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Do Flavonoids Reduce Cardiovascular Disease Incidence or Mortality in US and European Populations?

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Abstract

Twenty publications from twelve prospective cohorts evaluated associations between flavonoid intakes and incidence or mortality from cardiovascular disease among adults in Europe and the United States (US). The most common outcome was coronary heart disease mortality, and four of eight cohort studies reported significant inverse associations for at least one flavonoid class (multivariate adjusted p_{trend} <.05). Three of seven cohorts reported that greater flavonoid intake was associated with lower risk of incident stroke. Comparisons were difficult because of variability in the flavonoid classes included, demographic characteristics of the populations, outcomes assessed, and length of follow up. The most common flavonoid classes examined were flavones and flavonols combined (11 studies). Only one study examined all seven flavonoid classes. The flavonol and flavone classes were most strongly associated with lower CHD mortality. Evidence for protection from other flavonoid classes and CVD outcomes was more limited. The hypothesis that flavonoid intakes are associated with lower CVD incidence and mortality requires further study.

Keywords

flavonoids; cardiovascular disease; coronary heart disease; stroke; prospective cohort studies; United States; Europe

INTRODUCTION

Flavonoids are bioactive, polyphenolic, non-caloric, non-nutrient compounds – which are ubiquitous in fruits, vegetables and other vascular plants and cannot be synthesized by

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humans.[1] They are present in relatively high amounts in the diets of US and European populations, who have total intakes of flavonoids that vary from ~200–400 mg/day.[2–8] Single cell,[9–11] in vitro,[12–14] animal,[15–24] and clinical studies[25–40] suggest that intakes of certain flavonoid classes reduce cardiovascular disease risk.[2,41–53] Consequently some experts have recommended increased intakes of flavonoid rich diets for preventive purposes.[54–62]

This article reviews the evidence on the association between intakes of all the flavonoid classes with cardiovascular disease mortality and incidence in prospective adult cohorts in Europe and the US.[63–82]

METHODS

Literature search method

We used Ovid Medline and Ovid Commonwealth Agricultural Bureau (CAB) to search the literature using the following basic search terms: [Flavonoids AND (Cohort or Prospective or Nested or Cross-sectional) AND Cardiovascular diseases]. Additional search terms used were Arteriosclerosis, Cerebrovascular Disorders, Cholesterol, Coronary Disease, Heart Diseases, Hypercholesterolemia, Hypertension, Metabolic Syndrome, Myocardial infarction, Phytoestrogens, and specific flavonoid classes to enhance our ability to identify all possible relevant studies. Retrospective (case-control and cross-sectional) studies[83,84] were excluded to avoid potential recall bias associated with retrospective data collection.[85]

We found twenty publications from twelve prospective cohorts in three European countries and the US, as described in Table 1: Finland (*alpha*-tocopherol *beta*-carotene Cancer Prevention [ATBC] Study,[69,70] Kuopio Ischemic Heart Disease Risk Factor Study,[78] the Finnish Mobile Clinic Health Examination Survey,[72–74] and the Turku and Environs Health Survey[76]), the Netherlands (Dutch Prospect - European Prospective Study into Cancer and Nutrition [EPIC] Cohort,[81] the Rotterdam Study,[65] and the Zutphen Elderly Study[63,66,67,71]), Wales, United Kingdom (Caerphilly Study[68]), and the United States (Health Professionals Follow-up Study [HPFS],[79] Iowa Women's Health Study,[64,77,82] Nurses' Health Study [NHS],[75] and the Women's Health Study [WHS][80]). Only three of these cohorts (the Finnish Mobile, Turku and Rotterdam cohorts) included both men and women. Five of the cohorts (ATBC, Kuopio, Zutphen, Caerphilly, and HPFS cohorts) included only men. One European cohort (Dutch EPIC) and three of the US cohorts (Iowa, NHS, and WHS cohorts) included only women.

Assessment of flavonoid intakes

Flavonoid intakes were assessed in eight cohorts using five different food frequency questionnaires,[64,65,68–70,75,77,79–82] which varied in length from 56[68] to 276[69,70] items. Diet histories were used in three cohorts,[63,66,67,71–74,76] a 4-day dietary record in one,[78] and the last used a checklist along with a dietician interview and food frequency questionnaire.[65]

The data sources for the flavonoid content of foods and beverages also varied. Thirteen studies[65–75,79,82] utilized flavonoid data developed by Hertog et al.[86–90] Two studies[63,64] utilized flavan-3-ol data developed by Arts et al.[91–93] One study[81] on isoflavones used data

and the assessment methodology of Boker et al.[94] Mink et al[77] and Mursu et al[78] used the USDA 2003 flavonoid database[95] and Mink et al[77] also used the USDA 1999 isoflavone database[96] and the USDA 2004 proanthocyanidin database.[97]

In addition to using Hertog's flavonoid data, four Finnish studies[69,70,72,74] used data from Hakkinen et al.[98] Knekt et al[73] (1996) employed flavonoid data from Starke et al[99] and Wildanger et al,[100] and Knekt et al (2002)[74] used data by Mattila et al.[101] The Finnish Turku study by Marniemi et al[76] did not explicitly state the source of its flavonoid data.

For three US studies (NHS,[75] HPFS,[79] WHS[80]), certain American foods were analyzed by Hertog's laboratory at the Netherlands State Institute for Quality Control of Agricultural Products for flavonoids and included in the food frequency composition tables maintained by the Harvard School of Public Health's Department of Nutrition.[102]

Flavonoid classes

Figure 1 provides examples of common compounds in the monomeric and polymeric flavonoid classes in foods used in the flavonoid food composition tables of the USDA.[97,103,104] The "monomeric" (single flavonoid structure) flavonoids studied listed here by class (and the compounds within each class) include: flavonols (isorhamnetin, kaempferol, myricetin, quercetin), flavones (apigenin, luteolin), flavanones (eriocitrin, hesperetin, naringenin), flavan-3-ols (catechin, epicatechin, epigallocatechin, epicatechin gallate, epigallocatechin gallate, gallocatechin), anthocyanidins (cyanidin, delphinidin, malvidin, pelargonidin, peonidin, petunidin), and isoflavones (daidzein, genistein). The "polymeric" (two or more connected flavan-3-ol structures) flavonoids are the proanthocyanidins (which include flavan-3-ol monomers [due to current analytic methods], dimers, trimers, 4–6mers, 7–10mers, and oligomers [usually up to twenty or twenty-five flavan-3-ol units]).

Total flavonoid intakes could not be considered because different classes were assessed from study to study. Only one study (Mink et al[77]) assessed all seven classes.

Classification of mortality outcomes

International Classification of Disease (ICD) codes shown in Table 2 were those for the time at which each study was done (8th and 9th revisions,[105,106] with the 10th revision[107] used only by Geleijnse et al[65] and Mursu et al[78]); Rimm et al,[79] and Sesso et al[80] used World Health Organization classifications[108,109] but did not explicitly state the ICD code revision used.

RESULTS

We present a synopsis of the studies of the various cardiovascular disease outcomes based on the flavonoid classes most frequently assessed. Although there is some evidence that total flavonoid intakes may be relevant to some cardiovascular disease endpoints in experimental animals,[15] the differences in which flavonoid classes were examined made calculation of total flavonoid intakes that were comparable from study to study impossible.

The most commonly measured flavonoids were the flavonol and flavone classes combined or flavonols alone. All studies, with the single exception of the Netherlands EPIC cohort,[81] assessed the flavonols[63–80,82] (two studies[63,64] included flavonol intake in their articles but not in their analyses because they were examining flavan-3-ols and cardiovascular disease endpoints only). All except three cohorts (Netherlands EPIC[81] and Rotterdam,[65] Caerphilly, Wales[68]) estimated intakes of the flavones, either as an individual class or compounds[74,76–78,80] or combined with the flavonols[66,67,69–71,73,75,76,79,80,82] (three studies did not use flavones[63,64,72] in their analyses). Only three cohorts (Iowa,[64,77] Kuopio,[78] and Zutphen[63]) assessed intakes of the flavan-3-ols. Similarly, three cohorts (Finnish Mobile,[74] Iowa,[77] Kuopio[78]) estimated flavanone intakes. Two cohorts (Netherlands EPIC[81] and Iowa[77]) estimated isoflavone intakes, two cohorts (Iowa[77] and Kuopio[78]) anthocyanidin intakes, and only one cohort (Iowa[77]) estimated intakes of the proanthocyanidins. In evaluating studies, results were declared significant if the multivariate adjusted test for trend was $p<.05$.

Tables 3 and 4 summarize the published studies on the relationship between flavonoid intakes and cardiovascular disease incidence or mortality in European and US prospective cohorts. The summary begins with the studies of flavonoid intakes and cardiovascular disease mortality because more publications had their primary analysis on flavonoid intakes and mortality than on incidence.

Mortality

Coronary Heart Disease Mortality—Coronary heart disease mortality was the most extensively studied outcome (with a total of thirteen publications from eight prospective cohorts)[63,65–69,73–75,77,79,82] in four countries (Finland, the Netherlands, United States and Wales). Only one of these studies (Iowa[77]) assessed intakes of all seven flavonoid classes. Most of the other studies assessed intakes of the flavonols and flavones combined (six cohorts). Five cohorts assessed associations with flavonol intakes, one with flavones, and two each with flavanones and flavan-3-ols.

Flavonols and Flavones: All studies of fatal coronary heart disease examined flavonol intakes (either the flavonols separately[65,68,74,75,77,82] or the flavone and flavonol classes combined[66,67,69,73,75,79,82]). Four[66,67,73,82] out of the seven[66,67,69,73,75,79,82] studies that examined the relationship of flavones and flavonols combined reported lower risk of fatal coronary heart disease with higher flavonoid consumption.

Specifically, flavonols and flavones were significantly associated with reduced coronary heart disease mortality in the Zutphen Elderly Study cohort at both five and ten years of follow-up (Hertog et al[66,67]). Although confidence intervals (CI) were less than 1.0 for point estimates, there was not a statistically significant trend for an inverse association over the intake range investigated in the small Finnish Mobile cohort (Knekt et al[73]) and the large Iowa cohort of postmenopausal women (Yochum et al[82]). These compounds were not associated with fatal coronary heart disease in the ATBC cohort in Finland (Hirvonen et al[69]), the female NHS (Lin et al[75]) or the male HPFS cohort (Rimm et al[79]).

Five studies[65,68,74,75,77] examined the flavonol class or its individual compounds separately. In the Dutch Rotterdam study[65] there was an inverse association between flavonol intake and risk of fatal coronary heart disease after almost six years of follow up. In the Finnish Mobile Clinic study by Knekt et al,[74] after twenty-eight years of followup, the flavonols quercetin (significantly) and kaempferol (borderline) were associated with lower coronary heart disease mortality but the flavonol myricetin was not. Lin et al,[75] who examined intakes of the individual flavonol compounds separately in the NHS, found that only the flavonol kaempferol was significantly associated with lower coronary heart disease mortality in US nurses after twelve years of followup. However, three other studies (Caerphilly,[68] Iowa[77,82]) reported no association with flavonol intake.

A 2003 meta-analysis[110] which included six[67–69,73,79,82] of the studies reviewed here, found a statistically significant 20% lower association between flavonol intakes in the highest compared to lowest tertile (RR [risk ratio] 0.80, 95% CI 0.69, 0.93 after adjustment for known coronary heart disease risk factors and other dietary components) and coronary heart disease mortality, and subsequent studies appear to be in the same direction.[65,74,75,77]

Other Flavonoid Classes (Flavan-3-ols, Flavanones, Isoflavones, Anthocyanidins and Proanthocyanidins): Far fewer studies examined the other classes (flavanones,[74,77] flavan-3-ols,[63,64,77] anthocyanidins,[77] isoflavones,[77] and proanthocyanidins[77]), probably because comprehensive food composition data for these five classes were lacking at the time the earlier studies were done.

Arts et al[63] studied intakes of the flavan-3-ols in the Dutch Zutphen cohort and found that higher intakes (catechins and epicatechins) were significantly associated with a lower risk of coronary heart disease mortality after ten years of followup. However, these same investigators[64] found no significant associations between flavan-3-ol intakes and deaths from coronary heart disease among Iowa women after thirteen years of followup, nor were flavan-3-ols associated with coronary heart disease mortality in a subsequent analysis in this same cohort (Mink et al[77]).

Knekt et al[74] studied the associations between flavanones individually and combined with the flavonol and flavone classes and found no associations with coronary heart disease mortality in the Finish Mobile clinic cohort. In the Iowa postmenopausal cohort with fifteen years of follow up, Mink et al[77] studied all seven classes of flavonoids and found significant inverse associations between intakes of anthocyanidins and flavanones and coronary heart disease mortality. However, the associations between flavonols, flavones, isoflavones, or proanthocyanidins and this outcome were not statistically significant in this study.[77]

In summary, six[63,66,67,74,75,77] out of the thirteen studies[63–69,73–75,77,79,82] (four out of eight cohorts) found significant inverse associations between at least one of the flavonoid classes and coronary heart disease mortality, and three additional studies[65,73,82] found nonsignificant trends toward lower risk. Only the Caerphilly Study (Hertog et al[68]) suggested a higher risk of fatal coronary heart disease with greater flavonol intake; however, the confidence interval included 1.0 and the trend was not statistically significant.

Stroke mortality—Only three studies from two cohorts (Iowa and Zutphen) examined the relationship between flavonoid intakes and fatal stroke.

Flavonols and Flavones: In the Iowa cohort, neither the flavonols and flavones combined at ten years of followup (Yochum et al[82]) nor the flavonol and flavone classes examined separately at sixteen years followup were associated with stroke mortality (Mink et al[77]).

Other Flavonoid Classes (Flavan-3-ols, Flavanones, Isoflavones, Anthocyanidins and Proanthocyanidins): The flavan-3-ols were not associated with stroke mortality in the Zutphen cohort (Arts et al[63]) at ten years followup. Intakes of flavan-3-ols, flavanones, anthocyanidins, isoflavones, proanthocyanidins, and total flavonoid intake were not associated with stroke mortality after sixteen years of followup in the Iowa cohort of postmenopausal women (Mink et al[77]).

In summary, no associations were observed between flavonoid intakes and fatal stroke in three different studies[63,77,82] of two cohorts.

Total Cardiovascular Disease Mortality—Three studies in three separate cohorts (Iowa,[77] Kuopio,[78] WHS[80]) assessed flavonoid intakes and total cardiovascular disease mortality (fatal coronary heart disease and stroke combined).

Flavonols and Flavones: Sesso et al[80] found no associations between intakes of flavonol plus flavone classes combined or their individual compounds and cardiovascular disease death after nearly seven years of follow up in a study of American postmenopausal women (WHS). Neither Mink et al[77] in the Iowa cohort at sixteen years of followup nor Mursu et al[78] in the Kuopio cohort at fifteen years of follow up found associations between the flavone or the flavonol classes examined separately and cardiovascular disease mortality.

Other Flavonoid Classes (Flavan-3-ols, Flavanones, Isoflavones, Anthocyanidins and Proanthocyanidins): Mink et al[77] also estimated intakes of the flavan-3-ols, flavanones, anthocyanidins, isoflavones, and proanthocyanidins in the Iowa cohort after sixteen years of follow up and associations with cardiovascular disease mortality. Flavanones were inversely associated with a borderline significantly lower risk and anthocyanidins with a significantly lower risk of cardiovascular disease mortality in this cohort.[77] However, in the Kuopio cohort, Mursu et al[78] found no associations between anthocyanidins, flavanones, and flavan-3-ols and cardiovascular disease mortality after more than fifteen years of followup.

In summary, in the three prospective cohorts in which flavone and flavonol intakes and total cardiovascular mortality were examined (Iowa,[77] Kuopio,[78] WHS[80]), there was no observed relationship between these intakes and death from cardiovascular disease. However, the flavanones and anthocyanidins were significantly associated with lower risk of cardiovascular disease mortality in a recent Iowa cohort analysis.[77]

Incidence

Coronary Heart Disease Incidence—The relationship between flavonoid intakes and coronary heart disease incidence (either as nonfatal or nonfatal and fatal disease combined) was investigated in eleven studies.[63,65–69,75,76,79–81]

Nonfatal coronary heart disease incidence

Flavonols and Flavones: Hirvonen et al[69] (2001) assessed intakes of the flavonol plus flavone classes combined among male Finnish smokers in the ATBC cohort. Higher intakes were nonsignificantly associated with lower incidence of coronary heart disease. In contrast, there were no observed associations between intakes of either the flavonols individually (kaempferol, myricetin, quercetin) or the flavonol and flavone classes combined and coronary heart disease incidence in the HPFS cohort (Rimm[79]) of US men after six years of follow up. Similar findings were observed in US women; Lin et al[75] found no association between intakes of the flavonols individually (kaempferol, myricetin, quercetin) or the flavones and flavonols combined and coronary heart disease incidence after twelve years of followup in the NHS cohort. In the Dutch Rotterdam study, Geleijnse et al[65] found no significant associations between flavonols and nonfatal coronary heart disease among Rotterdam men and women after almost six years of follow up.

Other Flavonoid Classes (None): No prospective cohort studies were available on nonfatal coronary heart disease and the other five classes of flavonoids.

In summary, three of the four of the cohorts[65,69,75,79] that examined flavonoid intakes and nonfatal coronary heart disease were null for flavonols and flavones. Only one study[69] reported a protective association with the flavonol plus flavones classes combined.

Nonfatal and fatal coronary heart disease incidence—Nine studies in seven cohorts[63,65–68,76,79–81] examined the relationship between flavonoid intake and fatal and nonfatal coronary heart disease combined.

Flavonols and Flavones: Among elderly Dutch men in Zutphen, flavonols and flavones combined were inversely but not significantly associated with nonfatal and fatal coronary heart disease at five years[66] and ten years[67] of followup. Intakes of flavonols plus flavones combined were also not associated with incident coronary heart disease in the HPFS cohort (Rimm et al[79]). In the Caerphilly study neither quercetin (a flavonol) nor total flavonol intakes were associated with incident coronary heart disease after ten years of followup.[68] In the Dutch Rotterdam study[65] there were no significant associations between flavonol intakes and nonfatal and fatal coronary heart disease after almost six years of follow up.

Sesso et al[80] reported no associations between intakes of flavonol plus flavone classes combined and incident coronary heart disease in the US WHS. Similarly, no significant associations for individual flavonol and flavone compounds or flavonols plus flavones combined were found among men and women in the Finnish Turku study[76] after ten years of followup except for the flavone luteolin which was significantly associated with lower coronary heart disease incidence.

Other Flavonoid Classes (Flavan-3-ols, Isoflavones): Arts et al[63] found no associations between flavan-3-ol intakes and fatal and nonfatal coronary heart disease in the Zutphen cohort. In the Dutch EPIC cohort, van der Schouw et al[81] found no associations between estimated median intakes of ~0.4 mg isoflavones per day and incident coronary heart disease in women. It should be noted that these isoflavone intakes were less than a fiftieth of those reported in recent Asian studies (~29 mg/day).[111]

In summary, only one cohort[76] found protective associations between flavonoid intake (the flavone luteolin) and lower risk of fatal and non-fatal coronary heart disease.

Stroke incidence—Nine studies from seven cohorts[63,70–72,74,76,78,80,81] assessed the relationship between flavonoid intakes and both fatal and nonfatal stroke.

Total stoke incidence

Flavonols and Flavones: In the Zutphen study after fifteen years of followup, Keli et al[71] found significant inverse associations between flavonol plus flavone intakes combined and stroke incidence for elderly Dutch men as did Mursu et al[78] for flavonols in the Kuopio cohort. In contrast, in the ATBC cohort of male Finnish smokers, Hirvonen et al[70] found no significant association between flavonol plus flavone intakes and stroke incidence. Likewise, Sesso et al[80] found no associations between flavonol and flavone intakes their combined and stroke incidence among American postmenopausal women from the WHS cohort with nearly seven years of follow up, and Marniemi et al[76] found no association between flavonols and flavones either as individual compounds or combined intake and stroke in the Turku cohort of Finnish men and women after ten years of follow up. Similarly, in the Finnish Mobile Clinic study of men and women, Knekt et al (2000,[72] 2002[74]) found no association between the intake of the flavonol quercetin[72,74] or myricetin[74] and stroke incidence in adults after twenty-eight years of followup. However, they did observe an association between intake of the flavonol kaempferol as well as total intakes of flavonols, flavones and flavanones combined and incident stroke.[74] A meta-analysis by Hollman et al[112] of six cohorts included in this review,[70,71,74,77,78,80] with a total of 111,067 participants, 2,155 cases, and six to twenty-eight years of followup, found borderline significant inverse associations between greater flavonol intake and incident stroke (RR 0.80, 95% CI 0.65, 0.98), for the top vs bottom intake quartile.

Other Flavonoid Classes (Flavan-3-ols, Flavanones, Isoflavones, Anthocyanidins): In studies of fatal and nonfatal stroke incidence, Arts et al[63] observed that flavan-3-ol intake was not associated with stroke incidence in the Zutphen cohort with ten years of follow-up. The EPIC study of Dutch women[81] found no association between isoflavone intakes (estimated median intakes ~0.4 mg/day) and incident stroke. In the Finnish Mobile Clinic cohort[74] in addition to the flavonol kaempferol, as noted above, the flavanone hesperetin and the flavanone naringenin as well as total intakes of flavonols, flavones and flavanones combined were inversely and significantly associated with stroke incidence. Mursu et al[78] found no association with intakes of anthocyanidins, flavanones, flavan-3-ols, or total intake of all five classes (flavonols, flavones, flavanones, flavan-3-ols, anthocyanidins) and stroke incidence in the Finnish Kuopio cohort.

In summary, only three[71,74,78] of nine studies (from seven prospective cohorts)[63,70–72,74,76,78,80,81] reported lower risk of fatal and nonfatal stroke combined and these inverse associations were confined to the flavonols, the flavones, and the flavanones.

Hemorrhagic and Ischemic stroke incidence—Three studies from two cohorts examined hemorrhagic stroke.[70,72,74] Ischemic stroke was considered in two studies of one cohort.[72,74]

Flavonols and Flavones: In the Finnish Mobile cohort, Knekt et al (2000[72] 2002[74]) reported a significant inverse association between kaempferol[74] and ischemic (RR 0.63, 95% CI 0.47, 0.85 p_{trend} 0.004), but not hemorrhagic, stroke. No association was seen between intake of the flavonols quercetin[72,74] and myricetin[74] and incident hemorrhagic or ischemic stroke. Hirvonen et al's study[70] of male Finnish smokers from the ATBC cohort found no significant associations between flavonol and flavone intakes combined and hemorrhagic stroke incidence.

Other Flavonoid Classes (Flavanones): In his study of the Finnish Mobile Clinic two years after his first report,[72] Knekt et al[74] found significant associations between the flavanone hesperetin (RR 0.74, 95% CI 0.55, 1.00; p_{trend} 0.01), the flavanone naringenin (RR 0.73, 95% CI 0.54, 0.98; p_{trend} 0.009), and the total of flavone, flavonol and flavanone intakes combined (RR 0.73, 95% CI 0.54, 0.98; p_{trend} 0.004) and ischemic stroke incidence but no associations with hemorrhagic stroke incidence.

In summary, only one[74] of the three studies (in two cohorts)[70,72,74] that examined flavonoid intakes in relation to hemorrhagic or ischemic stroke incidence found an significant association with intakes of the flavonol kaempferol, the flavanones hesperetin and naringenin and the flavanones, flavonols, and flavones combined and lower risk of ischemic stroke.[74]

Cardiovascular disease incidence—Only two cohorts (WHS[80] and Dutch EPIC[81]) examined the relationship between flavonoids and cardiovascular disease incidence, and neither cohort found any associations.

Flavonols and Flavones: Sesso et al[80] studied the associations between flavonols and flavones and cardiovascular disease incidence in American women from the WHS cohort. They found no associations between total intakes of flavones and flavonols or the individual compounds (quercetin, kaempferol, myricetin, apigenin, luteolin) and cardiovascular disease incidence.[80]

Other Flavonoid Classes (Isoflavones): Van der Schouw[81] estimated median intakes of isoflavones in Dutch women at (~0.4 mg/day) and found no association between isoflavone intakes and cardiovascular disease incidence.

In summary, the limited data on associations between flavonoids and cardiovascular disease incidence were null.

Overall Summary: Intakes of flavonoids, particularly of the flavonol and flavone classes, were associated with lower cardiovascular disease mortality and incidence in eight of the twenty prospective studies reviewed (six out of twelve cohorts), although results were not entirely consistent for any particular flavonoid class or compound (Table 4). The associations between flavonoid consumption and non-fatal cardiovascular disease were weaker, but there were fewer studies of these outcomes.

DISCUSSION

Our review of existing cohort studies of flavonoid intake and cardiovascular disease risk in the US and Europe provides some, albeit limited, evidence that certain flavonoids are related to lower risk of mortality from coronary heart disease. What was strikingly apparent in this review was the need for greater uniformity on a number of factors before definitive conclusions could be drawn from existing studies. Comparisons among the studies included in this review of European and American cohorts were complicated by variability of the study designs including flavonoid classes assessed, dietary assessment tools used, population characteristics (such as age, sex, and health status), cardiovascular endpoints chosen, and length of followup.

We did not consider total flavonoid intake in our summary because the term “total flavonoids” was used in the individual cohorts to represent the total of different and varying numbers of flavonoid classes. In addition to the questions of the practical utility of such a term, the theoretical basis for assessing the impact of “total” flavonoid intakes on cardiovascular disease is also uncertain. Although there are many putative biological mechanisms underlying a possible cardioprotective role for flavonoids,[113,114] including antioxidant,[16,115,116] vasodilatory,[117–123] antithrombotic[23,124–127] anti-inflammatory,[19,21,22,48,128] and endothelial protective[23,35,48,129,130] properties of some of the compounds,[131] the effects of the flavonoids appear to vary from compound to compound within each class, rather than being inherent in all compounds in each of the several classes.[1,50]

Because the flavonoids are very diverse in their physiochemical properties (lipophilicity, polarity, etc.) as well as very different in their bioavailability and bioactivity (such as antioxidant capacity or binding at receptor sites), the rationale for assuming that exposures to all flavonoid classes might have effects on cardiovascular disease needs more consideration. At present, the evidence that flavonoid classes or compounds have impact on cardiovascular disease relies chiefly on in vitro[12–14] and animal studies.[15–24] Thus, the biological rationale for suggesting that flavonoid classes grouped by their structural features have common functional effects that lower cardiovascular disease incidence or mortality remains unclear. Differences between compounds within each class may be significant.

The associations between flavonoid intakes and coronary heart disease mortality were strongest for the flavonol class. Our results support the findings of a prior meta-analysis[110] of flavonol intakes and coronary heart disease mortality that covered six[67–69,73,79,82] of the eight prospective cohorts[67–69,73–75,77,79,82] we reviewed. In the studies we reviewed, protective associations by the flavanones and anthocyanidins against coronary heart disease

mortality were somewhat stronger in a recent study[77] using more complete food flavonoid composition tables. In contrast to findings for coronary heart disease mortality, only one of the eleven studies[63,65–69,75,76,79–81] of coronary heart disease incidence in these nine cohorts was statistically significant, and solely for the flavone luteolin.[76]

Unlike the positive findings for reduced risk of coronary heart disease mortality, three studies (from two cohorts)[63,77,82] of stroke mortality were null. However, three[71,74,78] of the nine studies of stroke incidence[63,70–72,74,76,78,80,81] reported some associations between greater consumption of flavonols, flavones and flavanones and reduced risk.

Total cardiovascular disease (coronary heart disease and stroke combined) were examined in four studies from four cohorts,[77,78,80,82] but only one study[77] reported significant inverse associations for flavonoids, specifically for intakes of flavanones and anthocyanidins and cardiovascular mortality.

The inconsistencies across the epidemiologic studies that were evident in this review complicated interpretation. Differences in exposure assessment were many (due to varied dietary assessment instruments and incompleteness of flavonoid food composition databases used), making comparisons between studies difficult. Errors of exposure measurement were due in large part to the lack of analytic values for specific foods and flavonoid classes. The more recent studies assessed more flavonoid classes, taking advantage of the more recent flavonoid analytic techniques and flavonoid food data that has resulted in more comprehensive flavonoid databases.[104,132,133]

Additional errors in exposure assessment may have arisen from underestimates of flavonoid content due to the use of food frequency questionnaires which grouped several foods together into a single category (such as melons grouped with berries in early food intake studies). Although food frequency questionnaires may have limitations for assessing intakes of flavonoids, they are widely used in epidemiological studies of the type we reviewed here. In the future, the use of food frequency questionnaires that are constructed to target flavonoid food sources more precisely may provide better information on flavonoid intakes and cardiovascular outcomes.

Biomarkers of intakes were not used in these studies. Although there are several recent studies of flavonoid biomarkers[134–139] and several studies validating isoflavone intakes[140–153] very few validation studies[154–157] of other flavonoids have been done that examined blood or urine samples for biomarkers.[158,159] Thus, the errors in flavonoid intake assessment may have been considerable. Earlier investigations were probably too imprecise to uncover consistent statistically significant associations with cardiovascular endpoints if they were present.

Comparisons across studies were also challenging because of differences from study to study in age, sex, length of followup, health status and the cardiovascular endpoints studied. In most studies diet was assessed only once, so that consistency in diet over time could not be measured or accounted for in analyses. Eight of the studies included less than 200 cases[63,65–68,71,76,78] limiting statistical power. If the associations between these compounds

and risk do exist but are relatively small, larger studies and/or pooled analyses will be required to demonstrate these differences.

The European and US cohorts reviewed herein appeared to be quite similar in their flavonoid intakes. In contrast, flavonoid intakes of European and US cohorts differ strikingly from profiles reported for Asian populations in at least one respect; that the US and European populations ate lesser amounts of isoflavones (<1 mg/day) than Asians (~29 mg/day).[111] Differences between European and US diets[2–8] and Asian diets[140,160] in other flavonoid classes are not well documented. Explorations of the associations between intakes of isoflavones or other flavonoids in Asian diets and cardiovascular disease outcomes in Asian populations in were beyond the scope of this paper, but they also deserve attention. High levels of specific flavonoids such as those observed in Asian cohorts[111] or in studies of populations with greater intakes of these and other flavonoids (e.g. vegetarians) may be needed to replicate findings in Asian cohorts.[161,162]

The studies reviewed here were primarily of older men and women who may have had advanced cardiovascular disease already. If the effects of the flavonoids occur earlier in the disease process, younger populations might be more suitable. Additional research is warranted on flavonoid and cardiovascular disease prevention and survival, since several flavonoids, including the anthocyanins, flavones, flavan-3-ols and proanthocyanidins may have blood pressure lowering effects[2,30,122,163,164] and may have beneficial effects on other cardiovascular disease risk factors as well.[48,60,113,118,165] The studies reviewed here estimated flavonoid intakes from foods, which contain numerous flavonoids as well as other nutritive and non-nutritive compounds. Thus the potential for confounding by other nutrients and bioactive compounds exists. It is therefore not known, based on the existing literature, whether flavonoid supplements in larger doses are safe[166–174] or would afford meaningful protection.[175,176]

In spite of the limitations of many of the existing studies, particularly the earlier studies, evidence is building that some flavonoid classes (flavonols, anthocyanidins, flavanones, and possibly flavan-3-ols) appear to be associated with lower coronary heart disease mortality in these European and US cohorts. Randomized controlled trials for the effects of flavonoid containing foods on cardiovascular disease outcomes would be difficult and perhaps impractical to conduct, although studies of their effects on surrogate markers may be possible. The flavanones and flavonols were also inversely related to stroke incidence in three out of seven cohorts. The overall findings from these cohorts suggest but do not prove that higher flavonoid consumption may be associated both with primary prevention of cardiovascular disease and, perhaps even more so, with a lower risk of cardiovascular disease mortality.

CONCLUSION

There is intriguing but not yet compelling evidence that relatively small amounts of certain of the dietary flavonoids may lower risk of coronary heart disease mortality in European and US countries. More research is needed to establish that cardioprotective relationships exist with these bioactive compounds and, if they prove to be protective, what consumption levels

may be required to achieve health benefits. Future studies are needed that allow for more direct comparison of research findings using more complete and comprehensive flavonoid databases, more standardized and comprehensive dietary assessment methods, more information on the age, sex, health status and other characteristics of populations studied, more complete cardiovascular outcome measures, and longer lengths of follow-up that will allow for more direct comparison of research findings.

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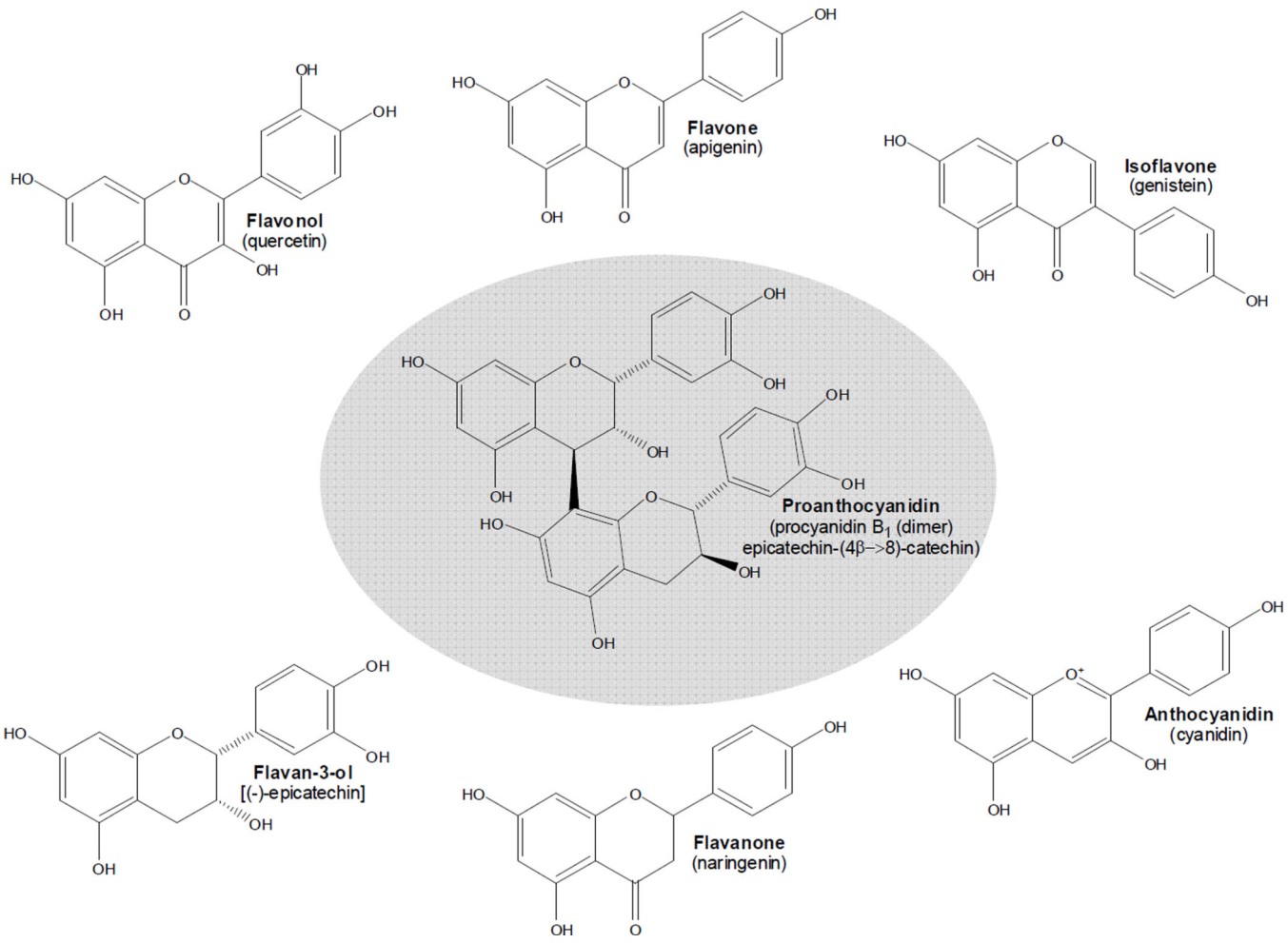

Figure 1.

Flavonoid classes commonly found in plant foods with representative examples of each. Except for flavan-3-ols and proanthocyanidins, most compounds in the other classes have sugars attached (flavonoid glycosides). Here they are all presented as aglycones (without sugars).

Table 1

Prospective cohorts examined

Cohort description	Studies N	Endpoints	Flavonoid intake mean mg/d (median mg/d)
Finland			
Finnish Mobile Clinic Health Examination Survey M & F, 1966–1972 ages 30–69	Knekt 1996[73] 2,748 M & 2,385 F	CHD mortality	Flavones & flavonols (3.4)
	Knekt 2000[72] 9,208 M & F	Stroke incidence	Flavonol (quercetin) 3.68 M, 4.07 F
	Knekt 2002[74] 9,131 M & F	CHD mortality Stroke incidence	Flavonols 4.0 Flavones <0.1 Flavanones 20.2
***alpha*-tocopherol, *beta*-carotene Cancer Prevention Study (ATBC)** M, 1985–1988 ages 50–69	Hirvonen 2000[70] 26,497 M	Stroke incidence	Flavones & flavonols (8.0)
	Hirvonen 2001[69] 25,372 M	CHD mortality CHD incidence	Flavones & flavonols 9.9
Turku and Environs Health Survey M & F, in 1986–1987 ages 65–99	Marniemi 2005[76] 361 M & 394 F	CHD incidence Stroke incidence	Flavones 0.5[1] Flavonols 9.6[1]
Kuopio Ischemic Heart Disease Risk Factor Study M, in 1984–1989 ages 42, 48, 54,or 60	Mursu 2008[78] 1,950 M	CVD mortality Stroke incidence	Flavones 0.3 Flavonols 10.0 Flavanones 3.1 Flavan-3-ols 119.7[2] Anthocyanidins 6.2
Netherlands			
Zutphen Elderly Study M, in 1985 ages 65–84	Hertog 1993[66] 805 M	CHD mortality CHD incidence	Flavones & flavonols 25.9
	Keli 1996[71] 552 M	Stroke incidence	Flavones & flavonols 22.2
	Hertog 1997[67] 804 (mortality) 692 (incidence)	CHD mortality CHD incidence	Flavones & flavonols 25.9[3]
	Arts 2001[63] 806 M	CHD mortality CHD incidence Stroke mortality Stroke incidence	Flavan-3-ols 72
Rotterdam Study M & F, 1990–1993 aged ≥55	Geleijnse 2002[65] 1836 M & 2971 F	CHD mortality CHD incidence	Flavonols 28.6
Dutch Prospect-European Prospective Study Into Cancer and Nutrition Cohort (EPIC) F, 1993–1997 ages 49–70	van der Schouw 2005[81] 16,165 F	CHD incidence Stroke incidence CVD incidence	Isoflavones (0.4)[4]
Wales, UK			
Caerphilly Study M, 1979–1983 ages 45–59	Hertog 1997[68] 1,900 M	CHD mortality CHD incidence	Flavonols 26.3
USA			
Health Professionals Follow-up Study (HPFS) M, in 1986 ages 40–75	Rimm 1996[79] 34,789 M	CHD mortality CHD incidence	Flavones & flavonols 20.1
Iowa Women's Health Study F, in 1986 ages 55–69	Yochum 1999[82] 34,492 F	CHD mortality Stroke mortality	Flavones & flavonols 13.9
	Arts 2001[64] 32,857 F	CHD mortality	Flavan-3-ols 25.4

Cohort description	Studies N	Endpoints	Flavonoid intake mean mg/d (median mg/d)
	Mink 2007[77] 34,492 F	CHD mortality Stroke mortality CVD mortality	Flavones (0.4) Flavonols (8.9) Flavanones (40.4) Flavan-3-ols (20.4)[5] Anthocyanidins (0.2)[6] Isoflavones (0.3) Proanthocyanidins (175.2)[7]
Women's Health Study (WHS) F, in 1992 ages ≥45	Sesso 2003[80] 38,445 F	CVD mortality CHD incidence Stroke incidence CVD incidence	Flavones & flavonols 24.6
Nurses' Health Study (NHS) F, in 1976 ages 30–55	Lin 2007[75] 66,360 F	CHD mortality CHD incidence	Flavones & flavonols 21.2

M – males, F- females

[1] Average of controls for stroke and acute myocardial infarction

[2] Includes theaflavins and thearubigins

[3] Not stated in article but article refers to Hertog et al[66]

[4] Isoflavone data is scored, analytical values not used

[5] Flavan-3-ols and proanthocyanidin monomers averaged to determine intake

[6] Approximation not specifically stated

[7] Proanthocyanidins minus proanthocyanidin monomers

Table 2

International Classification of Disease Codes (ICD) for Cardiovascular Disease

Cardiovascular Disease Outcomes	ICD 8	ICD 9	ICD 10
Mortality			
Coronary Heart Disease Deaths*	410–414	410–414, 429.2	I20–I25
Stroke Deaths	430–438	430–438	I60–I69
Cardiovascular Disease Deaths	410–438	390–459	I20–I99
Incidence			
Coronary Heart Disease Incidence*	410–414	410–414, 427.5	I20–I25
Stroke Incidence**	430–438	430–438	I60–I69
Cardiovascular disease Incidence	410–438	390–459	I20–I99

* Ischemic heart disease

** Hemorrhagic stroke ICD 8-430-431, ICD 9-430-432, ICD 10-I60-I62

** Ischemic stroke ICD 8-433-434, ICD 9-433-434, ICD 10-I63

Table 3

Associations between flavonoid intakes, incidence of coronary heart disease, stroke, and total cardiovascular disease mortality and incidence by cohort and country (multivariate adjusted p_{trend} <.05 in bold face)*

Cohort	Study	Flavonoid classes studied	Population	Follow up yrs	Covariate measures	CHD mortality (deaths)	Stroke mortality (deaths)	CVD mortality (deaths)	CHD incidence (events)	Stroke incidence (events)	CVD incidence (events)
Finland											
Finnish Mobile Clinic Health Examination Survey	Knekt 1996[73]	**Flavones & flavonols**	2,748 M & 2,385 F	26	age, BMI, BP, chol, smoking BC, energy, FA, fiber, vit C, vit E	Flavones & flavonols 0.67 RR (0.44, 1.00) CI p_{trend} 0.12 [4.8 vs 2.1 mg/d][b] (n 324 men) Flavones & flavonols 0.73 RR (0.41, 1.32) CI p_{trend} 0.21 [5.5 vs 2.4 mg/d][b] (n 149 women)					
	Knekt 2000[72]	**Flavonol (Quercetin)**	9,208 M & F	28	age, BMI, BP, chol, diabetes, region, SE, smoking BC, energy, FA, fiber, quercetin, vit C, vit E,					Flavonols 0.99 RR (0.71, 1.38) CI p_{trend} 0.80 [4.6 vs 2.0 mg/d][b] (n 445 men) Flavonols 0.85 RR (0.60, 1.21) CI p_{trend} 0.62 [5.2 vs 2.3 mg/d][b] (n 378 women)	
	Knekt 2002[74]	**Flavanones, flavones, flavonols**	9,131 M & F	28	age, BMI, BP, chol, diabetes, region, SE, sex, smoking	**Flavonol** (Quercetin) 0.79 RR (0.63, 0.99) CI p_{trend} 0.02 [M 3.9 vs 1.5, F 4.7 vs 1.8 mg/d][b] (n 681) (Kaempferol) 0.82 RR (0.66, 1.02) CI p_{trend} 0.06 [M 0.8 vs 0.1, F 0.9 vs 0.2 mg/d][b] (n 681)				**Flavonol** (Kaempferol) 0.70 RR (0.56, 0.86) CI p_{trend} 0.003 [M 0.8 vs 0.1, F 0.9 vs 0.2 mg/d][b] (n 806) **Flavanones** (Hesperetin) 0.80 RR (0.64, 0.99) CI p_{trend} 0.008 [M 15.4 vs 0, F 26.8 vs 3.2 mg/d][b]	

Cohort	Study	Flavonoid classes studied	Population	Follow up yrs	Covariate measures	CHD mortality (deaths)	Stroke mortality (deaths)	CVD mortality (deaths)	CHD incidence (events)	Stroke incidence (events)	CVD incidence (events)
										(n 806) (Naringenin) 0.79 RR (0.64, 0.98) CI p_{trend} 0.006 [M 4.7 vs 0, F 7.7 vs 0.9 mg/d][b] (n 806) **Flavanones & flavones & flavonols** 0.79 RR (0.64, 0.98) CI p_{trend} 0.006 [M 26.9 vs 4.3, F 39.5 vs 8.5 mg/d][b] (n 806)	
***alpha*-tocopherol, *beta*-carotene Cancer Prevention Study (ATBC)**	Hirvonen 2000[70]	**Flavones & flavonols**	26,497 M	6.1	age, BMI, BP, chol, diabetes, hist CHD, SE, smoking alcohol, suppl					Flavones & flavonols 0.98 RR (0.80, 1.21) CI p_{trend} 0.81 [16.4 vs 4.2 mg/d (medians)][b] (n 736)	
	Hirvonen 2001[69]	**Flavones & flavonols**	25,372 M	6.1	age, BMI, BP, chol, diabetes, hist CHD, MS, PA, SE, smoking suppl,	Flavones & flavonols 0.89 RR (0.71, 1.11) CI trend not given [17.8 vs 3.94 mg/d (medians)][c] (n 815)			Flavones & flavonols 0.77 RR (0.64, 0.93) CI trend not given [17.8 vs 3.94 mg/d (medians)][c] (n 1,122, nonfatal)		
Turku and Environs Health Survey	Marniemi 2005[76]	**Flavones & flavonols**	361 M & 394 F elderly	10	age, FC, sex, smoking energy				**Flavone** (Luteolin) 0.53 RR (0.33, 0.86) CI p = 0.0096[a] (n 130, fatal & nonfatal)	Flavones & flavonols 0.65 RR (0.34, 1.23) CI[a] p not given (n 70)	
Kuopio Ischemic Heart Disease Risk Factor study	Mursu 2008[78]	**5 classes (flavonols, flavones, flavanones, flavan-3-ols, anthocyanidins)**	1,950 M	15.2	age, BMI, BP, BP meds, chol, diabetes, exam, fam CHD, O2, smoking, TAG alcohol, FA, folate, vit E			5 classes 1.25 RR (0.74, 2.11) CI p_{trend} 0.73 [435 vs 9.5 mg/d][b] (n 153) Flavanones		**Flavonols** 0.55 RR (0.31, 0.99) CI p_{trend} 0.027 [10.0 mg/d][b] (n 102) 5 classes	

Cohort	Study	Flavonoid classes studied	Population	Follow up yrs	Covariate measures	CHD mortality (deaths)	Stroke mortality (deaths)	CVD mortality (deaths)	CHD incidence (events)	Stroke incidence (events)	CVD incidence (events)
								0.54 RR (0.32, 0.92) CI p_{trend} 0.27 [3.1 mg/d][b] (n 153)		0.71 RR (0.37, 1.37) CI p_{trend} 0.137 [435 vs 9.5 mg/d][b] (n 102)	
Netherlands											
Zutphen Elderly Study	Hertog 1993[66]	**Flavones & flavonols**	805 M	5	BMI, BP, chol, PA, smoking energy, FA	**Flavones & flavonols** 0.32 RR (0.15, 0.71) CI p_{trend} 0.003 [29.9 vs 19.0 mg/d][a] (n 43)			Flavones & flavonols 0.52 RR (0.22,1.23) CI p_{trend} 0.15 [29.9 vs 19.0 mg/d][a] (n 38, fatal & nonfatal)		
	Keli 1996[71]	**Flavones & flavonols**	552 M	15	age, BP, chol, smoking alcohol, energy, fish					**Flavones & flavonols** 0.27 RR (0.11, 0.70) CI p_{trend} 0.004 [28.6 vs 18.3 mg/d][a] (n 42)	
	Hertog 1997[67]	**Flavones & flavonols**	804 (mortality) 692 (incidence)	10	BMI, BP, chol, PA, smoking energy, FA,	**Flavones & flavonols** 0.47 RR (0.27, 0.82) CI p_{trend} 0.006 [29.9 vs 19.0 mg/d][a] (n 90)			Flavones & flavonols 0.62 RR (0.24,1.05) CI p_{trend} 0.078 [29.9 vs 19.0 mg/d][a] (n 92, fatal & nonfatal)		
	Arts 2001[63]	**Flavan-3-ols**	806 M	15	age, BMI, PA, smoking alcohol, BC, coffee, diet, energy, FA, fiber, fish, vit C, vit E	**Flavan-3-ols** 0.49 RR (0.27, 0.88) CI p_{trend} 0.017 [85.9 vs 49.0 mg/d][a] (n 90)	Flavan-3-ols 0.81 RR (0.36, 1.83) CI p_{trend} 0.61 [85.9 vs 49.0 mg/d][a] (n 47)		Flavan-3-ols 0.70 RR (0.39, 1.26) CI p_{trend} 0.23 [85.9 vs 49.0 mg/d][a] (n 90, fatal & nonfatal)	Flavan-3-ols 0.921 RR (0.51, 1.68) CI p_{trend} 0.606 [85.9 vs 49.0 mg/d][a] (n 88)	
Rotterdam Study	Geleijnse 2002[65]	**Flavonols**	1836 M & 2971 F	5.6	age, BMI, SE, sex, smoking alcohol, coffee, energy, FA, fiber, vit E	Flavonols 0.35 RR (0.13, 0.98) CI trend not given			Flavonols 0.93 RR (0.57, 1.52) CI nsd		

Cohort	Study	Flavonoid classes studied	Population	Follow up yrs	Covariate measures	CHD mortality (deaths)	Stroke mortality (deaths)	CVD mortality (deaths)	CHD incidence (events)	Stroke incidence (events)	CVD incidence (events)
						[32.9 vs 22.8 mg/d][a] (n 30)			[32.9 vs 22.8 mg/d][a] (n 116, nonfatal) Flavonols 0.76 RR (0.49, 1.18) CI nsd [32.9 vs 22.8 mg/d][a] (n 146, fatal & nonfatal)		
Dutch Prospect-EPIC (European Prospective Study Into Cancer and Nutrition) Cohort	Van der Schouw 2005[81]	**Isoflavones**	16,165 F	6.25 median	age, BMI, BP, chol, diabetes, HRT, OC, PA, smoking alcohol, energy, F&V, FA, fiber, protein,				Isoflavones 0.94 HR (0.68, 1.30) CI nsd [0.54 vs 0.26 mg/d][b,d] (n 372, fatal & nonfatal)	Isoflavones 1.05 HR (0.64, 1.70) CI nsd [0.54 vs 0.26 mg/d][b,d] (n 147)	Isoflavones 0.97 HR (0.74, 1.27) CI nsd [0.54 vs 0.26 mg/d][b,d] (n 519)
Wales, UK											
Caerphilly Study	Hertog 1997[68]	**Flavonols**	1,900 M	10 incidence 14 mortality	age, BMI, BP, chol, hist CHD, SE, smoking alcohol, BC, energy, FA, vit C, vit E,	Flavonols 1.6 RR (0.9, 2.9) CI p_{trend} 0.119 [34 vs 19 mg/d][b] (n 131)			Flavonols 1.1 RR (0.6, 1.6) CI p_{trend} 1.00 [34 vs 19 mg/d][b] (n 186, fatal & nonfatal)		
US											
Health Professionals Follow-up Study (HPFS)	Rimm 1996[79]	**Flavones & flavonols**	34,789 M	2 or 6	age, BMI, BP, chol, diabetes, fam CHD, SE, smoking alcohol, vit E,	Flavones & flavonols 0.77 RR (0.45, 1.35) CI nsd [40.0 vs 7.1 mg/d (medians)][c] (n 140, 2 yr FU, N 38,036) Flavones & flavonols 0.63 RR (0.33, 1.20) CI nsd [40.0 vs 7.1 mg/d (medians)][c] (n 105, 2 yr FU, N 4838 CHD prevalent)			Flavones & flavonols 1.08 RR (0.81, 1.43) CI nsd [40.0 vs 7.1 mg/d (medians)][c] (n 486 6 yr FU nonfatal) Flavones & flavonols 0.94 RR (0.68 – 1.31) CI nsd [40.0 vs 7.1 mg/d (medians)][c] (n 373, 2 yr FU, fatal & nonfatal)		

Cohort	Study	Flavonoid classes studied	Population	Follow up yrs	Covariate measures	CHD mortality (deaths)	Stroke mortality (deaths)	CVD mortality (deaths)	CHD incidence (events)	Stroke incidence (events)	CVD incidence (events)
Iowa Women's Health Study	Yochum 1999[82]	**Flavones & flavonols**	34,492 F post	10	BP, chol, diabetes, HRT, MS, PA, SE, smoking, WH alcohol, energy, FA, fiber, grains, vit E,	Flavones & flavonols 0.62 RR (0.44, 0.87) CI p_{trend} 0.11 [32.3 vs 4.3 mg/d][C] (n 438)	Flavones & flavonols 1.18 RR (0.70, 2.00) CI p_{trend} 0.83 [18.7 vs 5.7 mg/d][C] (n 131)				
	Arts 2001[64]	**Flavan-3-ols**	32,857 F post	13	age, BMI, BP, diabetes, HRT, MS, PA, SE, smoking, WH alcohol, BC, energy, FA, folate, grains, vit C, vit E, vit suppl,	Flavan-3-ols 0.85 RR (0.67, 1.07) CI nsd [36.8 vs 6.3 mg/d][C] (n 767)					
	Mink 2007[77]	**7 classes (flavonols, flavones, flavanones, flavan-3-ols, anthocyanidins, isoflavones, proanthocyanidins)**	34,492 F post	16	age, BMI, BP, diabetes, HRT, MS, PA, SE, smoking, WH energy	**Flavanones** 0.78 RR (0.65, 0.94) CI p_{trend} 0.010 [72.8 vs 16.1 mg/d][C] (n 1329) **Anthocyanidins** 0.88 RR (0.78, 0.99) CI p_{trend} 0.031 [0.01 vs 0 mg/d] (n 1329)	7 classes 0.94 RR (0.69, 1.29) CI p_{trend} 0.80 [425.3 vs 133.2 mg/d] [C] (n 469)	**Flavanones** 0.88 RR (0.77, 1.01) CI p_{trend} 0.054 [72.8 vs 16.1 mg/d][C] (n 2316) **Anthocyanidins** 0.91 RR (0.83, 0.99) CI p_{trend} 0.032 [0.1 vs 0 mg/d][C] (n 2316)			
Women's Health Study (WHS)	Sesso 2003[80]	**Flavones & flavonols**	38,445 F	6.9	age, aspirin, BMI, BP, chol, diabetes, fam CHD, HRT, PA, smoking alcohol, BC, F&V, FA, fiber, folate, vit E			Flavones & flavonols 1.05 RR (0.62, 1.78) CI nsd [47.4 vs 8.9 mg/d (medians)][C] (n not given)	Flavones & flavonols 0.82 RR (0.51, 1.30) CI nsd [47.4 vs 8.9 mg/d (medians)][C] (n not given, fatal & nonfatal)	Flavones & flavonols 0.70 RR (0.46, 1.07) CI nsd [47.4 vs 8.9 mg/d (medians)][C] (n not given)	Flavones & flavonols 0.80 RR (0.59, 1.09) CI p_{trend} 0.80 [47.4 vs 8.88 mg/d (medians)][C] (n 519 events)
Nurses' Health Study (NHS)	Lin 2007[75]	**Flavones & flavonols**	66,360 F	12	age, aspirin, BMI, BP, chol, diabetes, fam CHD, HRT,	**Flavonol** (Kaempferol) 0.66 RR (0.48, 0.93) CI p_{trend} 0.04			Flavones & flavonols 1.05 RR (0.85, 1.29) CI		

Cohort	Study	Flavonoid classes studied	Population	Follow up yrs	Covariate measures	CHD mortality (deaths)	Stroke mortality (deaths)	CVD mortality (deaths)	CHD incidence (events)	Stroke incidence (events)	CVD incidence (events)
					meno, PA, smoking meno, PA, smoking alcohol, energy, vit E, vit suppl	[4.7 mg/d mean][c] (n 324)			p_{trend} 0.55 [30.9 vs 9.6 mg/d][c] (n 938, nonfatal)		

*Blank cells – outcome not studied

Bold font indicates the class(es) significant for inverse association with the given event at multivariate adjusted $p_{trend}<.05$ or less.

nsd – association not significant at $p_{trend}<.05$ for compounds or classes studied.

F – females, HR – Hazard ratios, M – males, Post – postmenopausal, RR – Risk ratios

General covariate measures: age; aspirin – aspirin use; BMI – body mass index; BP – blood pressure (diastolic, hypertension, systolic); BP meds – blood pressure medication; chol – cholesterol (HDL, high, LDL, total cholesterol); diabetes; exam - examination years; fam CHD – history of family CHD; FC - functional capacity; hist CHD - history of CHD; HRT – hormone replacement therapy; meno - menopausal; MS - marital status; O2 - oxygen uptake; OC - oral contraceptive; PA - physical activity; region - geographic region; SE – socioeconomic demographic (education, occupation, profession, social class); sex; smoking; TAG - triglycerides; WH - waist to hip ratio

Intake covariate measures: alcohol; BC – *beta*-carotene; coffee; diet - prescribed diet; energy - total energy; F&V - fruit & vegetable; FA – fat (cholesterol, fat, monounsaturated fatty acids, polyunsaturated fatty acids, saturated fatty acids); fiber; fish; folate; grains - whole grains; protein - animal protein; quercetin; suppl - supplementation group; vit C - vitamin C; vit E - vitamin E; vit suppl - multivitamin supplement

a tertiles

b quartiles

c quintiles

d Intake from FFQ but food items scored for isoflavones, analytical values were not used.

Table 4

Summary of significant (multivariate adjusted $p_{trend}<.05$) associations between flavonoid intakes and various cardiovascular outcomes in prospective cohorts in US and European countries

Number of cohorts with significant associations/number of cohorts examined

	Mortality			Incidence			Number cohorts	All publications
Flavonoid Class	**CHD**	**Stroke**	**CVD**	**CHD**	**Stroke**	**CVD**		
Flavonols & flavones	1[a]/6[e]	0/1	0/1	0/6[e]	1/4	0/1	1/8	3/11
Flavonols	2/5[d]	0/1	0/2	0/5	2/3[c]	0/1	3/9	3/10
Flavones	0/1[a]	0/1	0/2	1/1	0/2	0/1	1/4	1/5
Flavanones	1/2	0/1	1/2		1/2		2/3	2/3
Flavan-3-ols	1/2[b]	0/2	0/2	0/1	0/2		1/3	1/4
Anthocyanidins	1/1	0/1	1/2		0/1		1/2	1/2
Isoflavones	0/1	0/1	0/1	0/1	0/1	0/1	0/2	0/2
Proanthocyanidins	0/1	0/1	0/1				0/1	0/1
Number of cohorts studied	4/8	0/2	1/3	1/9	3/7	0/2	6/12	
All publications	6/13	0/3	1/3	1/11	3/9	0/2		8/20

[a] two publications

[b] three publications

[c] four publications

[d] six publications

[e] seven publications

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