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Systematic Reviews and Meta- and Pooled Analyses

Dietary Flavonoid and Lignan Intake and Mortality in Prospective Cohort Studies: Systematic Review and Dose-Response Meta-Analysis

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Recent evidence has suggested that flavonoid and lignan intake may be associated with decreased risk of chronic and degenerative diseases. The aim of this meta-analysis was to assess the association between dietary flavonoid and lignan intake and all-cause and cardiovascular disease (CVD) mortality in prospective cohort studies. A systematic search was conducted in electronic databases to identify studies published from January 1996 to December 2015 that satisfied inclusion/exclusion criteria. Risk ratios and 95% confidence intervals were extracted and analyzed using a random-effects model. Nonlinear dose-response analysis was modeled by using restricted cubic splines. The inclusion criteria were met by 22 prospective studies exploring various flavonoid and lignan classes. Compared with lower intake, high consumption of total flavonoids was associated with decreased risk of all-cause mortality (risk ratio = 0.74, 95% confidence intervals: 0.55, 0.99), while a 100-mg/day increment in intake led to a (linear) decreased risk of 6% and 4% of all-cause and CVD mortality, respectively. Among flavonoid classes, significant results were obtained for intakes of flavonols, flavones, flavanones, anthocyanidins, and proanthocyanidins. Only limited evidence was available on flavonoid classes and lignans and all-cause mortality. Findings from this meta-analysis indicated that dietary flavonoids are associated with decreased risk of all-cause and CVD mortality.

all-cause mortality; cardiovascular disease mortality; flavonoids; lignans; meta-analysis; prospective studies

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; RR, risk ratio.

Dietary polyphenols represent a large group of compounds contained in several commonly consumed fruits and vegetables, herbs, cocoa, and beverages (e.g., wine, tea, and coffee) (1). The great variety of compounds existing in nature is divided on the basis of their chemical structure into flavonoids and nonflavonoids. Flavonoids are characterized by a common skeleton of diphenylpropane (C6-C3-C6) and are placed in a number of classes, such as flavonols, flavones, flavanones, flavan-3-ols (including catechins and their oligomers proanthocyanidins), isoflavones, and anthocyanins (2). Nonflavonoids comprise all other main classes of polyphenols having a broad variety of chemical structures, including phenolic acids, stilbenes, and lignans (2).

Flavonoids may contribute to the beneficial effects of plant-based dietary patterns against cardiovascular disease (CVD) due to their antioxidant and antiinflammatory activity (3, 4). Several flavonoid-rich foods have been demonstrated to be associated with lower risk of chronic diseases such as CVD, neurodegenerative diseases, and some cancers (5–9). A number of quantitative reviews of observational studies have indicated that dietary flavonoids are potentially related to decreased risk of common chronic diseases. Two recent studies estimated that a 10-mg/day increment in flavonol and 500 mg/day in flavonoid intake were associated with 5% decreased risk of CVD (10) and diabetes (11), respectively. Other studies have suggested that flavonoids may have anticarcinogenic effects, particularly against gastrointestinal (12, 13) and smoking-related cancers (14), with which the main classes of compounds showed an inverse association.

Lignan-rich foods, such as various seeds, whole-grain cereals, and nuts, have been found to be associated with lower risk of chronic diseases (15). Analyses restricted to lignans

suggested that their association with CVD and some hormone-related cancers might be attributed to their weak estrogen-like activity (16, 17). Such beneficial effects of lignans reinforce the hypothesis that this group of compounds may be responsible for the health benefits conferred by consumption of the aforementioned food groups, but evidence is still limited and research ongoing due to the relative novelty of the topic.

Whether the association of dietary flavonoid and lignan intake with chronic diseases may be translated to lower risk of mortality is still unclear. Meta-analyses have reported decreased mortality risk associated with consumption of flavonoid- and lignan-rich foods (18–20), but meta-analyses that explored the association of flavonoid and lignan intake with all-cause and CVD mortality are lacking. Therefore, we aimed to review current evidence from prospective studies on flavonoid and lignan intake in relation to mortality and evaluate the estimated risk. We conducted a series of quantitative analyses to assess the association of total and individual classes of flavonoids (flavonols, flavones, flavanones, flavan-3-ols (including catechins and proanthocyanidins), isoflavones, and anthocyanidins) and lignans on risk of death, determining the dose-response association throughout the observed range of intakes reported in the reviewed studies.

METHODS

Study selection

A systematic search was performed using PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and EMBASE (http://www.embase.com/) databases to identify all relevant English-language studies published up to December 2015. The search terms used for the study selection were the following: 1) flavonoids, flavonols, flavones, anthocyanidins, flavanones, flavan-3-ols, catechins, isoflavones, proanthocyanidins, quercetin, myricetin, kaempferol; 2) lignans, phytoestrogens; 3) mortality; and 4) cohort, prospective. Inclusion criteria were: 1) had a prospective design; 2) evaluated association between intake of dietary flavonoids/lignans (and/or their classes) and risk of mortality; 3) and assessed and reported hazard ratios and the corresponding 95% confidence intervals for mortality (or sufficient data to compute them). Exclusion criteria were the following: 1) reported insufficient statistics or results and 2) assessed composite outcome from which was not possible to derive mortality risk (e.g., incidence of CVD event, including cardiovascular death). Reference lists of included manuscripts were also examined for any additional studies not previously identified. If more than 1 article was published that used the same cohort, only the study that included the entire cohort or had the longest follow-up was included. The selection process was independently performed by 2 authors (G.G. and J.G.), and the articles retrieved were examined.

Data extraction and study quality

Data were abstracted from each identified study by using a standardized extraction form. The following information was collected: 1) first author name; 2) year of publication; 3) study cohort name; 4) country; 5) number of participants; 6) sex of participants; 7) age range of the study population at baseline; 8) dietary food source; 9) follow-up period; 10) endpoints and cases; 11) distributions of cases and person-years, hazard ratios, and 95% confidence intervals for all categories of exposure; and 12) covariates used in adjustments. This process was independently performed by 2 authors (G.G. and A.M.), and discrepancies were discussed and resolved by consensus.

The quality of each study was assessed according to the Newcastle-Ottawa Quality Assessment Scale (21), which consists of 3 variables of quality as follows: selection (4 points), comparability (2 points), and outcome (3 points) for a total score of 9 points (9 representing the highest quality).

Statistical analysis

Outcomes evaluated in the analyses included all-cause mortality and CVD mortality. The analyses were performed for total flavonoid intake as well as for individual classes, if reported in the original studies. Hazard ratios with 95% confidence intervals for all categories of exposure were extracted for the analysis. Random-effects models were used to calculate risk ratios with 95% confidence intervals for highest versus lowest categories of exposure. We used the risk estimate from the models with the fullest adjustment in the analysis of the risk ratios. Heterogeneity was assessed by using the Q test and I^2 statistic. The level of significance for the Q test was defined as $P < 0.10$. The I^2 statistic represented the amount of total variation that could be attributed to heterogeneity. I^2 values ≤25%, ≤50%, ≤75%, and >75% indicated no, little, moderate, and significant heterogeneity, respectively. A sensitivity analysis by exclusion of one study at a time was performed to assess the stability of results and potential sources of heterogeneity. Additional sensitivity analyses were performed to check for potential sources of heterogeneity by grouping studies according to geographical area, sample size, type of exposure ascertainment method, and length of follow-up. Publication bias was evaluated by a visual investigation of funnel plots for potential asymmetry.

For dose-response analyses, we extracted data on the amount of flavonoid/lignan intake, distributions of cases and person-years (when available), and hazard ratios with 95% confidence intervals for ≥3 exposure categories. The median or mean daily take of flavonoids in each category was assigned to the corresponding hazard ratio with the 95% confidence interval for each study. When flavonoid consumption was reported by ranges of intake, the midpoint of the range was used. When the highest category was open-ended, we assumed the width of the category to be the same as that of the adjacent category. When the lowest category was open-ended, we set the lower boundary to zero if the width of the adjacent category exceeded that of the lowest. Two-stage random-effects dose-response meta-analysis was performed to examine linear and nonlinear relationships between flavonoid intake and both all-cause and CVD mortality. In the first stage, the method reported by Greenland and Orsini (generalized least-squares) was used to calculate study-specific coefficients on the basis of results across categories of flavonoid intake taking into account the correlation within each set of retrieved risk ratios (22, 23). Nonlinear dose-response analysis

was modeled by using restricted cubic splines with 3 knots at fixed percentiles (25th, 50th, and 75th) of the distribution (24). We combined the coefficients that had been estimated within each study by performing random-effects meta-analysis. In linear dose-response meta-analysis, the method of DerSimonian and Laird was used, and in nonlinear dose-response meta-analysis, the multivariate extension of the method of moments was used. We calculated an overall *P* value by testing that the 2 regression coefficients were simultaneously equal to zero. We then calculated a *P* value for nonlinearity by testing that the coefficient of the second spline was equal to zero. All analyses were performed with R, version 3.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study characteristics

The process of identification and study selection is summarized in Figure 1. Among the initial 95 articles screened on the basis of title, 34 articles were screened by reading full texts. Thirteen studies were excluded after a full-text examination: 1 study reported insufficient statistics; 4 studies included the same cohorts but with shorter follow-up periods; 3 studies reported markers of flavonoid consumption; and 5 studies reported composite outcomes (i.e., CVD incidence and mortality). One additional study that met the inclusion criteria was identified by hand searching reference lists.

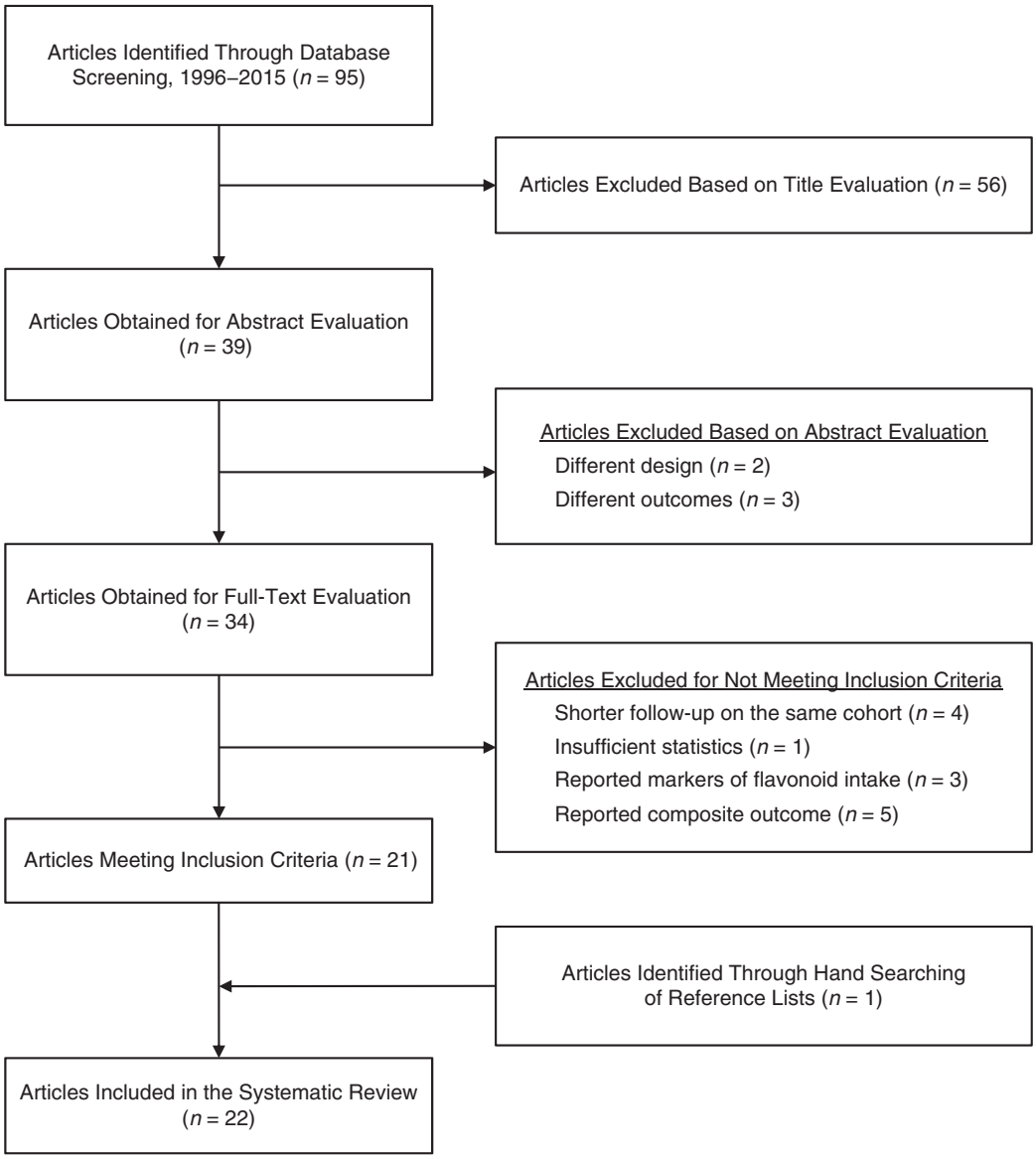

Figure 1. Process used for screening and selection of the studies assessed in this meta-analysis, evaluating association of flavonoid and lignan intake and risk of all-cause and cardiovascular disease mortality, 1996–2015.

This inclusion strategy resulted in the final selection of 22 studies (25–46) eligible to be included in the analysis, comprising 515,174 individuals, 18,036 all-cause deaths, and 11,795 CVD deaths.

Background characteristics of the included studies are presented in Table 1. Twelve studies were conducted in Europe (4 in the Netherlands, 4 in Finland, 2 in Spain, 1 in the United Kingdom, and 1 in Italy) (25, 27, 28, 29, 31–33, 35, 39, 42, 44, 46), 5 in the United States (26, 30, 37, 38, 40), 2 in Japan (34, 36), 2 in Australia (41, 45), and 1 in Singapore (43). Seven studies reported total flavonoid intake as sum of all classes (38–40, 42, 44–46), whereas others assessed flavonols and flavones, isoflavones, flavanones, catechins, and flavonols, 2 of which reported intakes of specific flavonol subgroups (33, 37). Three studies (35, 42, 44) were conducted on lignans, but only 1 reported information on specific subgroups (35). Most of the studies included individuals of age range 40–70 years. Study quality was on average good for the most of the studies, although older studies had substantial limitations in the number of flavonoid classes included (Web Table 1, available at http://aje.oxfordjournals.org/).

All studies included covariates that may have significantly influenced mortality outcomes, such as age, sex (when not analyzed separately), body mass index (BMI), education, physical activity, and smoking status (Table 1). The main differences across studies regarded 1) the representativeness of the exposed cohort—some cohorts included individuals with social (i.e., health-care workers, postgraduate students) or clinical (i.e., postmenopausal women, individuals at high CVD risk) characteristics different from general population; 2) the ascertainment of the exposure—some studies reported use of self-administered food frequency questionnaire whereas in others dietary habits were evaluated by interview; 3) the comparability of results—only the most recent studies reported detailed and comprehensive results on total and all classes of flavonoid (or lignan) intake; and 4) adjustment for dietary factors, which was not performed in 6 studies (26, 31, 33, 38, 40, 41).

Flavonoid intake and all-cause mortality

All the complete forest plots concerning flavonoid intake and all-cause mortality are shown in Web Figures 1 and 2. Findings from 5 studies (38, 42, 44–46) were analyzed to estimate risk of death of individuals with the highest compared with lowest intake of the sum of flavonoids according to quantiles of exposure and for a 100-mg/day increase in intake. The analysis was conducted for the studies including the most complete variety of flavonoid classes. The analysis by extreme quantiles of intake showed an association with decreased risk of all-cause mortality (risk ratio (RR) = 0.74, 95% confidence interval (CI): 0.55, 0.99; Figure 2A and Web Figure 1) with significant heterogeneity ($I^2 = 76\%$; $P_{\text{heterogeneity}} = 0.01$) but no evidence of publication bias (data not shown). Sensitivity analysis showed that exclusion of one study at a time reduced heterogeneity with relatively stable significant risk estimates. A sensitivity analysis of subgroups defined by variables that might be responsible for heterogeneity showed more homogeneity of results among studies with larger samples and longer follow-up (Web Table 2). The dose-response analysis is shown in Figure 3A and showed a linear association ($P_{\text{linearity}} < 0.001$; Table 2): a 100-mg/day increment in intake of total flavonoids was associated with a risk ratio of 0.94 (95% CI: 0.89, 1.00; Web Figure 2).

The analysis of individual flavonoid classes showed significant association with all-cause mortality risk reduction for intake of flavones, flavanones, and anthocyanidins, whereas no association for extreme categories of exposure for flavonols, isoflavones, flavan-3-ols, and proanthocyanidins was found (Figure 2A and Web Figure 1). The analyses of flavonols, flavanones, isoflavones, and flavan-3-ols showed significant heterogeneity. Sensitivity analysis conducted by excluding one study at a time revealed that heterogeneity was due to an individual study in the analyses on flavonols (28) and flavanones (38), while 2 studies (44, 46) reported very different risk ratios for isoflavone intake with no apparent explanation. Data on doses was limited to perform adequate dose-response analyses (Web Figure 2).

Flavonoid intake and CVD mortality

All the complete forest plots concerning flavonoid intake and CVD mortality are shown in Web Figures 3 and 4. Results from 5 studies (38–40, 45, 46) were analyzed to evaluate the association between total flavonoid intake and CVD mortality. There was no significant association when considering the extreme categories of intake and evidence of heterogeneity across studies (Figure 2B and Web Figure 3). No asymmetry was evident from the funnel plot (data not shown). Sensitivity analysis by exclusion of Ivey et al. (45) reduced heterogeneity and showed significant, reduced risk estimates (RR = 0.88, 95% CI: 0.79, 0.98; $I^2 = 20\%$, $P_{\text{heterogeneity}} = 0.29$). Further sensitivity analysis grouping studies according to background characteristics showed significant association of flavonoid consumption with reduced risk of CVD mortality when grouping studies with larger samples, although not adjusting for dietary variables may have biased the results (Web Table 2). Dose-response analysis revealed a significant, linear decreased risk of CVD mortality associated with increasing intake of total flavonoids ($P_{\text{linearity}} < 0.001$; Figure 3B and Table 2) and a 4% decreased risk of mortality due to CVD for a 100-mg/day increment (and Web Figure 4).

Four studies (25, 26, 31, 37) explored the association of flavonol and flavone intake with CVD mortality including selected compounds (such as quercetin, kaempferol, myricetin, hesperetin, and naringenin). Analysis of these studies revealed significant association, with 18% decreased risk of death for the highest versus the lowest exposure category (RR = 0.82, 95% CI: 0.70, 0.96; $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.82$), with no evidence of heterogeneity or publication bias. Significant decreased risk of CVD mortality was consistently associated with consumption of individual classes of flavonoids, such as flavonols (RR = 0.79, 95% CI: 0.63, 0.99; $I^2 = 67\%$ and $P_{\text{heterogeneity}} = 0.01$), flavones (RR = 0.85, 95% CI: 0.75, 0.96; $I^2 = 25\%$ and $P_{\text{heterogeneity}} = 0.25$), flavanones (RR = 0.84, 95% CI: 0.73, 0.96; $I^2 = 34\%$, $P_{\text{heterogeneity}} = 0.19$), anthocyanidins (RR = 0.89, 95% CI: 0.83, 0.95; $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.68$), flavan-3-ols (RR = 0.82, 95% CI: 0.71, 0.95; $I^2 = 53\%$, $P_{\text{heterogeneity}} = 0.05$), and proanthocyanidins

Table 1. Characteristics of the Studies Included in This Meta-Analysis Evaluating Association of Flavonoid and Lignan Intake and Risk of All-Cause, Cancer, and Cardiovascular Mortality, 1996–2015

First Author, Year (Reference No.)	Study Cohort	Country	Type of Polyphenol	Food Consumption Source	Population	Age Range, years	No. of Subjects	No. of Cases	Follow-up, years	Adjustments (Nondietary Factors)	Adjustments (Dietary Factors)
Knekt, 1996 (25)	Finnish mobile clinic health examination	Finland	Flavonols	FFQ	Men and women free of CVD	30–69	5,133	1,364	26	Age, smoking, serum cholesterol, hypertension, BMI, energy intake.	Intakes of carotene, vitamin E, vitamin C, fiber, saturated fatty acids, MUFA, PUFA.
Rimm, 1996 (26)	Health Professionals Follow-up Study	United States	Flavonols (quercetin, kaempferol, myricetin) and flavanones (hesperetin, naringenin)	FFQ	Male health professionals	40–75	51,529	486	6	Age, BMI, smoking, vitamin E, alcohol, hypertension, high cholesterol level, family history of CHD, profession.	None.
Hertog, 1997 (27)	Zutphen Elderly Study	The Netherlands	Flavonols	Dietary history interview	Elderly Men	65–84	804	90 CHD, 373 all causes	10	Age, total energy intake, marital status, educational attainment, high blood pressure, diabetes mellitus, BMI, waist-to-hip ratio, physical activity, pack-years of smoking, use of estrogen replacement therapy.	Use of vitamin supplements, alcohol intake, intake of whole grains, SFA, PUFA, cholesterol, vitamin C, vitamin E, folate, and carotene.
Hertog, 1997 (28)	Caerphilly Study	United Kingdom	Flavonols	FFQ	Men resident in Caerphilly, South Wales	45–59	1,900	131 CHD, 104 all causes	14	Age, smoking, baseline evidence of IHD, social class, BMI, systolic blood pressure, serum total cholesterol, total energy intake.	Intake of alcohol, fat, vitamin C, vitamin E, and beta-carotene.
Arts, 2001 (29)	Random sample	United States	Catechins	FFQ	Postmenopausal women with valid driver's license	55–69	34,492	767	13	Age, total energy intake, marital status, educational attainment, high blood pressure, diabetes mellitus, BMI, waist-to-hip ratio, physical activity, pack-years of smoking, use of estrogen replacement therapy.	Use of vitamin supplements, alcohol intake, intake of whole grains, SFA, PUFA, cholesterol, vitamin C, vitamin E, folate, and carotene.
Arts, 2001 (30)	Zutphen Elderly Study	The Netherlands	Catechins	Dietary history interview	Elderly men	65–84	806	374	10	Prevalent stroke at baseline, age, physical activity, total energy intake, BMI, alcohol intake, smoking status.	Prescribed diet and intakes of fish, coffee, SFA, PUFA, dietary cholesterol, fiber, vitamin C, vitamin E, and beta-carotene.
Hirvonen, 2001 (31)	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Finland	Flavonols and flavones	FFQ	Male smokers	50–69	25,372	815 CHD	6.1	Age, supplementation group, systolic and diastolic blood pressure, serum total cholesterol, serum HDL cholesterol, BMI, smoking years, number of cigarettes smoked daily, history of diabetes mellitus or CHD, marital status, educational level, and physical activity.	None.

Table continues

Table 1. Continued

First Author, Year (Reference No.)	Study Cohort	Country	Type of Polyphenol	Food Consumption Source	Population	Age Range, years	No. of Subjects	No. of Cases	Follow-up, years	Adjustments (Nondietary Factors)	Adjustments (Dietary Factors)
Geleijnse, 2002 (32)	Rotterdam Study	The Netherlands	Flavonols (quercetin, kaempferol, myricetin)	FFQ	Men and women resident in Rotterdam	>55	4,807	30	5.6	Age, sex, BMI, smoking status, pack-years of cigarette smoking, education level.	Daily intakes of alcohol, coffee, PUFA, SFA, fiber, vitamin E, and total energy.
Knekt, 2002 (33)	Finnish Mobile Clinic Health Examination Survey	Finland	Flavonols (quercetin, kaempferol, myricetin) and flavanones (hesperetin, naringenin)	FFQ	Men and women free of CVD	39–54	10,054	2,085 all-cause, 681 IHD	28	Age, sex, geographic area, occupation, blood pressure, smoking, serum cholesterol, BMI, and diabetes.	None.
Nagata, 2002 (34)	Takayama Study	Japan	Isoflavones	FFQ	Men and women resident in Takayama	>35	29,079	1,163	7	Age, total energy intake, marital status, BMI, smoking status, alcohol intake, coffee intake, exercise, and history of hypertension and diabetes mellitus (in women also age at menarche and menopausal status).	
Milder, 2006 (35)	Zutphen Elderly Study	The Netherlands	Lignans	Dietary history interview	Elderly men	64–84	570	392	15	Age, smoking status, amount and duration of smoking, physical activity, energy intake.	Beta-carotene and dietary fiber.
Kokubo, 2007 (36)	The Japan Public Health Center–Based (JPHC) Study Cohort I	Japan	Isoflavones	FFQ	Men and women free of CVD and cancer	40–59	40,462	1,230	12.5	Age, sex, smoking, alcohol use, BMI, history of hypertension or diabetes mellitus, medication use for hypercholesterolemia, education level, sports, menopausal status for women, public health center, energy intake.	Intakes of fruits, vegetables, fish, salt, and energy.
Lin, 2007 (37)	Nurses' Health Study (USA)	United States	Flavonols and flavones	FFQ	Female registered nurses free of CVD and cancer	30–55	66,360	268	12	Age, current smoking, parental history of myocardial infarction before age 60 years, history of hypertension, hypercholesterolemia, and diabetes, menopausal status, use of postmenopausal hormone and aspirin, BMI, physical activity, total energy intake.	Use of multivitamin and vitamin E supplements, alcohol consumption.
Mink, 2007 (38)	Iowa Women's Health Study	United States	Total flavonoids, flavonols, flavones, flavanones, isoflavones, proanthocyanidins, flavan-3-ols, and anthocyanidins	FFQ	Women with a valid driver's license and free of CVD	55–69	34,489	7,091 all-cause, 2,316 CVD	16	Age, marital status, education, blood pressure, diabetes, BMI, waist-to-hip ratio, physical activity, smoking, estrogen use, energy intake.	None.

Table continues

Table 1. Continued

First Author, Year (Reference No.)	Study Cohort	Country	Type of Polyphenol	Food Consumption Source	Population	Age Range, years	No. of Subjects	No. of Cases	Follow-up, years	Adjustments (Nondietary Factors)	Adjustments (Dietary Factors)
Mursu, 2008 (39)	Kuopio Ischaemic Heart Disease Risk Factor Study	Finland	Total flavonoids, flavonols, flavones, flavanones, flavan-3-ols and anthocyanidins	4-day record	Men free of CVD	42–60	1,950	153 CVD, 102 stroke	15.2	Age and examination years, BMI, systolic blood pressure, hypertension medication, serum HDL and LDL cholesterol, serum TAG, maximal oxygen uptake, smoking, family history of CVD, diabetes.	Alcohol intake, energy-adjusted intake of folate, vitamin E, total fat and SFA intake.
McCullough, 2012 (40)	Cancer Prevention Study II Nutrition Cohort	United States	Total flavonoids, flavonols, flavones, flavanones, isoflavones, proanthocyanidins, flavan-3-ols, and anthocyanidins	FFQ	Men and women	>69	98,469	2,771	7	Age, sex, smoking, beer and liquor intake, history of hypertension, history of high cholesterol, family history of myocardial infarction, BMI, physical activity, aspirin use, hormone replacement therapy (in women only), energy intake.	None.
Ivey, 2013 (41)	Calcium Intake Fracture Outcome Age Related Extension Study	Australia	Flavonols, flavones, flavanones, isoflavones, proanthocyanidins, flavan-3-ols, and anthocyanidins	FFQ	Women	>75	1,063	64 atherosclerotic vascular disease	5	Age, previous CVD, previous diabetes, energy expended in physical activity and history of smoking.	None.
Zamora-Ros, 2013 (42)	EPIC-Spain	Spain	Total flavonoids, flavonols, flavones, flavanones, isoflavones, proanthocyanidins, flavan-3-ols, anthocyanidins, and lignans	Dietary history interview	Men and women of different regions in Spain	29–69	40,622	1,915 all-cause, 416 CVD, 956 cancer	13.6	Age, sex, BMI, education level, physical activity, tobacco smoking, alcohol lifetime, total energy intake.	Vitamin C and fiber intake.
Talaei, 2014 (43)	Singapore Chinese adults	Singapore	Isoflavones	FFQ	Men and women free of cancer	45–74	63,257	2,697 CHD, 1,298 stroke	5	Age, sex, dialect, year of interview, educational level, BMI, physical activity, smoking duration, cigarette smoking per day, alcohol use, baseline history of self-reported diabetes, hypertension, CHD, stroke, total energy intake.	Dietary fiber, SFA, MUFA, and PUFA.
Tresserra-Rimbau, 2014 (44)	Spanish population	Spain	Flavonoids (flavonols, flavones, flavanones, isoflavones, proanthocyanidins, flavan-3-ols, and anthocyanidins) and lignans	FFQ	Men and women free of CVD but at high risk	55–80	7,172	327 (131 cancer, 81 CVD, 115 other causes)	4.8	Age, smoking, cigarettes, cigars and pipes, BMI, baseline diabetes, alcohol, total energy intake, physical activity, family history of CVD or cancer, aspirin use, antihypertensive, drug use, use of cardiovascular medication, use of oral hypoglycemic agents, insulin, other medication.	Intake of protein, SFA, PUFA, MUFAs and cholesterol.
Ivey, 2015 (45)	Calcium Intake Fracture Outcome Age Related Extension Study	Australia	Total flavonoids, flavonols, flavones, flavanones, isoflavones, proanthocyanidins, flavan-3-ols, anthocyanidins	FFQ	Women	>75	1,063	129	5	Age, prevalent CVD and cancer, overweight or obesity, physical inactivity, current cigarette smoking, and alcohol consumption.	Low fruit and vegetable intake.

Table continues

Table 1. Continued

First Author, Year (Reference No.)	Study Cohort	Country	Type of Polyphenol	Food Consumption Source	Population	Age Range, years	No. of Subjects	No. of Cases	Follow-up, years	Adjustments (Nondietary Factors)	Adjustments (Dietary Factors)
Ponzo, 2015 (46)	Population-based sample	Italy	Total flavonoids, flavonols, flavones, flavanones, isoflavones, proanthocyanidins, flavan-3-ols, anthocyanidins	FFQ	Men and women	45–64	1,658	220	12	Age, sex, BMI, education, living in a rural area, physical activity, alcohol intake, smoking, values of systolic and diastolic blood pressure, total and HDL cholesterol, fasting glucose, c-reactive protein, statin and aspirin use.	Fiber, SFA intakes.

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; FFQ, food frequency questionnaire; HDL, high-density lipoprotein; IHD, ischemic heart disease; LDL, low-density lipoprotein; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; TAG, triacylglycerol.

(RR = 0.89, 95% CI: 0.81, 0.97; $I^2 = 0\%$, $P_{heterogeneity} = 0.62$), while no association was found with isoflavones (Figure 2B and Web Figure 3). Heterogeneity found for flavonols and flavan-3-ols was mainly due to one study, by Mursu et al. (39); after this study was excluded, heterogeneity was reduced with no substantial changes in risk estimates. Dose-response analyses resulted in a significant linear association of increased intake of flavonols with decreased risk of CVD death (RR = 0.87, 95% CI: 0.76, 0.99; $I^2 = 78\%$ and $P_{heterogeneity} = 0.01$), flavones (RR = 0.93, 95% CI: 0.90, 0.97; $I^2 = 0\%$ and $P_{heterogeneity} = 0.45$), flavanones (RR = 0.99, 95% CI: 0.97, 1.00; $I^2 = 29\%$ and $P_{heterogeneity} = 0.24$), anthocyanidins (RR = 0.94, 95% CI: 0.88, 0.99; $I^2 = 0\%$ and $P_{heterogeneity} = 0.78$), flavan-3-ols (RR = 0.98, 95% CI: 0.97, 0.99; $I^2 = 0\%$ and $P_{heterogeneity} = 0.81$), and proanthocyanidins (RR = 0.97, 95% CI: 0.94, 1.00; $I^2 = 42\%$ and $P_{heterogeneity} = 0.18$; Web Figure 4).

Lignan intake and mortality

The association between lignan intake and mortality was examined in 3 studies (35, 42, 44). The highest versus the lowest intake of lignans was not associated with decreased risk of all-cause mortality (RR = 0.75, 95% CI: 0.50, 1.11; $I^2 = 35\%$ and $P_{heterogeneity} = 0.25$). Cause-specific mortality was evaluated in 2 studies (35, 42) considering lignans as continuous measure of exposure and showing contrasting results for CVD mortality (data not shown).

DISCUSSION

We conducted the first meta-analysis pooling results from prospective studies on flavonoid and lignan intake and mortality. Regarding phytoestrogens, we observed null results of isoflavone intake and both all-cause mortality and CVD mortality and contrasting findings for lignan intake. A significant, decreased risk of death was associated with higher intake of flavonoids with a linear dose-response relationship, but a limited number of studies contributed to this analysis. However, when analyzing individual classes of flavonoids, a generally decreased risk of all-cause mortality was associated with flavones, flavanones, and anthocyanidins. All flavonoids classes except for isoflavones were significantly associated with decreased risk of CVD mortality, possibly due to the higher number of studies included. These results support the recommendations for consumption of flavonoid-rich foods to prevent chronic and degenerative diseases. However, dose-response analyses were still unreliable for all-cause mortality due to the low number of studies included.

Flavonoid intake differed across studies. Dietary intake of flavonoid may have been derived from older, incomplete food composition databases and estimated by suboptimally designed food frequency questionnaires. Modern analytical techniques allowed a higher resolution in flavonoid food content, which resulted in more comprehensive databases. As a direct consequence, more recent studies assessed more flavonoid classes or included a larger variety of foods containing flavonoids. Even among the most comprehensive studies, some differences occurred. For instance, Tresserra-Rimbau et al. (44)

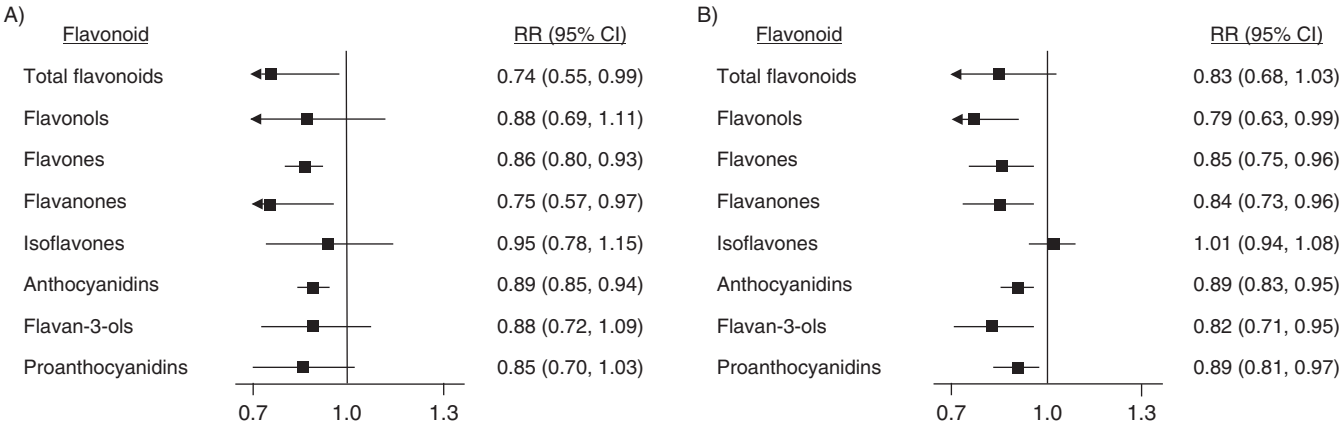

Figure 2. Risk ratios (RRs) of all-cause mortality (A) and cardiovascular disease mortality (B) associated with total intake of flavonoids and individual flavonoid classes, 1996–2015. Squares represent risk estimates for the highest versus the lowest category of exposure and for increased intake assessed by generalized least-squares; horizontal lines represent 95% confidence intervals.

reported much higher flavonol and flavone intake and lower isoflavone intake compared with others. In contrast, Nagata et al. (34) reported higher intake of isoflavones than other studies. Such differences may depend on the different nutritional habits of cohort studied (Spanish and Japanese, respectively, in those studies), which may be characterized by increased

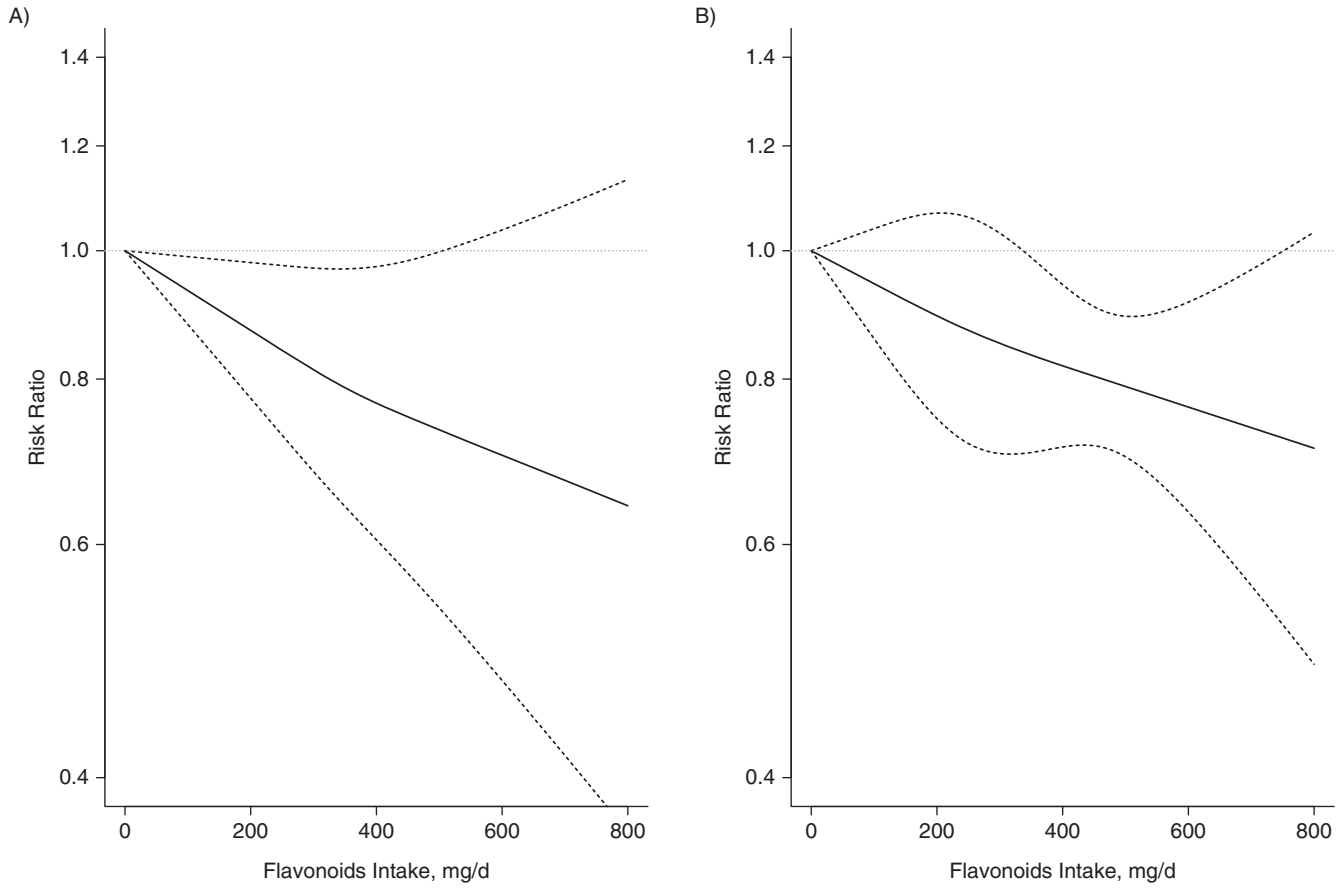

Figure 3. Dose-response analysis evaluating risk ratios of all-cause mortality (A) and cardiovascular disease mortality (B) associated with intake of total and individual flavonoid classes modeled with restricted cubic splines, 2007–2015. Solid lines represent risk estimates; dashed lines represent the 95% confidence intervals.

Table 2. Dose-Response Meta-Analysis of All-Cause and CVD Mortality Associated With Categories of Total Intake of Flavonoids, Compared With No Intake, From a Selection of Studies[a], 2007–2015

Total Flavonoids, mg/day	All-Cause Mortality		CVD Mortality	
	RR	95% CI	RR	95% CI
0	1.00	Referent	1.00	Referent
100	0.94	0.89, 0.98	0.94	0.86, 1.04
200	0.88	0.78, 0.98	0.89	0.75, 1.07
300	0.82	0.69, 0.97	0.85	0.70, 1.03
400	0.77	0.61, 0.97	0.82	0.71, 0.94
500	0.73	0.54, 1.00	0.79	0.70, 0.89
600	0.70	0.47, 1.04	0.76	0.64, 0.92
700	0.67	0.42, 1.08	0.74	0.56, 0.97
800	0.64	0.36, 1.13	0.71	0.49, 1.03
I^2, %	66		52	
$P_{heterogeneity}$	0.002		0.032	

Abbreviations: CI, confidence interval; RR, risk ratio.

[a] A subset of studies including the most complete variety of flavonoid classes was used for this analysis of all-cause mortality (38, 42, 44–46) and CVD mortality (38–40, 45, 46).

consumption of flavonol- and flavone-rich fruit or soy foods rich in isoflavones, respectively. Ivey et al. (41), whose study was responsible for moderate heterogeneity in certain analyses, conducted a relatively small study in Australia.

Our results are in line with previous meta-analyses of randomized controlled trials and observational studies on mortality or CVD-related outcomes and flavonoids and flavonoid-rich foods suggesting that individual flavonoid classes may exert different effects in protecting against CVD. Fruit and vegetable intake has been associated with a decreased risk of mortality in a recent meta-analysis (47). In line with our results, flavan-3-ols from green tea and cocoa products and anthocyanins from berry fruits have been associated with decreased risk of CVD (11, 48). In addition, wine and beer consumption have been demonstrated to have a J-shaped relationship with cardiovascular-related outcomes, although to what degree any potential protection is conferred by the alcoholic or phenolic content is unclear (5, 9). Studies on soy products (rich in isoflavones) and mortality are scarce, but the few investigations showed no significant association (34, 49). Meta-analyses of randomized trials showed that the strongest evidence for green tea and cocoa products was for lowering low-density lipoprotein (50, 51) and improving endothelial function and insulin sensitivity (48). Flavonoids have been extensively studied as compounds potentially responsible for the aforementioned beneficial effects. Previous quantitative reviews suggested that flavonoid intake may decrease the risk of several chronic diseases. Flavonoid intake has been associated with reduced risk of CVD (10), stroke (52), and diabetes (11), and individual studies have reported an inverse association with hypertension (53, 54). Other meta-analyses pointed out the possible association between flavonoid intake (particularly isoflavones) and incidence of certain cancers, such as breast cancer (55, 56), prostate cancer (57), lung cancer (58), and stomach and colorectal cancer (12).

Laboratory studies have demonstrated a number of possible mechanisms through which flavonoids may ameliorate health and decrease mortality risk. The basic pathways hypothesized to confer beneficial effects are related to their antioxidant and antiinflammatory actions. Flavonoids inhibit several processes involved in disease progression, such as oxidative stress and inflammation, as main determinants of CVD (7). More direct influence on CVD prevention may rely on flavonoid effects on endothelial function, regulating vascular homeostasis by producing factors that act locally in the vessel wall and lumen, such as nitric oxide, prostacyclin, and endothelin; antifibrotic effects, regulating fibrinolytic factors, such as tissue plasminogen activator and plasminogen activator inhibitor-1; and platelet aggregation, by regulating factors that affect coagulation (i.e., adhesion molecules and inflammatory cytokines) (59). Flavonoids have also demonstrated effectiveness against cancer; they have been reported to interfere in the initiation, promotion, and progression of cancer by providing a direct inhibition of oxidative stress and oxidative damage (8). Moreover, laboratory studies have shown that flavonoids also exert antiproliferative, antiangiogenic, and antimetastatic effects by modulating different enzymes and receptors in signal transduction pathways related to cellular proliferation, differentiation, and apoptosis (8). Overall, results from basic science mostly agree with the potential role of flavonoids in human diet as protective compounds, but further observational studies and experimental randomized trials are needed to confirm results from this study.

Epidemiologic studies on lignans and mortality risk are less numerous than those on flavonoids. A meta-analysis of 3 studies (35, 42, 44) included in this meta-analysis showed no significant results. Interestingly, Milder et al. (35) suggested that individual lignans, such as matairesinol, may exert different effects on human health, being independently associated with mortality risk. Due to the limited evidence

retrieved from the analyses, our findings preclude final conclusions. Lignans have been associated with decreased risk of chronic diseases (15), especially certain cancers (16). Several mechanisms of action have been hypothesized, including their estrogen-like activity, ability to inhibit several enzymes (i.e., aromatase and 5-alpha-reductase), and stimulation of sex hormone–binding globulin production (16). In addition, lignans have been proven to exert antioxidant activity (2). However, the lack of prospective cohort studies on cancer mortality does not allow us to draw conclusions on their efficacy.

Taken together, the findings of this study suggest flavonoids as potential key compounds for health benefits conferred by a series of functional foods, but research is far from exhaustive and some methodological concerns should be addressed. First, potential collinearity with dietary flavonoid sources may exist. Six studies (25, 30, 31, 34, 38, 40) showed significant association with decreased risk of mortality in unadjusted models and loss of significance when adjusting for potential confounding factors. Only a limited number of studies explored the potential bias with analyses beyond multivariate analyses—for instance, by stratification for tea consumption when exploring catechin (29, 30) and flavonol (41) intake or for main sources of flavonols and flavones, such as apples and onions (25, 37)—or conducted separate analyses on fruits and vegetables (31). Results were mainly confirmatory, but this issue should be further considered in future studies. Third, although all studies adjusted for main potential confounding factors, strata by sex and smoking status would be desirable to assess potential differences between the aforementioned population groups. Fourth, the limited number of studies in some analyses did not allow us to perform proper dose-response analyses (especially for all-cause mortality) and yielded limited power to assess heterogeneity. Fifth, certain data may affect the reliability of the information, such as 1) single baseline assessment of dietary intake, with lack of specific information of intake over time in relation with mortality; 2) limited number of cases in some studies potentially affecting the statistical power of the analyses; and 3) lack of data on association between flavonoid/lignan classes and specific types of mortality, limiting the results for individual classes of compounds and mortality. Finally, some of the studies included were conducted in specific groups of individuals, limiting the generalizability of results to the general population.

In conclusion, this study provides additional evidence of the association between dietary flavonoid intake and decreased risk of death. The potential benefits against CVD may be translated into decreased risk of mortality and may not be limited to cardiovascular-related outcomes due to their association with decreased risk of mortality from all causes. Nevertheless, studies on cancer mortality are scarce, and further research is needed to assess this issue. Due to the complexity of the potential effects of different flavonoids classes, recommendations should focus on dietary variety including different flavonoid sources. Additional research is also necessary to establish the specific role of individual flavonoid classes, whether they provide protection, and what level of consumption is required to achieve health benefits.

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