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Flavonoid intake and all-cause mortality^{1–3}

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ABSTRACT

Background: Flavonoids are bioactive compounds found in foods such as tea, chocolate, red wine, fruit, and vegetables. Higher intakes of specific flavonoids and flavonoid-rich foods have been linked to reduced mortality from specific vascular diseases and cancers. However, the importance of flavonoids in preventing all-cause mortality remains uncertain.

Objective: The objective was to explore the association between flavonoid intake and risk of 5-y mortality from all causes by using 2 comprehensive food composition databases to assess flavonoid intake.

Design: The study population included 1063 randomly selected women aged >75 y. All-cause, cancer, and cardiovascular mortalities were assessed over 5 y of follow-up through the Western Australia Data Linkage System. Two estimates of flavonoid intake (total flavonoid_{USDA} and total flavonoid_{PE}) were determined by using food composition data from the USDA and the Phenol-Explorer (PE) databases, respectively.

Results: During the 5-y follow-up period, 129 (12%) deaths were documented. Participants with high total flavonoid intake were at lower risk [multivariate-adjusted HR (95% CI)] of 5-y all-cause mortality than those with low total flavonoid consumption [total flavonoid_{USDA}: 0.37 (0.22, 0.58); total flavonoid_{PE}: 0.36 (0.22, 0.60)]. Similar beneficial relations were observed for both cardiovascular disease mortality [total flavonoid_{USDA}: 0.34 (0.17, 0.69); flavonoid_{PE}: 0.32 (0.16, 0.61)] and cancer mortality [total flavonoid_{USDA}: 0.25 (0.10, 0.62); flavonoid_{PE}: 0.26 (0.11, 0.62)].

Conclusions: Using the most comprehensive flavonoid databases, we provide evidence that high consumption of flavonoids is associated with reduced risk of mortality in older women. The benefits of flavonoids may extend to the etiology of cancer and cardiovascular disease. *Am J Clin Nutr* 2015;101:1012–20.

Keywords: flavonoid, cancer, cardiovascular disease, diet, mortality

INTRODUCTION

Flavonoids are the largest dietary polyphenolic class. They represent a diverse group of more than 4000 different biologically active compounds synthesized during plant metabolism (1). As outlined in **Figure 1**, flavonoids found in food can be divided into 6 main flavonoid classes: flavonols, flavan-3-ols, flavones, flavanones, anthocyanins, and isoflavones (1). A variety of biological effects have been identified for individual flavonoids, but the value of considering these monomeric flavonoids and the proanthocyanidins as a whole is that this can provide a biologically plausible way of considering the health effects of flavonoids with similar structural characteristics.

Following consumption, flavonoids may contribute to a variety of beneficial biological activities in humans. Strong and consistent data now show that flavonoids can maintain and augment nitric oxide status and improve endothelial function (2–5). There is also evidence that these compounds can influence blood pressure, oxidative damage, inflammation, platelet function and thrombosis, blood lipids, and glucose metabolism (6, 7). These effects may help to explain the findings that flavonoids and flavonoid-rich foods exhibit cardioprotective and antineoplastic properties (8–16). However, despite being associated with all-cause cardiovascular disease (CVD)⁴ mortality (10), intake of flavonols and flavones has not been associated with all-cause cancer mortality (17).

Particularly high dietary sources of flavonoids include tea (18), chocolate (19), fruit (20), and red wine (1). Meta-analyses of population-based studies have found that consumption of these flavonoid-rich foods is associated with a reduced risk of cancer (21, 22) and CVD (23, 24), which are the 2 leading causes of mortality (25). These foods have also been shown in prospective cohort studies to be associated with a reduced risk of all-cause mortality (26–29). However, the role that flavonoid intake specifically plays in the prevention of all-cause mortality is less clear.

Previous studies exploring this hypothesis (30, 31) were limited by the lack of comprehensive food composition data. In recent years, the quality of food composition databases has improved exponentially, both in terms of the flavonoid compounds and food items on which they provide data. The emergence and continued development of these databases provide the opportunity to explore

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⁴ Abbreviations used: CVD, cardiovascular disease; FFQ, food-frequency questionnaire; ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*; ICD-10-AM, *International Classification of Diseases, 10th Revision, Australian Modification*; PE, Phenol-Explorer.

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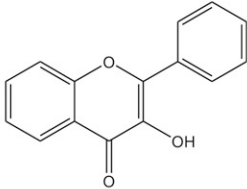
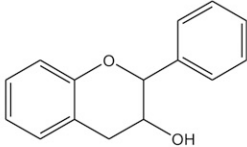
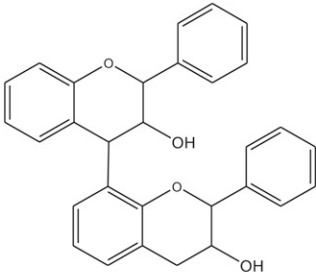
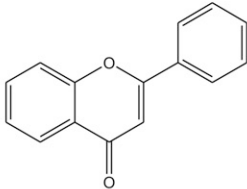
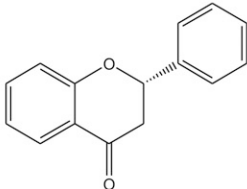
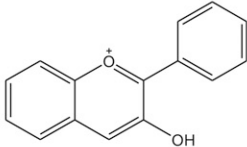
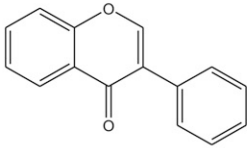
Class	Basic structure
Flavonol	
Flavanol	
Proanthocyanidin (dimer)	
Flavone	
Flavanone	
Anthocyanidin	
Isoflavone	

FIGURE 1 Basic structure of flavonoid classes.

the relation of all-cause mortality and intake of total flavonoids and 6 common flavonoid classes in foods (10, 32). The 2 most comprehensive databases describing the flavonoid content of foods

are the USDA (33–35) and the Phenol-Explorer (PE) (36) food content databases. This study aims to use these data to explore the prespecified hypothesis that total flavonoid intake is beneficially

associated with the risk of all-cause mortality in a population of elderly women.

METHODS

Participants

In total, 1136 postmenopausal women >75 y of age were recruited into the Calcium Intake Fracture Outcome Age Related Extension Study in 2003. These participants had previously completed a 5-y prospective, randomized controlled trial of oral calcium supplements to prevent osteoporotic fractures (37). Although from higher socioeconomic groups, participants in this cohort had similar disease burden and pharmaceutical consumption patterns for this age population as a whole (38). A total of 1063 participants had complete food-frequency and beverage intake data at baseline. This study was approved by the Human Ethics Committee of the University of Western Australia, and written informed consent was obtained from all participants.

Mortality

The primary outcome of interest was all-cause mortality. The mortality data from baseline (2003) until year 5 (2008) were retrieved from the Western Australian Data Linkage System for 100% of the participants.

Cardiovascular and cancer events were defined by using diagnosis codes from the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) (39) and the *International Classification of Diseases, 10th Revision, Australian Modification* (ICD-10-AM) (40). Cardiovascular codes included ICD-9-CM 390–459 and ICD-10-AM I00–I99. Cancer codes included ICD-9-CM 140–239 and ICD-10-AM C00–C97. The search for cardiovascular and cancer ICD codes from the Western Australian Data Linkage System mortality registry included all available diagnostic information that comprised parts 1 and 2 of the mortality records. All diagnosis text fields from the death certificate were used to ascertain the cause(s) of very recent deaths where these data were not yet available from the Western Australian Data Linkage System.

Baseline risk assessment

Using the aforementioned ICD codes, we determined previous CVD and cancer at baseline by using verified hospitalizations from 1980 to 2003 from the Western Australian Data Linkage System. Smoking status was coded as currently smoking or not currently smoking if participants reported smoking at least 1 cigarette/d for a minimum of 3 mo preceding their baseline visit.

Physical activity was assessed by using a questionnaire in which participants reported the time of involvement for up to 4 physical activities of moderate intensity undertaken in the preceding 3 mo (41, 42). Baseline weight was assessed by using digital scales with participants wearing light clothes and no shoes. Baseline height was assessed with a stadiometer, and BMI was calculated in kg/m².

Dietary assessment

Baseline (2003) dietary intake was assessed with a validated semiquantitative food-frequency questionnaire (FFQ) developed

by the Anti-Cancer Council of Victoria (43–45). Energy and nutrient intakes were estimated based on frequency of consumption and an overall estimate of usual portion size (46). A beverage questionnaire was used to assess average tea and coffee consumption over the past 12 mo.

Flavonoid intake

Two major sources summarize the flavonoid content of foods: the PE (36) and the USDA Flavonoid 2.1 (47), Isoflavone 2.0 (48), and Proanthocyanidin (33) food content databases. Both of these databases were used to derive 2 separate estimates of total flavonoid intake: flavonoid intake based on food composition data from the USDA (flavonoid_{USDA}) and flavonoid intake based on food composition data from the PE (flavonoid_{PE}). For the PE database, all data are either glycosides or aglycones in the form that they are naturally occurring in food. Specifically, in cases where HPLC data without hydrolysis were available, it was used without converting the glycosides to aglycones.

The method of computing flavonoid content of foods was similar to those described in Ivey et al. (49), and extraction procedures for the 2 databases were identical. Specifically, for each food, we computed the sum of assessed flavonoids for each flavonoid class by summing the individual compounds of each flavonoid class in the form expressed in each individual database. The exception was the isoflavone_{USDA} data, in which the total isoflavone value from the USDA database was used rather than summing the individual daidzein, genistein, and glycitein compounds (biochanin A, formononetin, and coumestrol were not included).

The terminology and classification systems used by each database varied; therefore, a standardized classification system was adopted throughout this study. The terms *anthocyanins* and *isoflavones* in this study refer to the PE anthocyanin and isoflavonoid classes, respectively. The term *flavanol* in this study encapsulates both the flavan-3-ol and proanthocyanidin classes in the USDA database. As such, flavanol_{USDA} represented the sum of proanthocyanidin polymer values in conjunction with total flavan-3-ol content. Flavanol intakes from both the USDA and PE databases included theaflavin consumption but did not include proanthocyanidin monomer data. Because food content data for thearubigins were available only in the USDA database, flavanol_{PE} did not include intakes of thearubigins.

The chalcone, dihydrochalcone, and dihydroflavonol contents of foods are described in the PE but not in the USDA database. Because these flavonoid classes are rarer in nature and not typically considered one of the major flavonoid classes, they were not used to estimate total flavonoid intake. They were instead summed and investigated for a relation with all-cause mortality in a separate exploratory analysis.

Intakes of flavonoid classes in milligrams per day were calculated by multiplying the estimated intake (g edible portion/d) from the FFQ and beverage questionnaires by the flavonoid class content (mg/g edible portion) of each food item on the questionnaires. Where multiple varieties of a food listed in the FFQ were reported in the databases, the mean flavonoid content of all similar varieties was computed, consistent with the descriptors used in the FFQ output. For each database, foods in the FFQ that were not represented were entered as zero values for analysis for that particular database. Of the 93 individual food items



specified in the FFQ, 19 foods in the USDA computation and 47 in the PE computation were recorded as not containing flavonoids in the respective database or did not appear in the database. This includes foods such as Vegemite (Mondelēz International), butter, dairy products, and sugar but no plant-based or plant-containing food.

Statistical analysis

Before commencing statistical analysis, a prespecified analytic protocol was produced. SAS (version 9; SAS Institute) was used to identify and categorize the hospital and mortality data from the Western Australian Data Linkage System. SPSS (version 20; SPSS Inc.) was then used for all further analyses.

Five-year all-cause mortality HRs and 95% CIs were obtained by using Cox regression of total flavonoid intake by SD scores and tertiles of total flavonoid intake by using unadjusted and multivariate-adjusted models.

The multivariate-adjusted model included age, prevalent CVD, prevalent cancer, and the presence of assessed all-cause mortality risk factors identified by the World Health Organization (50). These included overweight or obese (BMI >25), low fruit and vegetable intake (<600 g total fruit and vegetable intake/d), physical inactivity (<2.5 h of moderate-intensity physical activity per week), current cigarette smoker, and current alcohol consumer. The multivariate-adjusted model included 1022 participants because of missing variables in 41 women.

We performed post hoc analyses by using tertiles of flavonoid class intake to identify which flavonoid classes may contribute to the observed relations. To address a potential source of outcome bias, we conducted a Cox regression analysis of total flavonoid intake with the 2 major mortality causes, CVD and cancer (25). To take into account multiple comparisons, we set the level of significance for post hoc comparisons at $P < 0.0056$.

RESULTS

The mean age of participants was 80 ± 3 y (Table 1). The mean alcohol intake among alcohol consumers was 8 ± 10 mg/d, and mean fruit and vegetable intake was 520 ± 206 g/d. Mean total energy consumption was 1643 ± 607 kJ/d. Mean total flavonoid consumption was 696 ± 322 mg/d (median: 668; IQR: 468–889) and 674 ± 326 mg/d (median: 648; IQR: 449–872), as computed by the USDA and PE databases, respectively. During the 5-y follow-up period, 129 (12%) deaths were documented.

Total flavonoid intake and all-cause mortality

Total flavonoid intake was associated with a lower risk of all-cause mortality in unadjusted analyses [flavonoid_{USDA} unadjusted HR per SD: 0.64 (95% CI: 0.52, 0.78); flavonoid_{PE} unadjusted HR per SD: 0.66 (95% CI: 0.54, 0.80)]. The association remained significant after multivariate adjustment [flavonoid_{USDA} multivariate-adjusted HR per SD: 0.67 (95% CI: 0.54, 0.82); flavonoid_{PE} multivariate-adjusted HR per SD: 0.68 (95% CI: 0.55, 0.84)].

To explore this association further, we trichotomized the cohort into groups based on tertiles of total flavonoid intake. Irrespective of the food composition database used to assess total flavonoid intake, high consumers were at lower risk of all-cause mortality (Table 2), and there were 62% fewer deaths in high compared with low total flavonoid consumers (Figures 2 and 3).

TABLE 1

Baseline characteristics of the cohort stratified by total flavonoid intake group ($n = 1063$)¹

	Low intake	Moderate intake	High intake
<i>n</i> (%)	354 (33)	355 (33)	354 (33)
Flavonoid _{USDA} , ² <i>n</i> (%)			
Age, y	80 ± 3^3	80 ± 3	80 ± 3
Prevalent cardiovascular disease	125 (35)	97 (27)	107 (30)
Prevalent cancer	103 (29)	100 (28)	115 (32)
Overweight or obese ⁴	215 (64)	222 (65)	228 (66)
Low fruit and vegetable intake ⁵	297 (84) ^a	262 (74) ^b	197 (56) ^c
Physical inactivity ⁶	163 (46)	142 (40)	151 (43)
Current smoker	13 (4)	8 (2)	11 (3)
Current alcohol consumer	255 (72) ^a	287 (81) ^b	264 (75) ^{a,b}
Flavonoid _{PE} , ⁷ <i>n</i> (%)			
Age, y	80 ± 3	80 ± 3	80 ± 3
Prevalent cardiovascular disease	123 (35)	98 (28)	108 (30)
Prevalent cancer	101 (28)	105 (30)	112 (32)
Overweight or obese ⁴	222 (65)	214 (64)	229 (66)
Low fruit and vegetable intake ⁵	295 (83) ^a	261 (74) ^b	200 (56) ^c
Physical inactivity ⁶	160 (45.2)	142 (40)	154 (44)
Current smoker	12 (3)	10 (3)	10 (3)
Current alcohol consumer	260 (73)	285 (80)	261 (73)

¹Row values with different superscript letters differ significantly by Bonferroni, $P < 0.05$. PE, Phenol-Explorer.

²Flavonoid_{USDA}: low (<547 mg/d), moderate (547 to <813 mg/d), and high (≥ 813 mg/d).

³Mean $\pm$ SD (all such values).

⁴BMI ≥ 25 kg/m². $n = 1023$.

⁵Low fruit and vegetable intake: <600 g total fruit and vegetable intake/d.

⁶Physical inactivity: <2.5 h moderate-intensity physical activity/wk.

⁷Flavonoid_{PE}: low (<525 mg/d), moderate (525 to <788 mg/d), and high (≥ 788 mg/d).

Analysis was repeated in 1055 participants with an estimated energy intake between 500 and 4000 kcal/d. Excluding participants with extreme dietary intake estimates did not alter the relation between total flavonoid intake and all-cause mortality [flavonoid_{USDA} multivariate-adjusted HR per SD: 0.67 (95% CI: 0.54, 0.83); flavonoid_{PE} multivariate-adjusted HR per SD: 0.68 (95% CI: 0.55, 0.84)]. Similarly, excluding the 13 participants who died in the first year of the study did not ameliorate the total flavonoid and all-cause mortality relation [flavonoid_{USDA} multivariate-adjusted HR per SD: 0.67 (95% CI: 0.54, 0.84); flavonoid_{PE} multivariate-adjusted HR per SD: 0.69 (95% CI: 0.55, 0.86)].

Flavonoid class intake and all-cause mortality

Flavanols including proanthocyanidins, as well as thearubigins when using USDA data, derived mainly from consumption of black tea, were the major contributor to total flavonoid intake, accounting for 82% (flavanol_{USDA}) and 59% (flavanol_{PE}) of total daily flavonoid consumption. Flavonols, derived mainly from the consumption of tea, apples, pears, and onions, provided 4% and 26% of total USDA and PE intakes, respectively. Oranges and fruit juice were the predominant dietary sources of flavanones (flavanone_{USDA}: 8%; flavanone_{PE}: 8%). Less than 8 mg/d was supplied from the remaining classes: anthocyanins, isoflavones, and flavones.

TABLE 2
Association of total flavonoid intake group and risk of all-cause mortality¹

	Low intake	Moderate intake	High intake
<i>n</i> (%)	354 (33)	355 (33)	354 (33)
Flavonoid _{USDA} ²			
Unadjusted	1.00 (referent)	0.78 (0.53, 1.14)	0.37 (0.23, 0.59)*
Multivariate	1.00 (referent)	0.82 (0.54, 1.25)	0.38 (0.22, 0.64)*
Flavonoid _{PE} ³			
Unadjusted	1.00 (referent)	0.57 (0.39, 0.85)*	0.36 (0.23, 0.57)*
Multivariate	1.00 (referent)	0.52 (0.34, 0.81)*	0.36 (0.22, 0.60)*

¹Results are HRs (95% CIs). Multivariate-adjusted model includes age, prevalent cardiovascular disease and cancer, overweight or obesity, low fruit and vegetable intake, physical inactivity, current cigarette smoking, and alcohol consumption. *Significantly different from referent group by Cox regression, $P < 0.05$. PE, Phenol-Explorer.

²Flavonoid_{USDA}: low (<547 mg/d), moderate (547 to <813 mg/d), and high (≥ 813 mg/d).

³Flavonoid_{PE}: low (<525 mg/d), moderate (525 to <788 mg/d), and high (≥ 788 mg/d).

To identify which flavonoid classes contribute to the total flavonoid and all-cause mortality relation, we repeated the Cox regression analysis by using tertiles of flavonoid class intake.

Compared with low consumers as the referent group, high consumers of flavanols had a reduced risk (multivariate-adjusted HR for high tertile) of all-cause mortality [flavanol_{USDA} HR: 0.43 (95% CI: 0.26, 0.70), $P = 0.001$; flavanol_{PE} HR: 0.37 (95% CI: 0.23, 0.61), $P < 0.001$]. Similarly, compared with low consumers, high flavonol consumers were at a lower risk of all-cause mortality [flavonol_{USDA} HR: 0.39 (95% CI: 0.23, 0.65), $P < 0.001$; flavonol_{PE} HR: 0.43 (95% CI: 0.27, 0.70), $P = 0.001$]. A similar association was observed with tertiles of flavone_{PE} consumption: 0.51 (95% CI: 0.32, 0.82), $P = 0.005$. The relation, however, with flavone_{USDA} intake was attenuated after multivariate adjustment: 0.60 (95% CI: 0.35, 1.02), $P = 0.057$.

In multivariate-adjusted models, consumption of flavanones, anthocyanins, and isoflavones was not associated with all-cause mortality ($P > 0.05$). In post hoc exploratory analysis, intake of the chalcone, dihydrochalcone, and dihydroflavonol combined classes was not associated with all-cause mortality.

Total flavonoid intake and mortality from cancer and CVD

There were 78 (60%) deaths attributed to CVD and 49 (38%) cancer mortalities over the 5-y follow-up period. To explore the contribution of specific disease processes to the all-cause mortality relation, we performed Cox regression analysis with total flavonoid intake groups and mortality subtypes. There were at least 64% fewer CVD mortalities and 73% fewer cancer mortalities in high than in low total flavonoid consumers (**Table 3**).

Of the 129 deaths, both CVD and cancer appeared on the death certificate in 17 (13%) cases. To account for potential confounding, we repeated the analysis excluding these participants, which did not alter observed relations (data not shown).

DISCUSSION

This prospective cohort study found that participants with higher total flavonoid consumption were at reduced risk of all-cause mortality. Despite differences in intake estimates between the PE and USDA databases, the relations were similar and remained after adjustment for prespecified mortality risk factors and were irrespective of the database used to estimate flavonoid intake. The highest compared with the lowest tertile of flavonoid intake was associated with $\sim 60\%$ lower risk of all-cause mortality. Furthermore, a higher flavonoid intake of ~ 350 mg, equivalent to approximately 2 cups of tea, was associated with $\sim 40\%$ lower risk of all-cause mortality. The protective relation extended to both major causes of mortality. High total flavonoid consumers displayed a 40–50% reduced risk of CVD and cancer mortality compared with those with the lowest intake.

When contributors to this relation were explored, the association with all-cause mortality appeared to be class dependent. Those with high intakes of flavanols and flavonols experienced a lower mortality rate, whereas associations for the remaining flavonoid classes appeared to be attenuated by adjustment for prespecified risk factors. The varying structures and bioactivities of the different flavonoid classes, as well as the ability to adequately assess intakes from foods, may help to explain the lack of concurrency across different flavonoid classes (51, 52). However, the lack of a beneficial association for the flavone, isoflavone, and anthocyanin classes may also be explained by their low intakes

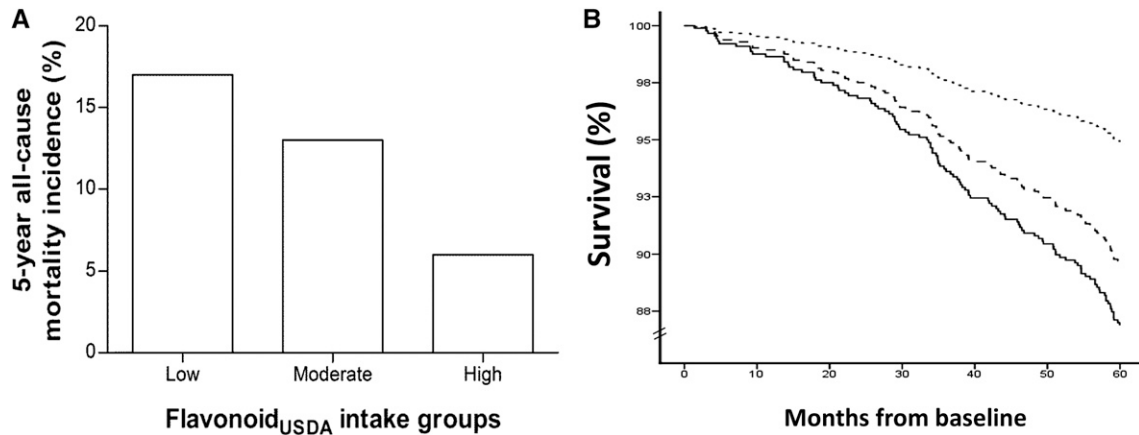


FIGURE 2 Proportional reduction in 5-y all-cause mortality incidence between low, moderate, and high total flavonoid consumption as estimated from the USDA database. (A) Low flavonoid_{USDA} intake: <547 mg/d, $n = 354$; moderate flavonoid_{USDA} intake: 547 to <813 mg/d, $n = 355$; high flavonoid_{USDA} intake: ≥ 813 mg/d, $n = 354$. (B) Cox proportional hazard model survival curve from baseline to 5-y follow-up stratified by total flavonoid_{USDA} consumption. Low flavonoid_{USDA} intake (solid line): <605 mg/d, $n = 354$; moderate flavonoid_{USDA} intake (dashed line): 605 to <915 mg/d, $n = 355$; high flavonoid_{USDA} intake (dotted line): ≥ 915 mg/d, $n = 354$.

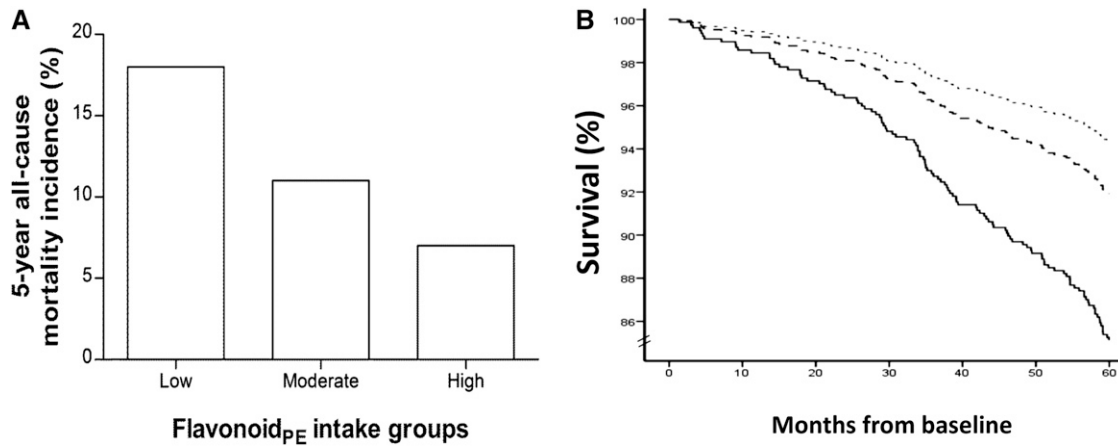


FIGURE 3 Proportional reduction in 5-y all-cause mortality incidence between low, moderate, and high total flavonoid consumption estimated from the Phenol-Explorer database. (A) Low flavonoid_{PE} intake: <525 mg/d, *n* = 354; moderate flavonoid_{PE} intake: 525 to <788 mg/d, *n* = 355; high flavonoid_{PE} intake: ≥788 mg/d, *n* = 354. (B) Cox proportional hazard model survival curve from baseline to 5-y follow-up stratified by total flavonoid_{PE} consumption. Low flavonoid_{PE} intake (solid line): <525 mg/d, *n* = 354; moderate flavonoid_{PE} intake (dashed line): 525 to <788 mg/d, *n* = 355; high flavonoid_{PE} intake (dotted line): ≥788 mg/d, *n* = 354. PE, Phenol-Explorer.

suggesting that the dose may be inadequate to confer health benefits in this population. For anthocyanins, the dose of exposure may be inadequately captured in population studies because foods that provide anthocyanins such as jams, jellies, and local berries are less commonly analyzed. This dosing effect may also explain the lack of association of total flavonoid intake and mortality in the study by Mink and colleagues (10), because the median flavonoid intake in the Iowa Women's Health Study (53) of 239.2 mg/d was nearly 3 times lower than the 696-mg/d median flavonoid intake assessed in this cohort by using USDA data. These intake estimates were based on USDA flavonoid and

isoflavone databases that preceded the databases used in the current study. Therefore, in addition to differing dietary patterns among different geographical locations, variations in food content databases may also explain variations in flavonoid intake observed between studies. The differences in database utilization may also explain the differences in flavonoid intake estimates between our study and other Australian data (54). PE intake estimates in this cohort are larger than those in another study that used PE data in a younger French population (55). This difference between reported intakes is likely explained by the age and geographic differences between the cohorts (56).

TABLE 3

Association of total flavonoid group and risk of mortality from cardiovascular disease and cancer¹

	Low intake	Moderate intake	High intake
<i>n</i> (%)	354 (33)	355 (33)	354 (33)
Cardiovascular disease mortality			
Flavonoid _{USDA} ²			
CVD mortality, <i>n</i> (%)	36 (10)	29 (8)	13 (4)
Unadjusted	1.00 (referent)	0.79 (0.48, 1.28)	0.34 (0.18, 0.64)*
Multivariate	1.00 (referent)	0.81 (0.47, 1.40)	0.34 (0.17, 0.69)*
Flavonoid _{PE} ³			
CVD mortality, <i>n</i> (%)	40 (11)	25 (7)	13 (4)
Unadjusted	1.00 (referent)	0.60 (0.36, 0.99)*	0.30 (0.16, 0.57)*
Multivariate	1.00 (referent)	0.47 (0.27, 0.86)*	0.32 (0.16, 0.61)*
Cancer mortality			
Flavonoid _{USDA} ²			
Cancer mortality, <i>n</i> (%)	26 (7)	16 (4)	7 (2)
Unadjusted	1.00 (referent)	0.60 (0.32, 1.23)	0.26 (0.11, 0.59)*
Multivariate	1.00 (referent)	0.63 (0.32, 1.22)	0.25 (0.10, 0.62)*
Flavonoid _{PE} ³			
Cancer mortality, <i>n</i> (%)	27 (8)	14 (4)	8 (2)
Unadjusted	1.00 (referent)	0.50 (0.26, 0.95)*	0.28 (0.13, 0.62)*
Multivariate	1.00 (referent)	0.44 (0.21, 0.89)*	0.26 (0.11, 0.62)*

¹Results are HRs (95% CIs). Multivariate adjusted model includes age, prevalent cardiovascular disease and cancer, overweight or obesity, low fruit and vegetable intake, physical inactivity, current cigarette smoking, and alcohol consumption. *Significantly different from referent group by Cox regression, *P* < 0.05. CVD, cardiovascular disease; PE, Phenol-Explorer.

²Flavonoid_{USDA}: low (<547 mg/d), moderate (547 to <813 mg/d), and high (≥813 mg/d).

³Flavonoid_{PE}: low (<525 mg/d), moderate (525 to <788 mg/d), and high (≥788 mg/d).

Our findings of a cardioprotective association with flavonoids are generally consistent with the findings of previous studies of flavonoids and CVD (57, 58). Intervention studies have shown that flavonoids and flavonoid-rich foods can improve CVD risk factors such as blood pressure (13, 14, 59), endothelial function (2, 3, 60), and platelet formation (61). It is likely that these protective functions explain the benefits of flavonoids in protecting against subcategories of CVD, including coronary artery disease (62), stroke (63), and myocardial infarction (64). Further support for a vascular benefit of flavonoids comes from our previous data showing an inverse association between the intake of flavonols and atherosclerotic vascular disease, a subcategory of CVD (49).

Many observational epidemiologic studies have investigated the relations of flavonoid intake with specific cancer sites, such as breast (65), lung (66), and gastrointestinal (67). However, there are few previous studies of total flavonoid intake and all-cause cancer mortality, which to date have not observed a beneficial association (17, 31, 68). The lack of agreement of our findings with those from Knekt et al. (68) and Hertog et al. (17, 31) may be a result of lower flavonoid intakes in some populations or the use of earlier versions of food composition databases, in which only 2–3 flavonoid classes were assessed. Similarly, the lack of association with all-cause cancer mortality observed by Cutler and colleagues (53) is most likely explained by the aforementioned low total flavonoid consumption in their cohort. Despite the lack of agreement in current all-cause cancer data, although not conclusive (53), epidemiologic and in vitro data suggest the protective role of flavonoids on particular cancer types such as lung cancer (68–71) and breast cancer (72–75). Data also link intake of high-flavonoid foods such as green tea with particular cancer types (76).

The flavonoid content of foods is affected by variety, growing conditions, and maturation, processing, and storage (77–80), making flavonoid intake particularly difficult to assess. This issue is further exacerbated by the inability of the FFQ used in this study to identify or find all food items expressed in the databases. Our data were further limited by the strong likelihood of some degree of measurement error in flavonoid exposure, as evidenced by the discrepancies in intake estimates derived from the USDA and PE databases, as well as differences in flavonoid compounds assessed in each database. This type of measurement error would typically tend to weaken our findings and increase the likelihood of type II statistical errors. However, because the flavonoid intake estimates were based on the same frequency of food consumption data, the bias is introduced only because of the databases and not because of measurement error in the food intake assessment. This highlights the major strength of this study, in which we used the 2 most comprehensive food composition databases to derive 2 separate estimates of flavonoid intake to minimize bias in flavonoid intake estimations and to confirm our findings.

Thearubigins are present in the USDA database but not in the PE database. The contribution of thearubigins to total flavonoid_{USDA} intake likely describes the discrepancies between flavanol_{USDA} and flavanol_{PE} estimates. In addition, although thearubigins are included in the USDA database, because of difficulties in quantifying these compounds, the values provide only an estimate that is less accurate than that for most other flavonoids (80). Similarly, the larger flavanol intake estimates by the PE database are likely to arise primarily because of the

expression of food composition data in glycoside and aglycone flavanol forms, whereas the aglycone data were used from the USDA database. As functional groups influence flavonoid bioactivities (81), there is the possibility that because of the differences in USDA and PE food composition data, the subsequent different flavonoid intake estimates based on these data may have different associations with outcome variables. This highlights the importance of using 2 distinctly different databases when estimating flavonoid intake. The strength of this approach is that despite the many differences between the 2 databases, we observed similar relations with all-cause mortality.

In summary, we found a beneficial relation between the dietary intake of total flavonoids and the risk of mortality from all causes, which was attributable primarily to the consumption of flavanols and flavonols, the main sources of flavonoids in the present population. It appears that the benefits of flavonoids extend to the etiology of both cancer and CVD.

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