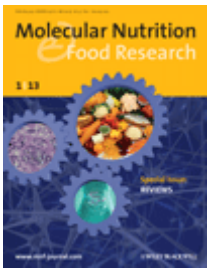
Dietary Flavonoids and Cardiovascular Disease: A Comprehensive Dose–Response Meta-Analysis



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Dietary flavonoids and cardiovascular disease: a comprehensive dose-response meta-analysis

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Abbreviations:

CHD coronary heart disease

CIs confidence intervals

CVD cardiovascular disease

DALYs disability-adjusted life-years

FFQ food frequency questionnaire

FMD flow-mediated dilation

HRs hazard ratios

MOOSE meta-analysis of observational studies in epidemiology

NF-Kβ nuclear factor kappa-light-chain-enhancer of activated B cells

NO nitric oxide

NOS newcastle-ottawa quality assessment scale

Nrf2 nuclear factor erythroid 2-related factor 2

RCTs randomized controlled trials

RRs relative risks

TNF- α tumor necrosis factor

Keywords: cardiovascular diseases; cohort; flavonoid; meta-analysis; stroke.

Abstract

Scope Dietary flavonoids have shown potential in the prevention of non-communicable diseases. The aim of the present study was to conduct a dose-response meta-analysis on the association between dietary intake of total, subclasses and individual flavonoids and risk of cardiovascular disease (CVD). **Methods and results** Electronic databases were searched. A total of 39 prospective cohort studies were included, comprising 1,501,645 individuals and a total of 33,637 cases of CVD, 23,664 of coronary heart disease (CHD), and 11,860 of stroke. Increasing dietary intake of total flavonoids was linearly associated with lower risk of CVD. Among the main classes of flavonoids, increasing intake of anthocyanins and flavan-3-ols was inversely associated with risk of CVD, while flavonols and flavones with CHD. Only increasing flavanones showed a linear inverse association with stroke risk. Catechins showed a favourable effect toward all cardiovascular outcomes. Among individual compounds, intake of quercetin and kaempferol was linearly associated with lower risk of CHD and CVD, respectively. However, higher intake of all the aforementioned compounds was associated, with a various extent, to lower risk of CVD when considering comparison of extreme categories of consumption. **Conclusion** The results of this study provide evidence of potential cardiovascular benefits of a flavonoid-rich diet.

Introduction

In 2017, cardiovascular disease (CVD) has been estimated to have caused 17,8 million deaths worldwide.[1] Among the leading modifiable risk factors, dietary risks accounted for 10,9 million deaths and 255 million disability-adjusted life-years (DALYs) worldwide.[2] Epidemiological research has globally demonstrated that dietary patterns rich in plant-based foods may play an important role in reducing the risk of CVD. Together with high consumption of fruit and vegetables,[3] other dietary components such as olive oil,[4] nuts,[5] whole-grains,[6] cocoa,[7] coffee[8] and tea[9] have been reported to exert beneficial effects toward CVD. Based on current evidence, public health experts advocate for healthier diets in order to achieve significant improvements in decreasing the global burden of CVDs.[10, 11] Besides their content in vitamins and fiber, the aforementioned food groups are known for a relatively high content in polyphenols.[12] These compounds are bioactive molecules with diverse chemical structure, bioavailability, and biological activity, catabolised by the gut microbiome into smaller phenolic and aromatic acids.[12]

Dietary polyphenols have been shown to modulate multiple cell pathways, mainly through exerting anti-oxidant and anti-inflammatory properties, ultimately with potential positive effects toward human health. Previous comprehensive analyses of observational studies showed an inverse association between dietary flavonoid intake and mortality, including CVD related mortality,[13] risk of hypertension,[14] as well as cancer risk and survival.[15] Meta-analyses of intervention trials also showed the potentiality of specific flavonoids in positively affecting intermediary cardiovascular biomarkers, such as endothelial function, blood pressure, blood lipids,[16–18] and mediators of inflammation.[19] Recently, a systematic review pointed out possible implications of dietary flavonoids in cardiovascular health.[20] However, it is of paramount importance to assess and quantify the association between dietary flavonoid intake and risk of CVD among existing prospective cohort studies. A

previous meta-analysis evaluated the association for total flavonoid intake and risk of CVD but did not take into account individual classes nor provided dose-response analysis.[21] Moreover, distinction between type of CVD, such as coronary heart disease (CHD) and stroke, have not been provided. Thus, the aim of the present study was to update and provide a more comprehensive estimate of the association between dietary flavonoid intake, individual subclasses and compounds and risk of CVDs in prospective cohort studies.

Materials and methods

The reporting and methodology were conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Supporting information Table S1).

Study selection

To find all relevant reports we performed systematic search of Pubmed (http://www.ncbi.nlm.nih.gov/pubmed/) and EMBASE (http://www.embase.com/) databases. Only articles published in English-language up to January 2020 were included. Search strategy comprised clue terms defining the exposure, outcome and study type. The consecutive words and phrases were combined with conjunction: (i) polyphenols OR flavonoids OR isoflavones OR soy OR phenolic OR anthocyanins OR flavan-3-ols OR flavones OR flavonoids OR flavanones OR catechins AND (ii) cardiovascular OR ischaemic heart disease OR myocardial ischemia OR ischemic heart disease OR coronary artery disease OR coronary heart disease OR stroke OR myocardial infarction OR cerebral infarction AND (iii) cohort studies OR longitudinal studies OR prospective OR follow-up. The search terms and strategy used for the study selection is shown in Supporting information Table S2. Studies were included in the meta-analysis if met the following criteria: (i) having prospective design; (ii) reporting dietary intake of total/classes/individual flavonoids as the exposure of interest; (iii)

reporting hazard ratios (HRs) or relative risks RRs (as equivalent measure) and the corresponding 95% confidence intervals (CIs) for exposure divided to at least 3 categories, (iv) being published in English language (v) reporting on the incidence of CVD or its subtype as an outcome variable. We excluded: (i) non-original research and intervention trials (commentaries, editorials or reviews); (ii) studies lacking sufficient statistics (method with other measures of association than RRs or RRs given only for linear association); (iii) studies with appropriate results given only for outcome other than CVD. Reference lists of selected manuscripts were additionally examined to find any study not previously identified. If more than one article characterising the same cohort was published, only the study describing the entire cohort or with the longest follow-up was included. The selection process was independently performed by two authors (J.G. and G.G.).

Data extraction and study quality

Data was abstracted from selected studies using a standardized extraction form collecting the following information: 1) first author name; 2) study cohort name; 3) countries where the studies were conducted; 4) year of publication; 5) sex of participants; 6) number of participants; 7) age of examined population at baseline; 8) follow-up period; 9) type of dietary assessment instrument; 10) endpoints; 11) distributions of cases and person-years, HRs/RRs, and 95% CIs across categories of exposure; 12) covariates used in adjustments. This process was independently performed by two authors (A.M. and G.G.) and discrepancies were discussed and resolved by consensus.

The quality of studies was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS),[22] which consists of 3 domains: selection (4 points), comparability (2 points), and outcome (3 points) for a total score of 9 points (higher score represents the higher quality).

Statistical analysis

The analyses were conducted for total flavonoid intake as well as for individual subclasses and compounds. When a study reported results separately for sex and for both in total, we included sex-specific estimations in analyses. As a measure of the association HRs or RRs with 95% CIs for all categories of exposure were extracted; both were deemed equivalently and further referred to as RRs. We collected only the most fully adjusted RRs from articles. The mean or median or midpoint of the range of intake in each category of flavonoid was assigned to the corresponding RR. To obtain summary statistics across the studies, the individual results were combined by random-effects meta-analyses. Heterogeneity was assessed by Cochran's Q test and I2 statistic. The amount of total variation attributed to heterogeneity was categorised as no, small, moderate and high, according to following categories of I2 values: <25%, 25–50%, 50–75%, and >75%, respectively. The level of significance of the Q test was set equal to 0.10. Dose-response relationship was modelled by restricted cubic splines with three knots at fixed percentiles of the flavonoid distribution (10%, 50%, and 90%).[23] Meta-analysis was conducted in two-stages. Firstly, study-specific coefficients were estimated on the basis of the results across the categories of flavonoid intake. The generalised least squares method was applied regarding the correlation within each set of retrieved RRs.[24, 25] Missing data on distribution of the number of participants/person-years or cases across categories of flavonoids were the prerequisite for using standard weighted least squares meta-regression.[24] By the multivariate extension of the method of moments between-study covariance matrices were assessed. Significant non-linearity was checked by testing whether the coefficient of the second spline was equal to zero. A sensitivity analysis by exclusion of one study at the time was conducted to assess the stability of the results and to detect the potential sources of heterogeneity. Subgroup analyses were performed for extreme categories of flavonoid consumption (highest versus lowest) by

grouping according to the following conditions: distinguishing between cardiovascular risk and mortality, sex, geographical area, follow-up time, sample size, quality of the study and adjustment for energy intake, diabetes status, BMI and dietary factors was performed. Publication bias was evaluated by visual inspection of funnel plots for potential asymmetry. All analyses were conducted using R software (Development Core Team, Vienna, Austria, version 3.6.1). Significance, except of Cohran's Q test, was set below the probability level of 0.05.

Results

Study selection

The article selection process is shown in Figure 1. Out of 46 studies evaluated in extenso, seven were excluded because of completely lack of RRs with 95% CIs or availability of estimations only for linear dose-response association (n = 3), or for soy food or specific classes of polyphenol not considered in the review (n = 4), leaving 39 articles for inclusion in the meta-analysis.[26–64]

Characteristics of the studies included

The studies included 1,501,645 individuals and a total of 33,637 cases of CVD, 23,664 of coronary heart disease (CHD), and 11,860 of stroke. The countries where the studies were conducted were US (n = 12),[29, 32, 35, 38, 41, 43, 45–47, 55, 57, 58] Europe (n = 21),[26–28, 30, 31, 33, 34, 36, 37, 39, 40, 44, 49, 52, 53, 56, 60–64] Asia (n=5),[42, 48, 50, 54, 59] Australia (n=1).[51] Food frequency questionnaires (FFQs) were used as a tool to collect dietary information in 28 studies [29, 30, 32, 33, 35, 36, 38, 40–43, 45–52, 54, 55, 57–59, 61–64] while dietary history interviews were used in 11 studies.[26–28, 31, 34, 37, 39, 44, 53, 56, 60] In order to estimate the dietary flavonoid intake, 8 studies used the Phenol-Explorer, 11 used the USDA (among which 2 used it in conjunction with

Phenol-Explorer) and 22 used other databases (Table 1 and Supporting information Table S3). Based on the evaluation of the NOS criteria, the majority of the studies scored high quality (NOS = 7 or more) (Supporting information Table S4).

Association between flavonoid intake and CVD

The summary RR for the highest versus the lowest category of total flavonoid intake from 8 cohorts was 0.81 (95% CI: 0.71-0.91), with moderate heterogeneity (I^2 = 62%) and no publication bias (p = 0.073 from Egger's test) (Figure 2 and Supporting information Figure S1). Among individual main classes of flavonoids, individuals with the highest intake of flavonols (RR = 0.85, 95% CI: 0.79-0.91; I^2 = 28%), flavanones (RR = 0.88, 95% CI: 0.79-0.98; I^2 = 63%), flavan-3-ols (RR = 0.85, 95% CI: 0.76-0.95; I^2 = 67%), catechins (RR = 0.75, 95% CI: 0.63-0.89; I^2 = 0%), proanthocyanidins (RR = 0.83, 95% CI: 0.73-0.95; I^2 = 54%), and anthocyanins (RR = 0.82, 95% CI: 0.70-0.96; I^2 = 75%) showed lower risk of CVD compared to those with the lowest intake; however, only results for flavonol intake were consistent and showed no heterogeneity (Table 2, Supporting Information Figure S2). No publication bias was detected for all analyses except for small asymmetry of funnel plot for proanthocyanidins (evidence from Egger's test is limited due to small number of studies included) (Supporting information Figure S3).

The dose-response analysis performed on 8 cohorts showed a linear decreased risk of CVD for increasing intake of flavonoid intake (Figure 3); compared to hypothetical no consumption, intake up to 500 mg/d of total flavonoids was associated with 27% lower risk of CVD (RR = 0.73, 95% CI: 0.62-0.86) despite with evidence of moderate heterogeneity among results (I^2 = 51%) (Table 3). The subgroup analysis by CVD outcome revealed that risk for both CVD incidence and mortality was reduced with increasing intake of total flavonoids, despite wider CIs have been observed for the former (Table 3). Among individual

main classes of flavonoids (Supporting information Table S5), anthocyanins and flavan-3-ols showed a linear decreasing risk of CVD for higher intakes, with small/moderate evidence of heterogeneity (RR = 0.90, 95% CI: 0.83-0.98; I^2 = 48% and RR = 0.91, 95% CI: 0.83-1.00 for 200 mg/d of flavan-3-ols, I^2 = 59%). Only one study supplied data sufficient to calculate a dose-response for individual compounds and showed a decreasing risk of CVD for higher intake of kaempferol (RR = 0.75, 95% CI: 0.56-1.00).

Association between flavonoid intake and CHD

In the meta-analysis comparing extreme categories, no association between total flavonoid intake and CHD risk was observed (Figure 2). In contrast, a consistent relationship with reduced risk of CHD was observed in studies exploring the intake of flavonols and flavones (RR = 0.86, 95% CI: 0.77-0.97; I^2 = 34%), catechins (RR = 0.81, 95% CI: 0.68-0.97; I^2 = 0%), proanthocyanidins (RR = 0.79, 95% CI: 0.65-0.97; I^2 = 50%), and anthocyanins (RR = 0.79, 95% CI: 0.64-0.98; I^2 = 66%), and a marginally significant association with large CIs was shown in studies exploring the intake of flavonols (RR = 0.90, 95% CI: 0.80-1.01; I^2 = 0%) and flavan-3-ols (RR = 0.93, 95% CI: 0.86-1.01; I^2 =0%). Small asymmetry of funnel plot was detected only for anthocyanidins, despite the limited number of studies investigated and the low power of Egger's test (Supporting information Figure S3). Among individual compounds, individuals with higher intake of both quercetin and kaempferol (in borderline) had lower risk of CHD, with no evidence of heterogeneity nor publication bias, despite the wide CIs (Table 2, Supporting Information Figure S2).

The dose-response analysis showed a decreasing risk of CHD for higher intake of total flavonoids, despite the association was not linear, reaching a plateau for 400 mg/d (RR = 0.75, 95% CI: 0.61-0.94; I^2 = 1.0%; Table 3 and Figure 3). Both CHD incidence and mortality risk were decreased with higher intake of flavonoids, despite nonsignificant results

for the highest intake and a nonlinear association were evident for the latter (Table 3). Among individual classes of flavonoids, the strongest association with decreasing risk of CHD for higher intake of flavonols and flavones was found with an optimal intake equal to 18-24 mg/d (RR = 0.88, 95% CI: 0.81-0.97; for 30 mg/d of intake, I^2 = 1%; Supporting information Table S6). Among individual compounds, the summary risk estimates from 5 studies showed a decreased risk of CHD for higher intake of quercetin, despite the association with the lowest risk was observed for up to 12-14 mg/d (RR = 0.72, 95% CI: 0.66-0.78; for 12 mg/d of intake, I^2 = 1%; Supporting information Table S5).

Association between flavonoid intake and stroke

The highest consumption of total flavonoids was not associated with a significant change of stroke risk compared to no consumption (Figure 2); among individual subgroups of flavonoids, flavanones intake was associated with 14% reduced risk of stroke (RR = 0.86, 95% CI: 0.77-0.96) with no evidence of heterogeneity (I^2 = 0%) nor publication bias (Table 2, Supporting Information Figure S2 and Supporting information Figure S3). Also, higher intake of catechins was associated inversely with risk of stroke (RR = 0.70, 95% CI: 0.55-0.88; I^2 =0%). Among individual compounds, two studies showed that individuals with a higher intake of kaempferol were less likely to have stroke compared to those with lower intake (RR = 0.72, 95% CI: 0.59-0.88, I^2 = 0%; Table 2, Supporting Information Figure S2).

The dose-response analysis demonstrated a decreasing risk of stroke for higher intake of total flavonoids up to 400 mg/d (RR = 0.79, 95% CI: 0.63-1.00 for 400 mg/d of intake), with no evidence of heterogeneity (I^2 = 1%); when considering stroke incidence and mortality risk separately, a marginally significant association was observed for the former (Table 3). Among individual compounds, only flavones and flavanones consumption was associated with reduced risk of stroke with a decreasing trend across higher intake. Significant results

were found for 1.2-1.6 mg/d intake of flavones (RR = 0.37, 95% CI: 0.22-0.64; for 1.6 mg/d), but a high between studies heterogeneity was observed (I^2 = 98%), and for up to 36 mg/d intake of flavanones (RR = 0.79, 95% CI: 0.63-0.98; I^2 = 1%; Supporting information Table S5).

Association between lignan intake and CVD outcomes

Higher dietary intake of lignan was not associated with lower risk of none of the explored outcomes including CVD (RR = 0.82, 95% CI: 0.65-1.04; I^2 = 40%), CHD (RR = 0.82, 95% CI: 0.65-1.01; I^2 = 1.0%), and stroke (RR = 0.92, 95% CI: 0.71-1.19; I^2 = 0%). Similar results were found when exploring the dose-response association between dietary lignan intake and risk of cardiovascular outcomes (Supporting Information Table S5).

Stratified and subgroup analyses

In order to evaluate stability of the results and role of potential confounding factors, a sensitivity analysis by excluding one study at a time (data not shown) and by excluding studies with no complete data on number of cases/person-years, as well as stratified analyses, were performed and revealed no substantial differences from the main analysis (Supporting information Table S6).

Subgroup analyses for the association between total flavonoid intake and CVD risk (fatal/non-fatal) are reported in Table 4. The results were mainly stable across most subgroups, including CVD outcome (incidence/mortality), location (US/Europe), follow-up (10-year cut off), adjustment for energy intake and other dietary factors. Moreover, subgroup analysis by sex depicted marginally significant results only for women (Table 4). Although studies adjusting for BMI showed a decreased risk of CVD when compared to those not adjusting, a different result was observed for adjustment for type-2 diabetes. Specifically, a

decreased risk of CVD for higher intake of flavonoids was found in studies not adjusting for type-2 diabetes, but lack of association was found in those that adjusted the results (Table 4).

Discussion

In this comprehensive meta-analysis, we found that higher dietary intake of total flavonoids is associated with lower risk of CVD in a linear manner (with the highest intake calculated at 500 mg/d); specific CVD outcomes were both CHD and stroke, despite the lowest risk was reached at 400 mg/d for the former. Among the main classes of flavonoids investigated, anthocyanins and flavan-3-ols are the best candidate to provide the strongest protection against CVD, while higher intake of flavonols and flavones resulted associated with lower risk of CHD; regarding stroke risk, flavanones were the most relevant class, despite the lowest risk was reached for relatively low consumption. Among individual compounds, intakes of quercetin and kaempferol were linearly associated with lower risk of CHD and CVD, respectively. Finally, higher dietary intake of lignan has not been significantly associated with none of the investigated outcomes, however possibly due to the limited number of analyzed studies. These findings significantly update results from previous meta-analyses, which had several limitations, including lack of focus on individual compounds or specific cardiovascular outcomes (i.e., only stroke or CHD), misclassification of flavonoid groups, and lack of dose-response analysis.

The results of this study support the evidence provided by meta-analyses of clinical randomized controlled trials (RCTs) on total and individual classes of flavonoids and major cardiovascular intermediary biomarkers.[65] Among them, flavan-3-ols have been demonstrated to improve flow-mediated dilation (FMD), considered the gold standard measure of endothelial function, blood lipids levels, systolic and diastolic blood pressure, and

HOMA-IR.[19] Also meta-analyses of RCTs on anthocyanins and anthocyanin-rich foods showed significant improvements in glycemic control and blood lipids levels,[66] as well as FMD and pulse wave velocity,[67] supporting the benefits of anthocyanins in the prevention and management of cardiometabolic disease. Evidence from RCTs on flavonols showed improvement in cardiometabolic biomarkers, including reduction of total cholesterol, LDL cholesterol, triacylglycerol, fasting plasma glucose, blood pressure, and an increase in HDL cholesterol.[68]

Various mechanisms providing the rationale for the potential protective effects of dietary flavonoids on cardiovascular health have been described.[69] Flavonoids have proved to enhance the bioavailability and bioactivity of nitric oxide (NO) and other vascular relaxing factors (such as endothelium-derived hyperpolarizing factor and prostacyclin), which in turn might ameliorate vascular parameters, including vasodilation, platelet adhesion, and smooth muscle proliferation in the vessel wall.[70] Moreover, flavonoids have been shown to exert antioxidant and anti-inflammatory actions by modulating the expression of proteins involved in the control the anti-inflammatory nuclear factor erythroid 2-related factor 2 (Nrf2) pathway and the pro-inflammatory nuclear factor kappa-light-chain-enhancer of activated B cells (NF-Kβ) pathway, which it turn may lead to free radical scavenging, inhibition of the activity and/or expression of pro-inflammatory enzymes, and down-regulation of pro-inflammatory mediators (such as tumor necrosis factor-alpha TNF-α, interleukin IL-1b, and IL-6).[71] Finally, it has been also hypothesized that intake of dietary flavonoid may affect gut microbiome, which through the modulation of inflammation may influence biomarkers of cardiovascular risk.[72]

The present study has a number of strengths, as i) it included analyses for the highest number of compounds (subgroups and individual flavonoids) with a dose-response approach; ii) a proper evaluation of the exposure allowed for a correct classification of flavonoid groups, avoiding inaccurate comparisons; iii) the investigated outcomes allowed separating CVD risk and mortality, as well as specific subgroups of disease (CHD and stroke). However, the proposed findings should be also considered in light of some limitations. First, they are based on risk estimates extracted from observational population studies, which do not allow to fully assess a cause-effect relation; thus, the retrieved association may still be suffering from reverse causation, unmeasured confounding factors (including the role of potential effect modifiers and multicollinearity), and lack of adjustment for covariates potentially affecting the association. Second, although intuitive, it should be acknowledged that bioactive compounds are likely to also act synergistically with other compounds present in plant-based foods such as fiber, vitamins and other bioactive compounds, and that their effects may depend on the pattern of food consumed and on personal host microbiota, with a certain degree of inter-person variability in absorption, metabolism, and activity of dietary flavonoids that cannot be eliminated from this type of studies. Third, data on polyphenols included in the examined studies is estimated from FFQs or dietary recalls and then calculated from food composition databases, which may lead to two important limitations (besides the potential recall bias): the databases used in some studies may be outdated, lacking in some food sources of flavonoids or on retention factor for each group of compounds following cooking or variability directly related to food quality (plant variety, season and environmental factors, food storage and processing); and (ii) the current methodology does not take into account the metabolism and transformation of flavonoids after ingestion, thus potentially missing the identification of the compounds that really exert the desired effects.

In conclusions, the results of this study provide further evidence of the potentiality of a flavonoid-rich diet toward CVDs prevention. Plant-based diets with selected key foods might represent a valuable resource against the rising trends of the world's leading cause of death. Nevertheless, future research on flavonoids should focus also on inter-individual variability in the flavonoid metabolism linked to gut microbiome and nutrients interactions and aiming to explore not only dietary intake but also true exposure to their metabolites conditioned on the microbial species diversity.

Author contributions: conceptualization and methodology, A.M., J.G., G.G.; formal analysis and data curation, A.M., G.G.; writing, review and editing, A.M. J.G., D.D.R., F.G., G.G.

Conflict of interest: Authors declare that there is no conflict of interest.

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Figure legend

Figure 1. Flow chart of study selection process.

Figure 2. Summary relative risks for the highest *versus* the lowest category of total flavonoid intake and risk of cardiovascular disease, coronary heart disease and stroke.

Figure 3. Graphical representation of dose-response meta-analysis for total flavonoid intake and risk of cardiovascular disease, coronary heart disease and stroke.

Table legend

Table 1. Main characteristics of included studies in the meta-analysis.

Table 2. Summary relative risks for the highest *versus* the lowest category of individual classes of flavonoids and lignan intake and risk of cardiovascular disease, coronary heart disease and stroke.

Table 3. Dose-response meta-analysis for total flavonoid intake and risk of cardiovascular disease, coronary heart disease and stroke.

Table 4. Subgroup analyses by potential confounding factors for the association between the highest *versus* the lowest intake of total flavonoids and cardiovascular disease risk.

Supporting information legend

Supporting information Table S1. The Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.

Supporting information Table S2. Search strategy.

Supporting information Table S3. Characteristics of tools and measurements used to assess dietary intake in meta-analysed studies.

Supporting information Table S4. Assessment of quality of included studies using the Newcastle-Ottawa Quality Assessment Scale (NOS).

Supporting information Table S5. Dose-response meta-analysis of the association between individual classes of flavonoids intake and cardiovascular outcomes in prospective cohort studies.

Supporting information Table S6. Dose-response meta-analysis of the association between individual classes of flavonoids intake and cardiovascular outcomes in prospective cohort studies restricted only to studies with complete data about cases and person-years for each category of intake.

Supporting information Figure S1. Funnel plots for meta-analysis for the highest *versus* the lowest category of total flavonoid intake and risk of cardiovascular disease, coronary heart disease and stroke.

Supporting information Figure S2. Forest plots for meta-analysis for the highest versus the lowest category of the individual classes of flavonoid intake and risk of cardiovascular disease, coronary heart disease and stroke.

Supporting information Figure S3. Funnel plots for meta-analysis for the highest *versus* the lowest category of individual classes of flavonoids and lignan intake and risk of cardiovascular disease, coronary heart disease and stroke.

References

1. GBD, Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. **392**, 1736–1788 (2018).

2. GBD 2017 Risk Factor Collaborators, Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. **392**, 1923–1994 (2018).

3. D. Angelino *et al.*, Fruit and vegetable consumption and health outcomes: an umbrella review of observational studies. *Int. J. Food Sci. Nutr.* **70**, 652–667 (2019).

4. L. Schwingshackl *et al.*, Impact of different types of olive oil on cardiovascular risk factors: A systematic review and network meta-analysis. *Nutr. Metab. Cardiovasc. Dis.* **29**, 1030–1039 (2019).

5. L. Schwingshackl, G. Hoffmann, B. Missbach, M. Stelmach-Mardas, H. Boeing, An umbrella review of nuts intake and risk of cardiovascular disease. *Curr. Pharm. Des.* **23**, 1016–1027 (2017).

6. M. Tieri *et al.*, Whole grain consumption and human health: an umbrella review of observational studies. *Int. J. Food Sci. Nutr.* **71**, 668–677 (2020).

7. N. Veronese *et al.*, Is chocolate consumption associated with health outcomes? An umbrella review of systematic reviews and meta-analyses. *Clin. Nutr.* **38**, 1101–1108 (2019).

8. G. Grosso, J. Godos, F. Galvano, E. L. Giovannucci, Coffee, caffeine, and health outcomes: an umbrella review. *Annu. Rev. Nutr.* **37**, 131–156 (2017).

9. M. Yi *et al.*, Tea Consumption and Health Outcomes: Umbrella Review of Meta-Analyses of Observational Studies in Humans. *Mol. Nutr. Food Res.* **63**, e1900389 (2019).

10. GBD 2017 Diet Collaborators, Health effects of dietary risks in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. **393**, 1958–1972 (2019).

11. D. Martini *et al.*, Claimed effects, outcome variables and methods of measurement for health claims proposed under European Community Regulation 1924/2006 in the framework of protection against oxidative damage and cardiovascular health. *Nutr. Metab. Cardiovasc. Dis.* **27**, 473–503 (2017).

12. D. Del Rio *et al.*, Dietary (poly)phenolics in human health: structures, bioavailability, and evidence of protective effects against chronic diseases. *Antioxid. Redox Signal.* **18**, 1818–1892 (2013).

13. G. Grosso *et al.*, Dietary Flavonoid and Lignan Intake and Mortality in Prospective Cohort Studies: Systematic Review and Dose-Response Meta-Analysis. *Am. J. Epidemiol.* **185**, 1304–1316 (2017).

14. J. Godos *et al.*, Dietary Polyphenol Intake, Blood Pressure, and Hypertension: A Systematic Review and Meta-Analysis of Observational Studies. *Antioxidants (Basel)*. **8** (2019), doi:10.3390/antiox8060152.

15. A. Micek *et al.*, Dietary phytoestrogens and biomarkers of their intake in relation to cancer survival and recurrence: a comprehensive systematic review with meta-analysis. *Nutr. Rev.* (2020), doi:10.1093/nutrit/nuaa043.

16. A. González-Sarrías *et al.*, A Systematic Review and Meta-Analysis of the Effects of Flavanol-Containing Tea, Cocoa and Apple Products on Body Composition and Blood Lipids: Exploring the Factors Responsible for Variability in Their Efficacy. *Nutrients*. **9**, 746 (2017).

17. L. Hooper *et al.*, Flavonoids, flavonoid-rich foods, and cardiovascular risk: a meta-analysis of randomized controlled trials. *Am. J. Clin. Nutr.* **88**, 38–50 (2008).

18. L. Ellwood, G. Torun, Z. Bahar, R. Fernandez, Effects of flavonoid rich fruits on hypertension in adults: a systematic review. *JBI Database System. Rev. Implement. Rep.* (2019), doi:10.11124/JBISRIR-D-19-00050.

19. G. Raman *et al.*, Dietary intakes of flavan-3-ols and cardiometabolic health: systematic review and meta-analysis of randomized trials and prospective cohort studies. *Am. J. Clin. Nutr.* **110**, 1067–1078 (2019).

20. B. H. Parmenter *et al.*, An overview and update on the epidemiology of flavonoid intake and cardiovascular disease risk. *Food Funct.* **11**, 6777–6806 (2020).

21. X. Wang, Y. Y. Ouyang, J. Liu, G. Zhao, Flavonoid intake and risk of CVD: a systematic review and meta-analysis of prospective cohort studies. *Br. J. Nutr.* **111**, 1–11 (2014).

22. A. Stang, Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur. J. Epidemiol.* **25**, 603–605 (2010).

23. N. Orsini, R. Li, A. Wolk, P. Khudyakov, D. Spiegelman, Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. *Am. J. Epidemiol.* **175**, 66–73 (2012).

24. S. Greenland, M. P. Longnecker, Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am. J. Epidemiol.* **135**, 1301–1309 (1992).

25. N. Orsini, R. Bellocco, S. Greenland, Generalized least squares for trend estimation of summarized dose–response data. *The Stata Journal*. **6**, 40–57 (2006).

26. M. G. Hertog, E. J. Feskens, P. C. Hollman, M. B. Katan, D. Kromhout, Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. *Lancet*. **342**, 1007–1011 (1993).

27. S. O. Keli, M. G. Hertog, E. J. Feskens, D. Kromhout, Dietary flavonoids, antioxidant vitamins, and incidence of stroke: the Zutphen study. *Arch. Intern. Med.* **156**, 637–642 (1996).

28. P. Knekt, R. Jarvinen, A. Reunanen, J. Maatela, Flavonoid intake and coronary mortality in Finland: a cohort study. *BMJ*. **312**, 478–481 (1996).

29. E. B. Rimm, M. B. Katan, A. Ascherio, M. J. Stampfer, W. C. Willett, Relation between intake of flavonoids and risk for coronary heart disease in male health professionals. *Ann. Intern. Med.* **125**, 384–389 (1996).

30. M. G. Hertog, E. J. Feskens, D. Kromhout, Antioxidant flavonols and coronary heart disease risk. *Lancet*. **349**, 699 (1997).

31. M. G. Hertog, P. M. Sweetnam, A. M. Fehily, P. C. Elwood, D. Kromhout, Antioxidant flavonols and ischemic heart disease in a Welsh population of men: the Caerphilly Study. *Am. J. Clin. Nutr.* **65**, 1489–1494 (1997).

32. L. Yochum, L. H. Kushi, K. Meyer, A. R. Folsom, Dietary flavonoid intake and risk of cardiovascular disease in postmenopausal women. *Am. J. Epidemiol.* **149**, 943–949 (1999).

33. T. Hirvonen, J. Virtamo, P. Korhonen, D. Albanes, P. Pietinen, Intake of flavonoids, carotenoids, vitamins C and E, and risk of stroke in male smokers. *Stroke*. **31**, 2301–2306 (2000).

34. I. C. Arts, P. C. Hollman, E. J. Feskens, H. B. Bueno de Mesquita, D. Kromhout, Catechin intake might explain the inverse relation between tea consumption and ischemic heart disease: the Zutphen Elderly Study. *Am. J. Clin. Nutr.* **74**, 227–232 (2001).

35. I. C. Arts, D. R. Jacobs, L. J. Harnack, M. Gross, A. R. Folsom, Dietary catechins in relation to coronary heart disease death among postmenopausal women. *Epidemiology*. **12**, 668–675 (2001).

36. J. M. Geleijnse, L. J. Launer, D. A. M. Van der Kuip, A. Hofman, J. C. M. Witteman, Inverse association of tea and flavonoid intakes with incident myocardial infarction: the Rotterdam Study. *Am. J. Clin. Nutr.* **75**, 880–886 (2002).

37. P. Knekt *et al.*, Flavonoid intake and risk of chronic diseases. *Am. J. Clin. Nutr.* **76**, 560–568 (2002).

38. H. D. Sesso, J. M. Gaziano, S. Liu, J. E. Buring, Flavonoid intake and the risk of cardiovascular disease in women. *Am. J. Clin. Nutr.* **77**, 1400–1408 (2003).

39. J. Marniemi *et al.*, Dietary and serum vitamins and minerals as predictors of myocardial infarction and stroke in elderly subjects. *Nutr. Metab. Cardiovasc. Dis.* **15**, 188–197 (2005).

40. Y. T. van der Schouw *et al.*, Prospective study on usual dietary phytoestrogen intake and cardiovascular disease risk in Western women. *Circulation*. **111**, 465–471 (2005).

41. J. Lin *et al.*, Dietary intakes of flavonols and flavones and coronary heart disease in US women. *Am. J. Epidemiol.* **165**, 1305–1313 (2007).

42. Y. Kokubo *et al.*, Association of dietary intake of soy, beans, and isoflavones with risk of cerebral and myocardial infarctions in Japanese populations: the Japan Public Health Center-based (JPHC) study cohort I. *Circulation*. **116**, 2553–2562 (2007).

43. P. J. Mink *et al.*, Flavonoid intake and cardiovascular disease mortality: a prospective study in postmenopausal women. *Am. J. Clin. Nutr.* **85**, 895–909 (2007).

44. J. Mursu *et al.*, Flavonoid intake and the risk of ischaemic stroke and CVD mortality in middle-aged Finnish men: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Br. J. Nutr.* **100**, 890–895 (2008).

45. A. Cassidy *et al.*, Dietary flavonoids and risk of stroke in women. *Stroke*. **43**, 946–951 (2012).

46. M. L. McCullough *et al.*, Flavonoid intake and cardiovascular disease mortality in a prospective cohort of US adults. *Am. J. Clin. Nutr.* **95**, 454–464 (2012).

47. A. Cassidy *et al.*, High anthocyanin intake is associated with a reduced risk of myocardial infarction in young and middle-aged women. *Circulation*. **127**, 188–196 (2013).

48. M. Talaei, W.-P. Koh, R. M. van Dam, J.-M. Yuan, A. Pan, Dietary soy intake is not associated with risk of cardiovascular disease mortality in Singapore Chinese adults. *J. Nutr.* **144**, 921–928 (2014).

49. A. Tresserra-Rimbau *et al.*, Inverse association between habitual polyphenol intake and incidence of cardiovascular events in the PREDIMED study. *Nutr. Metab. Cardiovasc. Dis.* **24**, 639–647 (2014).

50. D. Yu *et al.*, Association of soy food intake with risk and biomarkers of coronary heart disease in Chinese men. *Int. J. Cardiol.* **172**, e285-7 (2014).

51. K. L. Ivey, J. M. Hodgson, K. D. Croft, J. R. Lewis, R. L. Prince, Flavonoid intake and all-cause mortality. *Am. J. Clin. Nutr.* **101**, 1012–1020 (2015).

52. V. Ponzo *et al.*, Dietary flavonoid intake and cardiovascular risk: a population-based cohort study. *J. Transl. Med.* **13**, 218 (2015).

53. A. Vogiatzoglou *et al.*, Associations between flavan-3-ol intake and CVD risk in the Norfolk cohort of the European Prospective Investigation into Cancer (EPIC-Norfolk). *Free Radic. Biol. Med.* **84**, 1–10 (2015).

54. D. Yu *et al.*, Dietary isoflavones, urinary isoflavonoids, and risk of ischemic stroke in women. *Am. J. Clin. Nutr.* **102**, 680–686 (2015).

55. A. Cassidy *et al.*, Habitual intake of anthocyanins and flavanones and risk of cardiovascular disease in men. *Am. J. Clin. Nutr.* **104**, 587–594 (2016).

56. J. I. Dower, J. M. Geleijnse, P. C. Hollman, S. S. Soedamah-Muthu, D. Kromhout, Dietary epicatechin intake and 25-y risk of cardiovascular mortality: the Zutphen Elderly Study. *Am. J. Clin. Nutr.* **104**, 58–64 (2016).

57. M. E. Goetz *et al.*, Dietary flavonoid intake and incident coronary heart disease: the REasons for Geographic and Racial Differences in Stroke (REGARDS) study. *Am. J. Clin. Nutr.* **104**, 1236–1244 (2016).

58. M. E. Goetz *et al.*, Flavanone Intake Is Inversely Associated with Risk of Incident Ischemic Stroke in the REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *J. Nutr.* **146**, 2233–2243 (2016).

59. C. Nagata *et al.*, Dietary soy and natto intake and cardiovascular disease mortality in Japanese adults: the Takayama study. *Am. J. Clin. Nutr.* **105**, 426–431 (2017).

60. S. Adriouch *et al.*, Prospective Association between Total and Specific Dietary Polyphenol Intakes and Cardiovascular Disease Risk in the Nutrinet-Santé French Cohort. *Nutrients*. **10** (2018), doi:10.3390/nu10111587.

61. N. P. Bondonno *et al.*, Flavonoid intake is associated with lower mortality in the Danish Diet Cancer and Health Cohort. *Nat. Commun.* **10**, 3651 (2019).

62. F. Dalgaard *et al.*, Associations between habitual flavonoid intake and hospital admissions for atherosclerotic cardiovascular disease: a prospective cohort study. *Lancet Planet. Health*. **3**, e450–e459 (2019).

63. R. D. Mendonça *et al.*, Total polyphenol intake, polyphenol subtypes and incidence of cardiovascular disease: The SUN cohort study. *Nutr. Metab. Cardiovasc. Dis.* **29**, 69–78 (2019).

64. T. Hirvonen *et al.*, Intake of flavonols and flavones and risk of coronary heart disease in male smokers. *Epidemiology*. **12**, 62–67 (2001).

65. M. Marino, C. Del Bo', D. Martini, M. Porrini, P. Riso, A review of registered clinical trials on dietary (poly)phenols: past efforts and possible future directions. *Foods*. **9** (2020), doi:10.3390/foods9111606.

66. L. Yang *et al.*, Effects of Anthocyanins on Cardiometabolic Health: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Adv. Nutr.* **8**, 684–693 (2017).

67. L. Fairlie-Jones, K. Davison, E. Fromentin, A. M. Hill, The Effect of Anthocyanin-Rich Foods or Extracts on Vascular Function in Adults: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. *Nutrients*. **9** (2017), doi:10.3390/nu9080908.

68. R. Menezes *et al.*, Impact of Flavonols on Cardiometabolic Biomarkers: A Meta-Analysis of Randomized Controlled Human Trials to Explore the Role of Inter-Individual Variability. *Nutrients*. **9** (2017), doi:10.3390/nu9020117.

69. F. Perez-Vizcaino, J. Duarte, Flavonols and cardiovascular disease. *Mol. Aspects Med.* **31**, 478–494 (2010).

70. B. Almeida Rezende, A. C. Pereira, S. F. Cortes, V. S. Lemos, Vascular effects of flavonoids. *Curr. Med. Chem.* **23**, 87–102 (2016).

71. R. M. da Costa *et al.*, Nrf2 as a potential mediator of cardiovascular risk in metabolic diseases. *Front. Pharmacol.* **10**, 382 (2019).

72. E. Salvucci, The human-microbiome superorganism and its modulation to restore health. *Int. J. Food Sci. Nutr.* **70**, 781–795 (2019).

Table 1. Main characteristics of included studies in the meta-analysis.

Author, year	Cohort name, country	Follow-up	Population's characteristic	Age at baseline	N & sex	Outcomes	Cases
Hertog, 1993[26]	Zutphen Elderly Study, Netherlands	4.6y (median)	Residents of Zuthpen	65-84	M 805	CHD (fatal, fatal and nonfatal)	73 CHD
Keli, 1996[27]	Zutphen Elderly Study, Netherlands	15y	Residents of Zuthpen	50-69	M 552	Stroke (fatal and nonfatal)	42 Stroke
Knekt, 1996[28]	Finnish Social Insurance Institution, Finland	26y	Population-based	30-68	M 2,748	CHD (fatal)	473 CHD
Rimm, 1996[29]	Health Professionals Follow-up Study, US	6y	Men in health professions	40-75	M 34,789	MI (nonfatal)	486 MI
Hertog, 1997[31]	Caerphilly Study, Wales	14y	Residents of Caerphilly	45-59	M 1,900	CHD (fatal and nonfatal; fatal)	186 CHD
Hertog, 1997[30]	Zutphen Elderly Study, Netherlands	10y	Residents of Zuthpen	65-84	M 804	CHD (fatal); MI (fatal and nonfatal)	90 CHD
Yochum, 1999[32]	Iowa Women's Health Study, US	10y (median)	Postmenopausal women with valid Iowa drivers licenses	55-69	F 34,492	CHD (fatal)	438 CHD
Hirvonen, 2000[33]	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, Finland	6.1y (median)	Male smokers	50-69	M 26,593	Stroke (fatal and nonfatal)	736 Stroke
Arts, 2001[34]	Zutphen Elderly Study, Netherlands	10y, 7.5y (median)	Residents of Zuthpen	65-84	M 806	CHD (fatal); MI (fatal and nonfatal)	180 CHD
Arts, 2001[35]	Iowa Women's Health Study, US	10y	Postmenopausal women with valid Iowa drivers licenses	55-69	F 34,492	CHD (fatal)	767 CHD
Hirvonen, 2001[64]	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, Finland	5-8y, 6.1y (median)	Male smokers	50-69	M 25,372	MI (nonfatal); CHD (fatal)	1,937 MI
Geleijnse, 2002[36]	Rotterdam Study, Netherlands	5.6y (median)	Residents of defined district of Rotterdam	55+	MF 4,807	MI (fatal and nonfatal; nonfatal; fatal)	146 MI
Knekt, 2002[37]	Finnish Mobile Clinic Health Examination Survey, Finland	28y	Population-based	15+	MF 10,054	CHD (fatal); Stroke (fatal)	681 CHD; 806 Stroke
Sesso, 2003[38]	Women's Health Study, US	6.9y (median)	Health professionals	45+	MF 38,445	CVD (fatal and nonfatal)	729 CVD
Marniemi, 2005[39]	Finnish elderly Study, Finland	R 10	Residents of city of Turku and surrounding rural areas	65-99	M 361, F 394	MI (fatal and nonfatal); Stroke (fatal and nonfatal)	130 MI; 70 Stroke
van der Schouw, 2005[40]	Dutch Prospect-EPIC, Denmark	6.3y (median)	Population-based	49-70	F 16,165	CHD (fatal and nonfatal); Stroke (fatal and nonfatal); CVD (fatal and nonfatal)	372 CHD; 147 Stroke; 519 CVD
Lin, 2006[41]	Nurses' Health Study, US	12y	Registered nurses	30-55	F 66,369	MI (nonfatal); CHD (fatal)	1,262 MI
Kokubo, 2007[42]	Japan Public Health Center–Based Study, Japan	12.5y (median)	Population-based	40-59	MF 40,462	Stroke (fatal and nonfatal); MI (fatal and nonfatal); CVD (fatal and nonfatal; fatal)	308 MI; 468 Stroke; 776 CVD
Mink, 2007[43]	Iowa Women's Health Study, US	16y	Postmenopausal women with valid Iowa drivers licenses	55-69	F 34,489	Stroke (fatal); CHD (fatal); CVD (fatal)	1,329 CHD; 469 Stroke; 2,316 CVD

Mursu, 2008[44]	Kuopio Ischaemic Heart Disease Risk Factor Study, Finland	15.2y (median)	Population-based	42-60	M 1,950	Stroke (fatal and nonfatal); CVD (fatal)	102 Stroke (ischemic); 153 CVD
Cassidy, 2012[45]	Nurses' Health Study, US	14y	Registered nurses	30-55	F 69,622	Stroke (fatal and nonfatal)	1,803 Stroke
McCullough, 2012[46]	Cancer Prevention Study II Nutrition Cohort, US	7y	Population-based	30-55	M 38,180, F 60,289	CVD (fatal)	2771 CVD
Cassidy, 2013[47]	Nurses' Health Study II, US	18y	Registered nurses	25-42	F 93,600	MI (fatal and nonfatal)	405 MI
Talaei, 2014[48]	Singapore Chinese Health Study, China	13.6y (median)	Population-based	45–74	MF 40,622	CVD (fatal); CHD (fatal); Stroke (fatal)	2,697 CHD; 1,298 Stroke; 4,780 CVD
Tresserra-Rimbau, 2014[49]	PREvención con DIeta MEDiterránea Study, Spain	4.3y (median)	Population-based	55-80	MF 7,172	CVD (fatal and nonfatal)	273 CVD
Yu, 2014[50]	Shanghai Men's Health Study, China	5.4y (median)	Population-based	40–74y	M 55,474	CHD (fatal and nonfatal)	217 CHD
Ivey, 2015[51]	Calcium Intake Fracture Outcome Age Related Extension Study, Australia	5y	Postmenopausal women	75+	F 1,063	CVD (fatal)	78 CVD
Ponzo, 2015[52]	Prospective Italian Study, Italy	12y (median)	Residents of the province of Asti	45-64	MF 1,877	CVD (nonfatal); CVD (fatal)	209 CVD
Vogiatzoglou, 2015[53]	European Prospective Investigation into Cancer and Nutrition-Norfolk Study, UK	11.5y (median)	Population-based	40-75	M 11,252, F 13,633	CVD (fatal and nonfatal); CHD (fatal and nonfatal); Stroke (fatal and nonfatal); CVD (fatal)	6,395 CHD; 1,920 Stroke; 5,557 CVD
Yu, 2015[54]	Shanghai Women's Health Study, China	10y (median)	Population-based	40-70	F 66,832	Stroke (fatal and nonfatal)	3,110 Stroke
Cassidy, 2016[55]	Health Professionals Follow-Up Study, US	24y	Men in health professions	32-81	M 43,880	MI (fatal and nonfatal; nonfatal; fatal)	4,046 MI
Dower, 2016[56]	Zutphen Elderly Study, Netherlands	R 25	Residents of Zuthpen	65-84	M 744	CVD (fatal); CHD (fatal); Stroke (fatal)	148 CHD; 72 Stroke; 329 CVD
Goetz, 2016 (CHD)[57]	Reasons for Geographic And Racial Differences in Stroke study, US	6.0y (median)	Population-based	45+	MF 16,678	CHD (fatal and nonfatal)	589 CHD
Goetz, 2016 (Stroke)[58]	Reasons for Geographic And Racial Differences in Stroke study, US	6.0y (median)	Population-based	45+	MF 20,024	Stroke (fatal and nonfatal)	524 Stroke
Nagata, 2017[59]	Takayama Study, Japan	16y	Residents of Takayama City	35+	MF 29,079	CVD (fatal)	1,678 CVD
Adriouch, 2018[60]	NutriNet-Sante, France	Me 4.9	Volunteers from the NutriNet-Santé study	18+	MF 84,158	CVD (fatal and nonfatal); CHD (fatal and nonfatal); Stroke (fatal and nonfatal)	309 CHD; 293 Stroke; 602 CVD
Bondonno, 2019[61]	Danish Diet, Cancer, and Health Study, Denmark	23y, 19.4y (median)	Residents of Copenhagen and Aarhus	50-65	MF 56,048	CVD (fatal)	3,981 CVD
Dalgaard, 2019[62]	Danish Diet, Cancer, and Health Study, Denmark	23y, 21y (median)	Residents of Copenhagen and Aarhus	50-65	MF 53,552	CVD (nonfatal)	8,773 CVD
Mendonca, 2019[63]	Seguimiento Universidad De Navarra Study, Spain	10.1y	University graduates	20-89	MF 17,065	CVD (fatal and nonfatal)	113 CVD

Abbreviations: CHD (coronary heart disease); CVD (cardiovascular disease); F (female); M (male); MI (myocardial infarction); RR (relative risk).

Table 2. Summary relative risks for the highest *versus* the lowest category of individual classes of flavonoids and lignan intake and risk of cardiovascular disease, coronary heart disease and stroke.

	CHD				Stroke				CVD			
Polyphenol class	Datasets (studies)	RR (95% CI)	I^2	$P_{heterogeneity}$	Datasets (studies)	RR (95% CI)	I^2	$P_{heterogeneity}$	Datasets (studies)	RR (95% CI)	I^2	$P_{heterogeneity}$
Flavonoids	3 (3)	0.91 (0.80, 1.05)	0.00	0.782	4 (4)	0.91 (0.78, 1.06)	19.93	0.290	9 (8)	0.81 (0.71, 0.91)	62.25	0.007
Flavonols and flavones	8 (7)	0.86 (0.77, 0.97)	34.52	0.153	4 (4)	0.75 (0.55, 1.03)	66.16	0.031	1 (1)	0.88 (0.68, 1.14)	0.00	1.000
Flavonols	7 (7)	0.90 (0.80, 1.01)	0.00	0.696	5 (5)	0.90 (0.72, 1.13)	65.18	0.022	8 (7)	0.85 (0.79, 0.91)	28.99	0.197
Quercetin	8 (7)	0.87 (0.76, 1.00)	31.68	0.175	2 (2)	0.85 (0.70, 1.03)	0.00	0.694	1 (1)	0.96 (0.74, 1.25)	0.00	1.000
Myricetin	4 (4)	1.07 (0.95, 1.20)	0.00	0.576	2 (2)	1.00 (0.83, 1.21)	0.00	0.545	1 (1)	0.93 (0.73, 1.19)	0.00	1.000
Kaempferol	5 (5)	0.90 (0.81, 1.01)	0.00	0.623	2 (2)	0.72 (0.59, 0.88)	0.00	0.467	1 (1)	0.95 (0.75, 1.21)	0.00	1.000
Flavanones	5 (5)	0.96 (0.84, 1.09)	49.99	0.092	5 (5)	0.86 (0.77, 0.96)	0.00	0.697	8 (7)	0.88 (0.79, 0.98)	63.38	0.008
Flavones	4 (4)	0.99 (0.87, 1.13)	0.00	0.824	5 (5)	0.98 (0.88, 1.09)	0.00	0.773	8 (7)	0.91 (0.82, 1.01)	68.90	0.002
Flavan-3-ols	6 (5)	0.93 (0.86, 1.01)	0.00	0.485	7 (6)	0.95 (0.87, 1.05)	0.00	0.710	9 (7)	0.85 (0.76, 0.95)	67.99	0.002
Catechins	3 (3)	0.81 (0.68, 0.97)	0.00	0.808	2 (2)	0.70 (0.55, 0.88)	0.77	0.315	2 (2)	0.75 (0.63, 0.89)	0.00	0.780
Proanthocyanins	3 (3)	0.79 (0.65, 0.97)	49.97	0.136	4 (4)	0.97 (0.86, 1.08)	0.00	0.825	5 (4)	0.83 (0.73, 0.95)	54.20	0.068
Anthocyanins	4 (4)	0.79 (0.64, 0.98)	66.19	0.031	4 (4)	0.85 (0.69, 1.05)	50.85	0.107	7 (6)	0.82 (0.70, 0.96)	75.09	0.001
Isoflavones	5 (4)	0.99 (0.80, 1.23)	51.65	0.082	5 (4)	0.92 (0.69, 1.21)	84.51	<0.001	6 (5)	0.87 (0.72, 1.04)	75.04	0.001
Lignans	2 (2)	0.82 (0.65, 1.01)	0.00	0.369	2 (2)	0.92 (0.71, 1.19)	0.00	0.601	4 (4)	0.82 (0.65, 1.04)	40.32	0.170
Abbreviations: CHD (coronary heart disease); CVD (cardiovascular disease); RR (relative risk).												

Table 3. Dose-response meta-analysis for total flavonoid intake and risk of cardiovascular disease, coronary heart disease and stroke.

		Flavonoids mg/d, RR (95% CI)								
Outcome	**Datasets (studies)**	**0**	**100**	**200**	**300**	**400**	**500**	I^2[%]	$P_{heterog}$	$P_{nonlinearity}$
CHD risk	2 (2)	1 (ref.)	0.89 (0.80, 1.00)	0.80 (0.64, 1.00)	0.74 (0.56, 0.99)	0.72 (0.52, 0.99)	0.72 (0.53, 1.00)	1	0.501	0.064
CHD fatal	1 (1)	1 (ref.)	0.90 (0.81, 1.00)	0.81 (0.66, 1.00)	0.77 (0.59, 1.00)	0.77 (0.59, 1.02)	0.81 (0.63, 1.05)	NA	NA	0.041
CHD incidence/mortality	3 (3)	1 (ref.)	0.90 (0.84, 0.97)	0.82 (0.70, 0.95)	0.77 (0.63, 0.94)	0.75 (0.61, 0.94)	0.77 (0.62, 0.96)	1	0.483	0.011
Stroke risk	3 (3)	1 (ref.)	0.91 (0.82, 1.01)	0.84 (0.69, 1.02)	0.80 (0.62, 1.03)	0.78 (0.57, 1.06)	0.76 (0.53, 1.10)	1	0.406	0.233
Stroke fatal	1 (1)	1 (ref.)	0.86 (0.68, 1.09)	0.76 (0.50, 1.17)	0.73 (0.44, 1.21)	0.74 (0.45, 1.21)	0.77 (0.49, 1.21)	NA	NA	0.237
Stroke incidence/mortality	4 (4)	1 (ref.)	0.91 (0.83, 0.99)	0.84 (0.71, 0.99)	0.80 (0.65, 0.99)	0.79 (0.63, 1.00)	0.80 (0.62, 1.03)	1	0.649	0.076
Stroke, ischemic	3 (3)	1 (ref.)	0.82 (0.73, 0.93)	0.71 (0.57, 0.88)	0.67 (0.52, 0.86)	0.67 (0.52, 0.86)	0.68 (0.53, 0.87)	1	0.818	0.009
CVD risk	4 (4)	1 (ref.)	0.87 (0.77, 1.00)	0.77 (0.59, 1.00)	0.68 (0.46, 1.00)	0.62 (0.37, 1.01)	0.57 (0.31, 1.03)	47.5	0.076	0.013
CVD fatal	7 (6)	1 (ref.)	0.93 (0.90, 0.97)	0.87 (0.80, 0.94)	0.82 (0.73, 0.92)	0.79 (0.67, 0.92)	0.77 (0.63, 0.94)	47.8	0.028	0.04
CVD incidence/mortality	9 (8)	1 (ref.)	0.93 (0.90, 0.96)	0.86 (0.81, 0.92)	0.81 (0.73, 0.89)	0.76 (0.67, 0.87)	0.73 (0.62, 0.86)	51.8	0.007	0.082

Abbreviations: CHD (coronary heart disease); CVD (cardiovascular disease); RR (relative risk).

Table 4. Subgroup analyses by potential confounding factors for the association between the highest *versus* the lowest intake of total flavonoids and cardiovascular disease risk.

Subgroups	Datasets (studies)	RR (95% CI)	I^2	$p_{heterogeneity}$
CVD incidence/mortality				
Incidence	5 (4)	0.65 (0.48, 0.88)	73.89	0.004
Mortality	7 (6)	0.87 (0.77, 0.99)	61.73	0.016
Sex				
Men	2 (2)	0.94 (0.65, 1.36)	53.36	0.143
Women	3 (3)	0.75 (0.56, 1.02)	80.07	0.007
Location				
Europe	5 (5)	0.77 (0.59, 1.00)	62.77	0.03
USA	3 (2)	0.87 (0.79, 0.95)	00.00	0.403
Follow-up, y				
<10	4 (3)	0.74 (0.59, 0.92)	60.59	0.055
≥10	5 (5)	0.85 (0.72, 0.99)	62.34	0.031
Sample size				
<10,000	4 (4)	0.65 (0.41, 1.04)	72.27	0.013
≥10,000	5 (4)	0.87 (0.82, 0.93)	15.63	0.315
Study quality				
high*	6 (5)	0.86 (0.78, 0.93)	22.68	0.263
moderate**	3 (3)	0.60 (0.36, 1.03)	86.14	0.001
Adjusted for energy intake				
Yes	6 (5)	0.85 (0.76, 0.96)	26.22	0.238
No	3 (3)	0.60 (0.36, 0.99)	86.08	0.001
Adjusted for diabetic status				
Yes	4 (4)	0.86 (0.65, 1.13)	45.05	0.141
No	5 (4)	0.76 (0.65, 0.90)	73.62	0.004
Adjusted for BMI				
Yes	7 (6)	0.81 (0.71, 0.93)	47.64	0.075
No	2 (2)	0.56 (0.21, 1.53)	88.77	0.003
Adjusted for other dietary factors				
Yes	5 (5)	0.77 (0.59, 1.00)	62.77	0.03
No	4 (3)	0.80 (0.67, 0.97)	70.47	0.017

Abbreviations: CVD (cardiovascular disease); RR (relative risk).

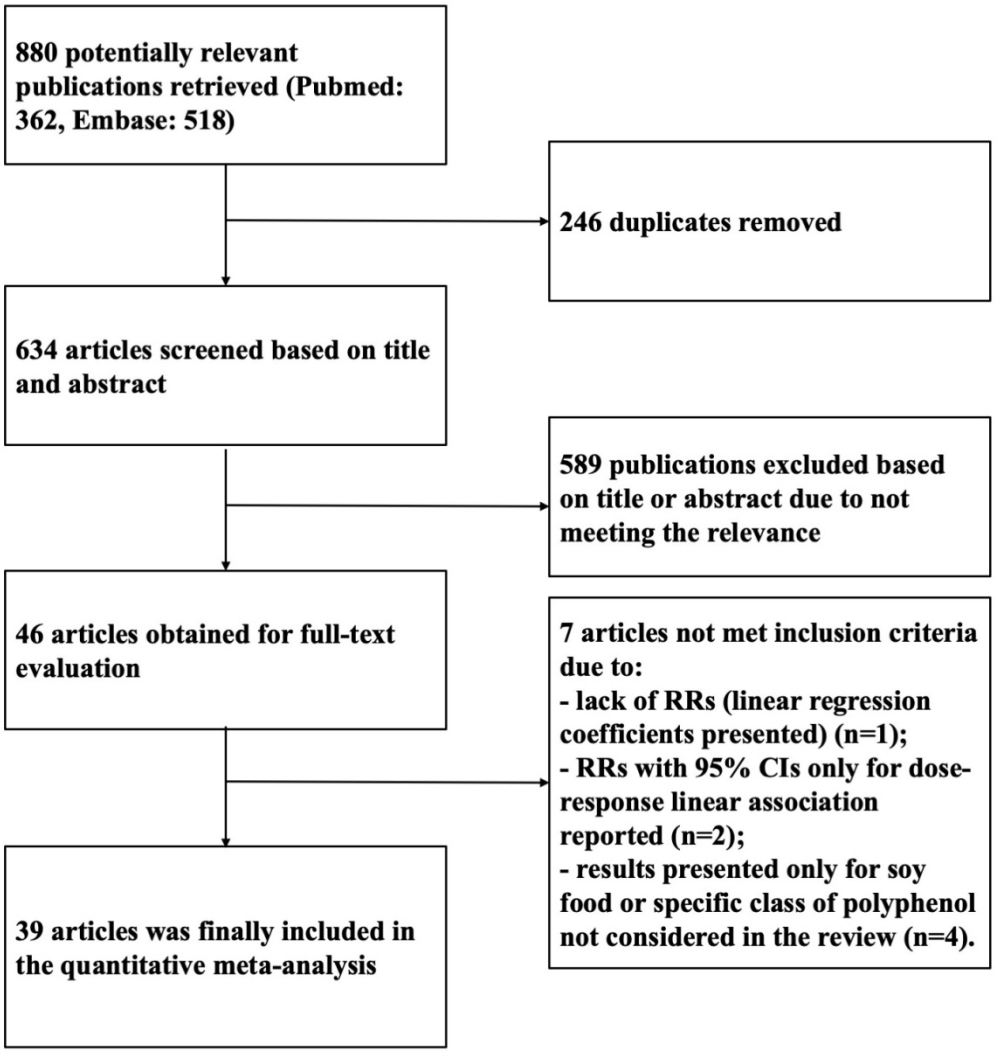


Figure 1. Flow chart of study selection process.

497x528mm (72 x 72 DPI)

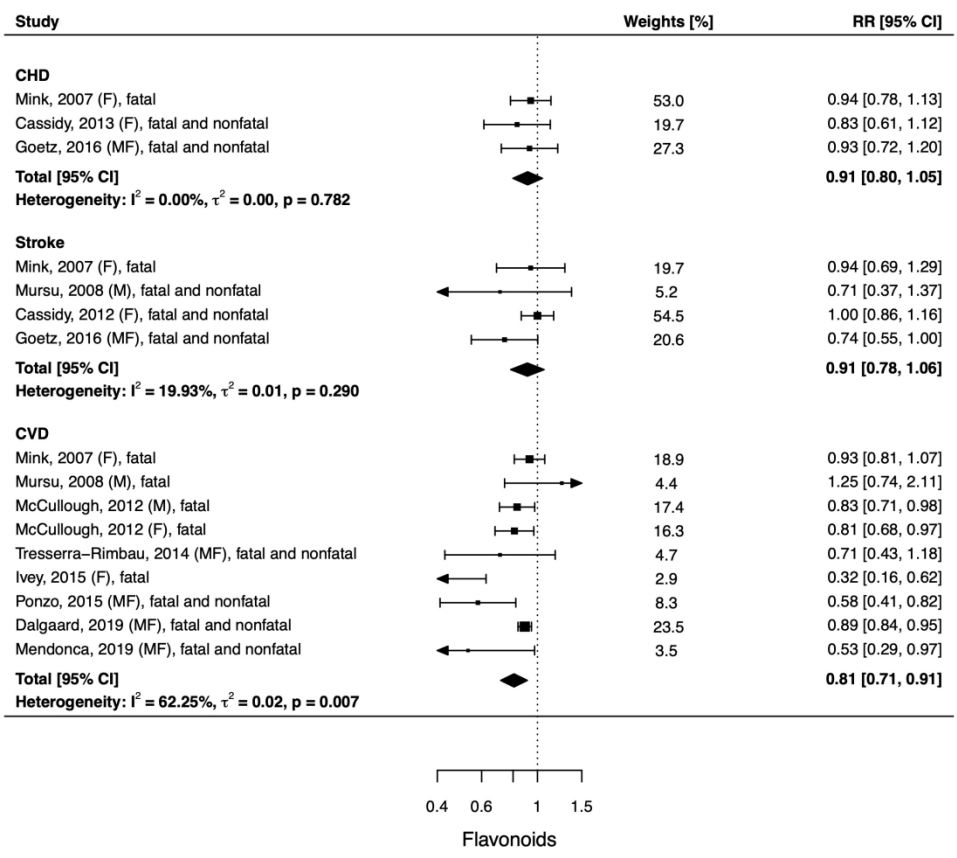


Figure 2. Summary relative risks for the highest versus the lowest category of total flavonoid intake and risk of cardiovascular disease, coronary heart disease and stroke.

177x177mm (350 x 350 DPI)

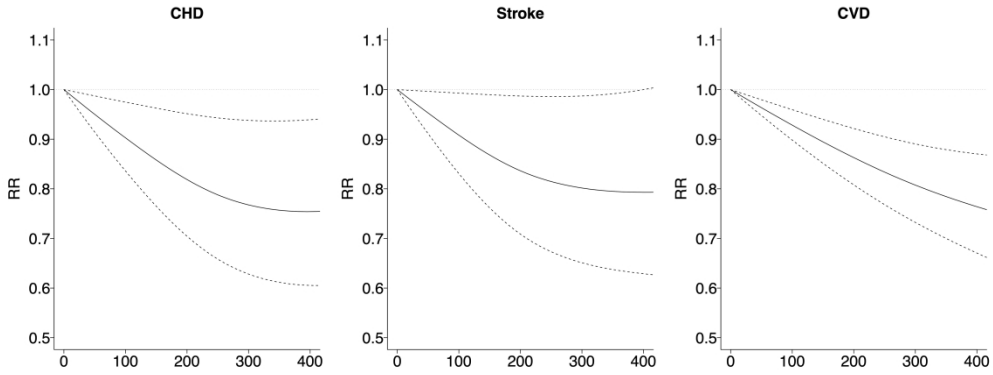
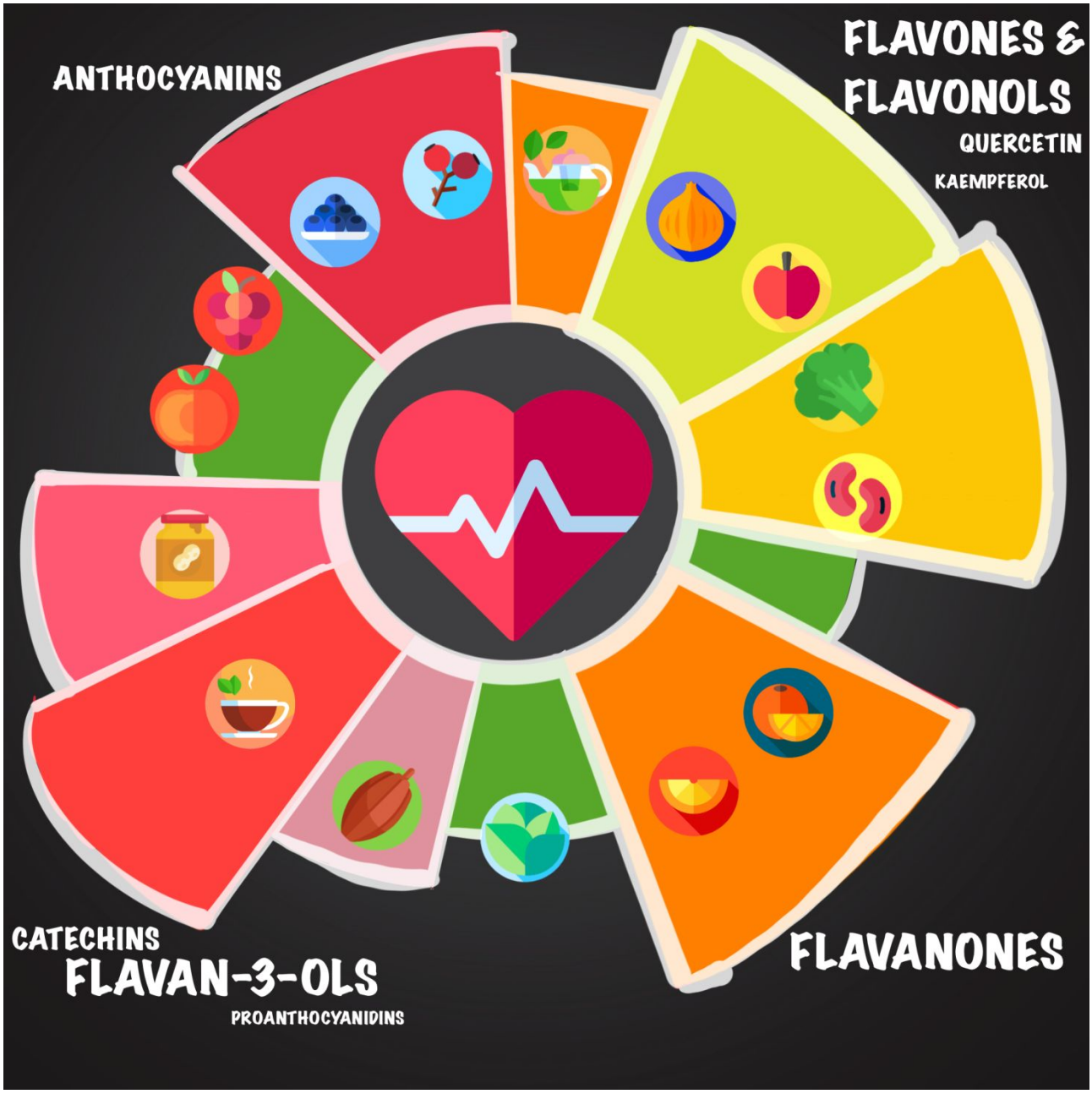


Figure 3

457x177mm (300 x 300 DPI)


ANTHOCYANINS
FLAVONES &
FLAVONOLS
QUERCETIN
KAEMPFEROL
CATECHINS
FLAVAN-3-OLS
PROANTHOCYANIDINS
FLAVANONES

This dose-response meta-analysis investigates the effect of dietary flavonoid intake toward risk of cardiovascular diseases, coronary heart diseases and stroke in prospective cohort studies. The results of this study show that diet rich in flavonoids may reduce the risk of cardiovascular diseases.