbers/frequencies (percentages) of study-level variables that represent the reporting characteristics of RCTs. CVD, cardiovascular disease; RCT, randomized controlled trial.

included RCTs are in **Supplemental Table 4**). The duration of the RCTs included in the meta-analysis ranged from 3 to 26 wk for the majority of the outcomes. The intervention dosages ranged from 40 to 1540 mg/d. Descriptions of study characteristics and outcomes of interest are presented in **Table 2**. Only 48 RCTs were rated good quality (**Supplemental Table 5**) and their references are given in **Supplemental Table 6**. A summary of the overall effects across the meta-analysis of all eligible outcomes can be found in **Figure 3**.

Lipids.

Meta-analysis of RCTs comparing the effect of flavan-3-ols with controls on serum lipids showed significant decreases in LDL cholesterol (net change: −0.07 mmol/L; 95% CI: −0.13, −0.009 mmol/L; $I^2 = 72.6\%$), triglycerides (TGs) (net change: −0.03 mmol/L; 95% CI: −0.07, −0.003 mmol/L; $I^2 = 64.3\%$), and total cholesterol (TC):HDL cholesterol (net change: −0.14 mmol/L; 95% CI: −0.28, −0.003 mmol/L; $I^2 = 0.0\%$), and

Outcome	Studies	Subjects	I^2	d	Net change (95% CI)
TC (mmol/L)	91	4455	77		−0.070 (−0.140, 0.007)
LDL-C (mmol/L)	87	4093	72.6		−0.070 (−0.130, −0.009)
HDL-C (mmol/L)	92	4335	55.3		0.030 (0.010, 0.040)
TG (mmol/L)	92	4548	64.3		−0.030 (−0.070, −0.003)
TC:HDL	5	260	0		−0.140 (−0.280, −0.003)
LDL:HDL	15	674	80.1		−0.120 (−0.310, 0.060)
SBP (mm Hg)	91	4208	65.3		−1.460 (−2.270, −0.650)
DBP (mm Hg)	91	4208	58		−0.990 (−1.500, −0.450)
HbA1c (%)	25	1372	0		−0.050 (−0.090, −0.010)
FBG (mmol/L)	81	4154	54.9		−0.030 (−0.070, 0.020)
HOMA–IR	35	1821	42.3		−0.150 (−0.290, −0.010)
Acute FMD (%)	24	646	90.6		1.700 (1.310, 2.080)
Chronic FMD (%)	23	787	96.2		1.210 (0.700, 1.730)

```
        −2.5   −1.5   −0.5 0 0.5   1.5    2.5
Decreased after flavan-3-ols intervention    Increased after flavan-3-ols intervention
```
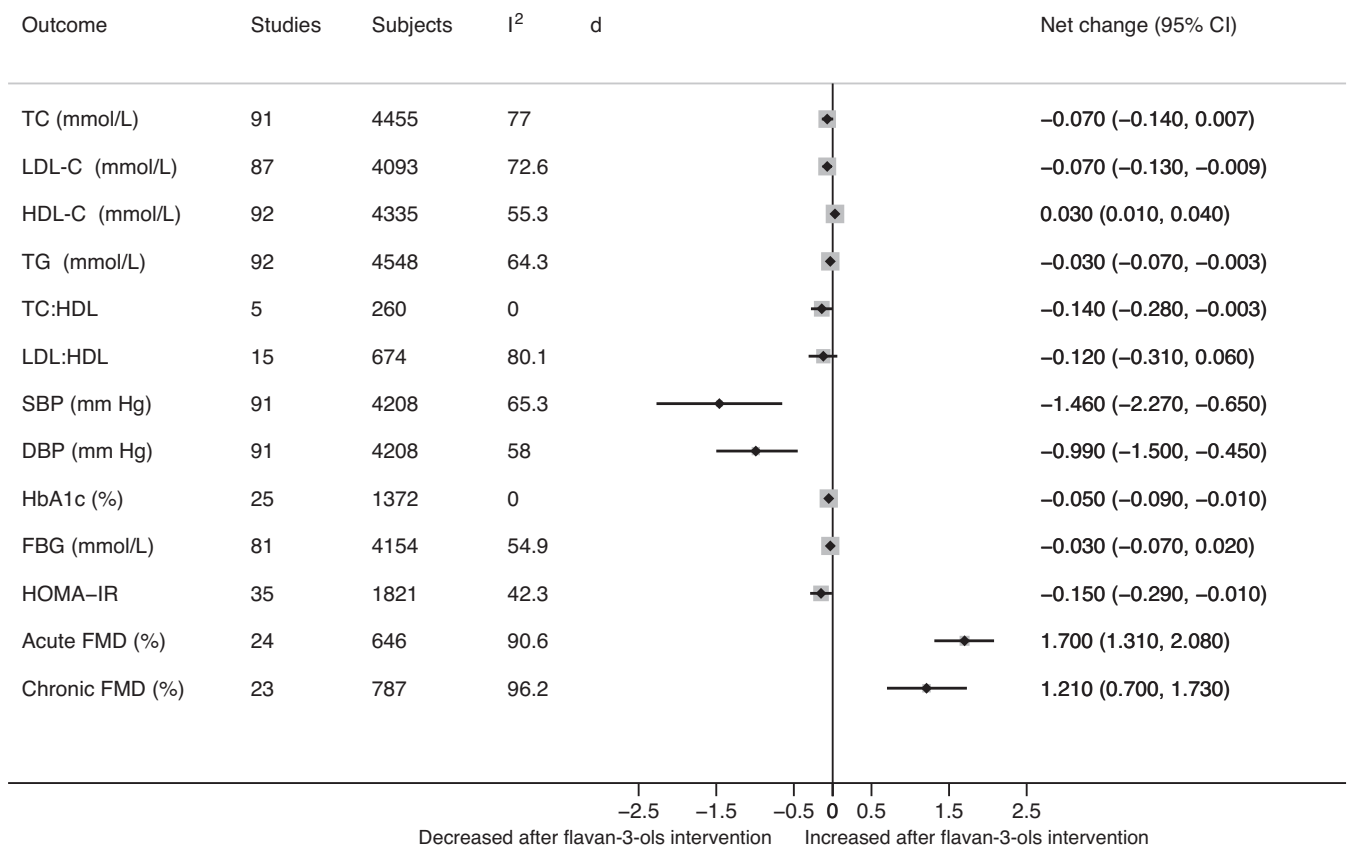
FIGURE 3 The effect of flavan-3-ols on cardiometabolic risk biomarkers from RCTs. Data estimates are from meta-analysis of the net change and 95% CI for each outcome. DBP, diastolic blood pressure; FBG, fasting blood glucose; FMD, flow-mediated dilation; HbA1c, hemoglobin A1c; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; RCT, randomized controlled trial; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

a significant increase in HDL cholesterol (net change: 0.03 mmol/L; 95% CI: 0.01, 0.04 mmol/L; $I^2 = 55.3\%$). There was no difference in serum TC and LDL cholesterol:HDL cholesterol. All lipid outcomes, except TC:HDL cholesterol, were associated with moderate to high heterogeneity.

When stratified by studies that reported components of flavan-3-ols, the change in serum LDL cholesterol, TC:HDL cholesterol, and HDL cholesterol remained significant comparing monomer intake with control, but all with moderate to high heterogeneity ($I^2 = 72.6\%$, $P < 0.001$; $I^2 = 0.0\%$, $P = 0.614$; $I^2 = 66\%$, $P < 0.003$, respectively). When stratified by studies that reported proanthocyanidins compared with control, only changes in serum TC:HDL cholesterol and HDL cholesterol remained significant—both without heterogeneity ($I^2 = 0.0\%$ and $I^2 = 16.0\%$, respectively). **Supplemental Tables 7–10** list data on TC, LDL cholesterol, HDL cholesterol, and TGs.

Blood pressure.

Meta-analysis of 91 RCTs comparing the effect of flavan-3-ols with controls on blood pressure showed a significant decrease in SBP (net change: −1.46 mm Hg; 95% CI: −2.27, −0.65 mm Hg; $I^2 = 65.3\%$) and DBP (net change: −0.99 mm Hg; 95% CI: −1.50, −0.45 mm Hg; $I^2 = 58.0\%$); both results were associated with moderate heterogeneity.

When stratified by studies that reported components of flavan-3-ols, the change in SBP and DBP remained significantly decreased for the comparison of monomers with controls, both with moderate heterogeneity ($I^2 = 65.9\%$ and $I^2 = 57.9\%$, respectively). When stratified by studies that reported proanthocyanidins compared with controls, the changes in SBP and DBP remained significantly decreased, but with moderate heterogeneity ($I^2 = 52.3\%$ and $I^2 = 61.2\%$, respectively) (**Supplemental Tables 11** and **12**).

Glucose metabolism.

Meta-analysis of RCTs comparing the effect of flavan-3-ols and controls on glucose metabolism parameters showed significant decreases in hemoglobin A1c (HbA1c) (27 RCTs, net change: −0.05%; 95% CI: −0.09%, −0.01%; $I^2 = 0.0\%$) without heterogeneity and in HOMA-IR (35 RCTs, net change: −0.15; 95% CI: −0.29, −0.01; $I^2 = 42.3\%$) with moderate heterogeneity. However, there was no difference in fasting blood glucose between groups.

When stratified by studies that reported components of flavan-3-ols, for the comparisons of monomers with controls, there was no difference in HbA1c, HOMA-IR, and fasting blood glucose outcomes. When stratified by studies

that reported proanthocyanidins compared with controls, only HbA1c remained significantly decreased, without heterogeneity ($I^2 = 0$%), and for both other outcomes there was no difference between proanthocyanidins and controls (**Supplemental Tables 13–15**).

Endothelial function.

Acute FMD. Meta-analysis of 24 RCTs comparing the effects of flavan-3-ols with controlsshowed a significant increase in the acute FMD response measured from 1 to 6 h (net change: 1.70%; 95% CI: 1.31%, 2.08%; $I^2 = 90.6$%), with high statistical heterogeneity. When stratified by studies that reported components of flavan-3-ols, there was a significant increase in acute FMD with monomer or proanthocyanidin interventions, as compared with the control group—both with high heterogeneity ($I^2 = 90.6$% and $I^2 = 91.5$%, respectively) (**Supplemental Table 16**).

Chronic FMD. Meta-analysis of 23 RCTs comparing the effect of flavan-3-ols with controls showed a significant improvement in chronic FMD measured after a few weeks of intervention (1–26 wk) (net change: 1.21%; 95% CI: 0.70%, 1.73%; $I^2 = 96.2$%), with high heterogeneity. When stratified by studies that reported components of flavan-3-ols, there was a significant increase in chronic FMD with monomer or proanthocyanidin interventions, as compared with the control group—both with high heterogeneity ($I^2 = 96.4$% and $I^2 = 92.1$%, respectively) (**Supplemental Table 17**).

Inflammatory biomarkers.

Meta-analysis of RCTs on inflammatory biomarkers found no difference between flavan-3-ols and controls for these outcomes: hsCRP (net change: 0.008 mg/L; 95% CI: −0.015, 0.030 mg/L; $I^2 = 0.0$%), IL-6 (net change: −0.05 pg/mL; 95% CI: −0.13, 0.22 pg/mL; $I^2 = 11.8$%), and TNF-α (net change: −0.20 pg/mL; 95% CI: −0.48, 0.08 pg/mL; $I^2 = 65.4$%).

Sensitivity analyses.

In sensitivity analyses, limiting analyses to RCT studies with a low risk of bias (good methodological quality), although there was no difference between flavan-3-ols and controls for serum lipids including LDL cholesterol and TGs, or glucose metabolism outcomes including HbA1C or fasting blood glucose (and there was no heterogeneity in these results) (Supplemental Tables 7–17), the following outcomes remained significant after flavan-3-ol interventions: TC (net change: −0.06 mmol/L; 95% CI: −0.11, −0.001 mmol/L; $I^2 = 0.0$%); HDL cholesterol (net change: 0.02 mmol/L; 95% CI: 0.001, 0.05 mmol/L; $I^2 = 0.0$%); SBP (net change: −1.29 mm Hg; 95% CI: −2.45, −0.13 mm Hg; $I^2 = 44.4$%) and DBP (net change: −1.24 mm Hg; 95% CI: −2.13, −0.34 mm Hg; $I^2 = 58.7$%); HOMA-IR (net change: −0.29; 95% CI: −0.48, −0.10; $I^2 = 0.0$%), and acute (net change: 1.15%; 95% CI: 0.71%, 1.59%; $I^2 = 89.0$%) and chronic FMD (net change: 1.30%; 95% CI: 0.59%, 2.00%; $I^2 = 81.7$%).

In additional sensitivity analyses, excluding studies that recruited participants with existing CVD did not alter the main results for all outcomes (Supplemental Tables 7–17).

Dose–response.

When studies were stratified by quartiles of median flavan-3-ol intake, intervention dosages in the first quartile (<220 mg/d) significantly decreased SBP and DBP and significantly increased FMD and HDL cholesterol. Intervention dosages in the second quartile (401–661 mg/d) significantly decreased HbA1c; in the third quartile between ~550 and 850 mg/d they significantly decreased LDL cholesterol, SBP, and HOMA-IR and significantly increased HDL cholesterol and FMD. Intervention dosages >800 mg/d significantly decreased TC, SBP, and DBP and significantly increased FMD (Supplemental Tables 7–17). There was no difference in TGs or fasting blood glucose by quartiles of median flavan-3-ol intake (Supplemental Tables 7–17). Meta-regression found no linear relations between net change in all outcomes and flavan-3-ol dosage.

Subgroup analyses.

Analyses by duration of intervention found that interventions >3 mo long significantly increased HDL cholesterol and decreased TGs, SBP, DBP, HbA1c, and HOMA-IR, but results were nonsignificant for TC, LDL cholesterol, and FMD.

In terms of the dietary form by which the flavan-3-ols were consumed, cocoa and tea significantly increased both the acute and chronic FMD responses, but fruit interventions only significantly increased the acute FMD response. Cocoa and fruit significantly decreased SBP and cocoa, fruit, and pure form significantly decreased DBP. Extracts decreased TC, LDL cholesterol, and TGs. In addition to extracts, cocoa and fruit also decreased TGs. For HDL cholesterol, there was no difference across intervention types. Cocoa also significantly decreased HOMA-IR and the pure form of flavan-3-ol significantly decreased HbA1c (Supplemental Tables 7–17).

Overall strength of evidence among RCTs.

There was moderate strength of evidence that flavan-3-ol intake increases HDL cholesterol and decreases TC, SBP, and HOMA-IR and a low strength of evidence that flavan-3-ol intake decreases DBP and improves FMD (both acute and chronic) (**Supplemental Table 18**).

Discussion

To our knowledge, this is the first review that has systematically examined the potential cardiometabolic health effects of flavan-3-ols per se (irrespective of source), integrating all available evidence from both prospective cohort studies and RCTs. We showed that higher habitual flavan-3-ol intakes were associated with a reduction in risk of CVD mortality (13%) and incident CHD (19%); higher habitual intakes of monomers were associated with a reduction in risk of T2DM (10%) and stroke (18%); and these data were calculated to be of moderate

strength after GRADE analyses. In RCTs, when we restricted analyses to good methodological quality interventions (low risk of bias), flavan-3-ols improved FMD, the gold-standard measure of endothelial function, acute (1.7%) and chronic FMD (1.14%), TC (−0.06 mmol/L), HDL cholesterol (0.02 mmol/L), SBP and DBP (−1.29 and −1.24 mm Hg, respectively), and HOMA-IR (−0.18). Although many of the biomarkers assessed were associated with significant statistical heterogeneity, after GRADE analyses, the strength of evidence was moderate that flavan-3-ol intervention decreases TC, SBP, and HOMA-IR and increases HDL cholesterol, whereas the strength of evidence for FMD and DBP was graded low.

Even though the evaluated populations in the prospective cohorts were high in number, the evidence primarily came from a few cohort studies and the number of cohorts was sparse. However, the available population-based data together with the supportive mechanistic data from RCTs provide growing evidence that flavan-3-ols may be important for cardiometabolic health. The magnitude of improvement in blood pressure and conduit artery endothelial function in the RCTs merits discussion because this translates into a significant reduction in future cardiovascular events based on previous meta-analysis (49). The authors showed that each 1% increase in FMD was associated with a relative risk of cardiovascular events of 0.87 (95% CI: 0.83, 0.91); the 1.14% chronic improvement in FMD would have important consequences for CVD risk and in combination with the small, but robust, improvements in HDL cholesterol, blood pressure, and HOMA-IR may be substantial. Our RCT results concur with 2 previous meta-analyses that only evaluated a limited number of foods and reported beneficial effects on outcomes including HDL cholesterol, blood pressure, HOMA-IR, and FMD (7, 50). Similar to their review, we did not find a linear relation between flavan-3-ol intake and outcomes of interest. Although our results concurred for LDL cholesterol, the beneficial effects of flavan-3-ol effects disappeared in sensitivity analyses of good methodological quality (low risk of bias) studies.

The molecular mechanisms by which dietary flavan-3-ols mediate these effects on vascular health include nitric oxide–dependent arterial function (51, 52), anti-inflammatory effects (53), and effects on glucose metabolism, β-cell function, and inhibition of glucose transporters (54–57). However, early mechanistic studies did not consider the absorption, distribution, metabolism, and excretion of the flavan-3-ols. After ingestion flavan-3-ols are extensively metabolized and transformed, with recent data suggesting that the gut microbiome–derived metabolites mediate the vascular-protective effects; recent data provide evidence for endothelium-protective effects of gut microbiome–derived circulating flavan-3-ol metabolites specifically through dynamic regulation of endothelial cell monocyte adhesion and permeability (52).

The GRADE analyses highlight an issue which affects many nutrition research trials: the fact that many conducted studies are of poor quality (high risk of bias). These data, like for many other areas of nutrition research, highlight the need to design and conduct higher-quality RCTs. For example, 70–72% of the trials that assessed lipid profiles were calculated to be of low quality (Supplemental Tables 7–10); for blood pressure 65% were of low quality although 30 trials had good-quality evidence (Supplemental Tables 11–12). Although systematic review and

meta-analysis approaches give a valuable insight into the state of the art for the flavan-3-ol evidence base, an inevitable limitation of the approach is the quality and scientific rigor of the included data, which needs to be considered in interpreting the results. However, the focus on only good methodological studies and the use of GRADE have allowed us to highlight the findings that remained significant when sensitivity analyses were restricted to the good-quality data.

We reviewed a large number of RCTs that either reported or had estimable flavan-3-ol content; our results are generalizable across a variety of sources rich in flavan-3-ols. Included cohorts examined a wide range of dosages of flavan-3-ols; the mean daily intake of flavan-3-ols in the United States is <200 mg/d (58), whereas in some cohorts dosages ≤1400 mg/d (36) were observed and total flavan-3-ol dosages in included RCTs ranged from 40 to 1540 mg/d. Only a handful of cohorts conducted both baseline and subsequent flavan-3-ol intake assessment. Most cohorts relied on a single baseline flavan-3-ol intake measure to evaluate an association between flavan-3-ol intake and CVD outcomes during follow-up, thereby making an assumption that flavan-3-ol intake did not change over time. Only 1 long-term RCT evaluated clinical outcomes: risk of CHD and stroke (48). From the currently available data, flavan-3-ol content from cocoa and fruits found the greatest number of improved outcomes, followed by the pure form, tea, and extracts.

Current epidemiological data solely rely on self-reported intake, with estimates of flavan-3-ol exposure calculated from food composition databases. Although these data can clearly differentiate between extremes of intake, current data do not account for the extensive metabolism these compounds undergo after ingestion. Future cohort studies should therefore integrate biomarker and dietary assessment methods to more accurately determine the relative importance of specific flavan-3-ols and their metabolites for cardiovascular health. This would also allow a more accurate determination of the relative importance of the different components of flavan-3-ol intake. Another limitation of the available data relates to the number of RCTs that had not independently calculated the flavan-3-ol content (estimated in 75 RCTs). By estimating intakes using a standardized approach, this allowed us to include these 75 RCTs in our analyses. There was considerable heterogeneity in terms of the dosages examined in both cohorts and RCTs, which precludes firm conclusions on the dosage required for health effects. Furthermore, the significance of many of the results from RCTs disappeared in sensitivity analyses of good methodological quality studies; only the data for TC, HDL cholesterol, BP, HOMA-IR, and FMD remained significant. A major strength of our approach includes the integration of flavan-3-ol intake from a range of sources and by focusing on good methodological studies and conducting GRADE we highlight the key research gaps in the field.

In conclusion, the beneficial effect of flavan-3-ols on cardiometabolic outcomes is evident from both cohort studies and RCTs. However, it is imperative that future cohort studies integrate biomarker and dietary assessment methods to more accurately determine the relative importance of specific flavan-3-ols and their metabolites for cardiovascular health. Moreover, high-quality dose–response RCTs are needed to further understand the relative importance of flavan-3-ol source and metabolism for cardiometabolic health.

The authors' responsibilities were as follows—GR, JAN, and AC: conceived and designed the study; GR, EEA, SC, JW, JM, and BG: performed the data extraction and quality assessment; GR and EEA: synthesized and analyzed the data; GR, EEA, and AC: interpreted and further analyzed the data; GR, EEA, BG, and AC: wrote the paper; GR: had primary responsibility for final content; and all authors: read and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

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