



Flavonoid intake and cardiovascular disease mortality: a prospective study in postmenopausal women¹⁻⁴

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ABSTRACT

Background: Dietary flavonoids may have beneficial cardiovascular effects in human populations, but epidemiologic study results have not been conclusive.

Objective: We used flavonoid food composition data from 3 recently available US Department of Agriculture databases to improve estimates of dietary flavonoid intake and to evaluate the association between flavonoid intake and cardiovascular disease (CVD) mortality.

Design: Study participants were 34 489 postmenopausal women in the Iowa Women's Health Study who were free of CVD and had complete food-frequency questionnaire information at baseline. Intakes of total flavonoids and 7 subclasses were categorized into quintiles, and food sources were grouped into frequency categories. Proportional hazards rate ratios (RR) were computed for CVD, coronary heart disease (CHD), stroke, and total mortality after 16 y of follow-up.

Results: After multivariate adjustment, significant inverse associations were observed between anthocyanidins and CHD, CVD, and total mortality [RR (95% CI) for any versus no intake: 0.88 (0.78, 0.99), 0.91 (0.83, 0.99), and 0.90 (0.86, 0.95)]; between flavanones and CHD [RR for highest quintile versus lowest: 0.78 (0.65, 0.94)]; and between flavones and total mortality [RR for highest quintile versus lowest: 0.88 (0.82, 0.96)]. No association was found between flavonoid intake and stroke mortality. Individual flavonoid-rich foods associated with significant mortality reduction included bran (added to foods; associated with stroke and CVD); apples or pears or both and red wine (associated with CHD and CVD); grapefruit (associated with CHD); strawberries (associated with CVD); and chocolate (associated with CVD).

Conclusion: Dietary intakes of flavanones, anthocyanidins, and certain foods rich in flavonoids were associated with reduced risk of death due to CHD, CVD, and all causes. *Am J Clin Nutr* 2007; 85:895-909.

KEY WORDS Flavonoids, diet, coronary heart disease, cardiovascular disease, mortality, postmenopausal women, prospective studies

INTRODUCTION

Flavonoids are polyphenolic compounds found in small quantities in numerous plant foods, including fruit and vegetables, tea, wine, nuts and seeds, and herbs and spices (1, 2). Flavonoids are antioxidants and thus may reduce the oxidation of LDL cholesterol, which is thought to be involved in the development of

atherosclerotic diseases (3-5). Other hypothesized mechanisms by which flavonoids may have cardioprotective effects include antiinflammatory action, improvement in endothelial function, and inhibition of platelet aggregation (3, 6, 7).

Epidemiologic data suggest that dietary flavonoids may have beneficial cardiovascular effects in human populations. Several prospective studies have reported statistically significant inverse associations between total flavonoid intake or the intake of specific classes of flavonoids and cardiovascular disease (CVD) incidence or mortality (2, 8-14), whereas other prospective studies have not (15-17). Epidemiologic studies of flavonoid intake and stroke incidence or mortality have also been inconsistent (9, 10, 18, 19). Sagara et al (20) reported data from an intervention study indicating that isoflavones may reduce baseline measures of several CVD risk factors, including systolic and diastolic blood pressures, total cholesterol, and non-HDL cholesterol.

Most epidemiologic studies to date have been limited by the information available in nutrient databases, and they have focused primarily on flavonols (quercetin, kaempferol, and myricetin), flavones (luteolin and apigenin), catechins (flavan-3-ols), and isoflavones. In 2003 and 2004, the US Department of Agriculture (USDA) released new databases of flavonoid (flavonols, flavones, flavanones, flavan-3-ols, anthocyanidins) and proanthocyanidin content of selected foods (225 and 205 foods, respectively) (21, 22). A database of isoflavone concentrations in selected (128) foods has been available since 1999 (23). These databases contain the most recent publicly available data on flavonoid content of foods, reported as aglycones, and include additional data generated by the USDA Agricultural Research

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Service. The combination of these 3 databases provides a more complete picture of the flavonoid concentrations in foods than was found with previously available databases.

The purpose of the current study was to examine the association between flavonoid intake and CVD and stroke in a prospective cohort study of postmenopausal women by using newly available nutrient composition information to calculate the intake of flavonoids. Our objective was to evaluate the hypothesis that flavonoid intake is inversely associated with CVD mortality. In addition, we evaluated the relation between individual foods that are major sources of flavonoids or that have high flavonoid content and specific mortality endpoints.

SUBJECTS AND METHODS

Study population

Participants in the Iowa Women's Health Study (IWHS) were recruited from a random sample of 99 826 women aged 55–69 y who had a valid Iowa driver's license in 1985. A 16-page baseline questionnaire was mailed to these women in 1986. The 41 836 women who returned the survey make up the cohort under study. Characteristics of nonrespondents were reported elsewhere (24). The baseline questionnaire included a food-frequency questionnaire (FFQ) and other questions relevant to the risk of coronary heart disease (CHD) and stroke (10). Follow-up questionnaires to confirm participants' place of residence, vital status, and ascertain additional information were mailed in 1987, 1989, 1992, and 1997.

Dietary assessment

The 127-item FFQ was adapted, with minor modifications, from the questionnaire used in the 1984 Nurses' Health Study survey (25). The FFQ, part of the 1986 baseline questionnaire, had detailed information on fruit (15 items) and vegetables (29 items) and included information on individual foods with high flavonoid content (eg, tea, chocolate, red wine, blueberries, and strawberries). For each food, a portion size was specified, and participants were asked to choose 1 of 9 frequency categories ranging from (as in the questionnaire) "never or less than once per month" to "6+ day." Onions, which have been cited in the literature as a potential significant source of flavonoids, were not included on the questionnaire. Participants were asked to indicate foods (serving size and servings/wk) that they usually ate ≥ 1 time/wk but that were not listed on the questionnaire. The brand and type of cold breakfast cereal usually consumed were ascertained; the questionnaire also collected information on the use of vitamin supplements. Validity of the FFQ to ascertain nutrient intake was evaluated in a subgroup of 44 women by comparing the mean nutrient intake according to the questionnaire with that estimated from five 24-h dietary recall interviews (26). The correlation coefficients for alcohol, caffeine, and vitamin C (without supplements) were 0.32, 0.82, and 0.53, respectively. The FFQ was not evaluated for its ability to assess flavonoid intake in this population; however, the questionnaire was previously validated in another population (27). Feskanich et al (27) reported correlation coefficients of 0.70, 0.77, and 0.83 for the important sources of flavonoids apples, tea, and red wine, respectively.

Follow-up

Women were followed annually through the State Health Registry of Iowa, which collects information on deaths in Iowa.

Deaths were also identified through the 4 follow-up questionnaires by linking women who did not respond to the questionnaire with the National Death Index. We used the *International Classification of Diseases, 9th Revision* (28) to classify the reported cause of death in the following categories (not mutually exclusive): CHD [codes 410–414 (ischemic heart disease) or code 429.2 (arteriosclerotic heart disease)]; stroke (codes 430–438); total CVD (codes 390–459); and total mortality (all ICD-9 codes for mortality). Follow-up time for each woman was calculated as the number of days from the date of return of the baseline questionnaire to the date of death or 31 December 2002, whichever came first.

Each woman's return of the questionnaire was considered to provide consent. This study was approved by the Committee on the Use of Human Subjects in Research of the University of Minnesota.

Data analysis

Cohort for analysis

Women were excluded from the current analyses if they reported on the baseline questionnaire that they were premenopausal ($n = 569$); that they had been told by a doctor that they had heart disease or angina or had had a heart attack ($n = 4115$); if their FFQ was incomplete (ie, ≥ 30 food items were left blank) ($n = 2782$); or if their total energy intake was implausibly low (< 600 kcal/d) or high (≥ 5000 kcal/d) ($n = 538$). Numbers excluded are not mutually exclusive. In addition, 3 women who had zero total person-years were excluded. After these exclusions, 34 489 women remained eligible for follow-up. In these women, 7091 total deaths, 2316 CVD deaths, 1329 CHD deaths, and 469 deaths due to stroke occurred.

Dietary variables

Preparing the dietary variables for analysis involved 2 main steps: 1) deriving estimates of the flavonoid content in foods on the IWHS FFQ on the basis of data from the 3 USDA databases and 2) calculating estimated daily flavonoid intake for each participant. We first merged the 3 USDA databases—the isoflavone database (23), the flavonoid database (21), and the proanthocyanidin database (22). The compounds included in each database, along with typical high-content foods, are summarized in **Table 1**. Merging of the databases resulted in a single datafile, which included the flavonoid contents reported in any of the 3 databases for each 5-digit USDA food code reported. If a food was included in both the flavonoid and proanthocyanidin databases, and if both a flavan-3-ol value (flavonoid database) and a monomer value (proanthocyanidin database) were reported, we averaged the 2 values. Several flavan-3-ols (eg, theaflavins and thearubigins) are found only in tea, and they were not included in the proanthocyanidin database; therefore, we did not average the 2 values and instead used the flavan-3-ol value for tea.

For each food, we computed the sum of assessed flavonoids (total flavonoids) for each flavonoid subclass by summing the appropriate compounds (Table 1). For each item on the FFQ (127 items) or each item written in by a participant as a food usually eaten ≥ 1 time/wk (105 foods), we attempted to identify matching food(s) in the USDA databases. We then assigned these FFQ items the flavonoid content of the matching USDA foods. For items on the FFQ that included just one food (eg, bananas), the flavonoid value for the matching food in the USDA databases



TABLE 1

Flavonoid subclasses and compounds included in the US Department of Agriculture databases

Database	Flavonoid subclass (typical high-content foods) (1, 21–23, 28, 29)	Compounds
Flavonoid (21)	Flavonols (onions, broccoli, apples) Flavones (celery, parsley) Flavanones (oranges, grapefruit, lemons) Flavan-3-ols (apples, red wine, green tea, black tea)	Quercetin, Kaempferol, Myricetin, Isorhamnetin Luteolin, Apigenin Hesperetin, Naringenin, Eriodictyol (+)-Catechin, (+)-Gallicocatechin, (–)-Epicatechin, (–)-Epigallocatechin, (–)-Epicatechin 3-gallate, (–)-Epigallocatechin 3-gallate, Theaflavin, Theaflavin 3-gallate, Theaflavin 3'-gallate, Theaflavin 3,3' digallate, Thearubigins
	Anthocyanidin (blueberries, raspberries, red wine)	Cyanidin, Delphinidin, Malvidin, Pelargonidin, Peonidin, Petunidin
Proanthocyanidin (22)	Proanthocyanidins (apples, chocolate, seeded grapes)	Monomers, dimers, trimers, 4-6mers, 7-10mers, and polymers
Isoflavone (23)	Isoflavones (tofu, soy milk)	Daidzein, Genistein, Glycitein

References in parentheses.

was used. For items in the IWHS FFQ that included >1 food (eg, yams or sweet potatoes), we calculated a weighted average of flavonoid values for corresponding items in the USDA databases, in which the weights for each food were based on the per capita consumption amount for that food as reported in the USDA's Economic Research Service Food Availability Database for 1986 (the year the FFQ was administered to the IWHS participants) (29). If no data were available, we used per capita consumption estimates from USDA's 1994–1996 and 1998 Continuing Survey of Food Intakes by Individuals (CSFII) (30). Items on the questionnaire that were mixed dishes (eg, pizza) or that included a combination of foods (eg, mixed vegetables) were assigned a weighted value on the basis of a USDA standard recipe. In the conduct of the matching, some instances occurred in which data were available but the food form or preparation method did not match (eg, dried rather than fresh apricots). When this occurred, we calculated a default processing factor from available flavonoid concentration data for similar foods. Foods in the IWHS FFQ that were not in any of the USDA flavonoid databases were assumed to contain no flavonoids.

We calculated total weekly consumption of a given flavonoid class by using the following equation:

$$FL_intake_{ij} = \sum_k FL_cont_{jk} \times food_cons_{ik} \quad (1)$$

where FL_intake_{ij} is the weekly intake (mg/wk) of flavonoid class (j) by the participant (i), FL_cont_{jk} is the flavonoid class (j) amount (mg) in one serving of food (k), and $food_cons_{ik}$ is the times per week that a food was reported to have been consumed (k) by the participant (i). Daily intake amounts were then derived by dividing the weekly amounts by 7.

Because the USDA databases have not been used in other epidemiologic studies to date, we compared correlation coefficients comparing for intakes of flavonoids that were evaluated in previous studies (31), and we calculated correlations among flavonoids evaluated in this study, as well as correlations between values obtained in this study compared with intakes calculated by Sampson et al (31).

Statistical analysis

We created quintiles of dietary flavonoid intakes and calculated the median intake and range of intakes for total flavonoids

and each flavonoid subclass. We summarized the baseline characteristics of the cohort (potential confounding factors) and stratified by quintile of total flavonoid intake. Mean values of the dietary variables were adjusted for total energy intake by using the residual method (32).

We estimated rate ratios (RR) associated with quintiles of flavonoid intake by using Cox proportional hazards analyses with the STCOX command in STATA software (version 7.0; Stata Corp, College Station, TX). In the initial analyses (model 1), intakes were adjusted for age and energy (kcal). We evaluated associations in additional multivariable models, adding covariates in groups. Model 2 included adjustment for age, energy, baseline marital status, education level, physical activity, smoking status (never, former, or current), and estrogen replacement therapy use (never, former, or current). Model 3 added baseline body mass index (BMI; in kg/m^2), waist-to-hip ratio (WHR), hypertension, and type 2 diabetes mellitus to the variables listed for model 2. Model 4 was adjusted for the variables in model 3, plus intake of the following dietary or nutrient factors: whole grains, fish and seafood, saturated fat, polyunsaturated fat, cholesterol, dietary fiber, vitamin C, vitamin E (from all sources), folate, and β -carotene (from all sources). A final model (model 5 or "parsimonious" model) removed from model 4 variables that had a P value > 0.15. In general, the most parsimonious model included the health and lifestyle variables (eg, marital status, blood pressure, WHR, physical activity, and smoking) but not the dietary variables. A typical exception was the inclusion in the final model of whole-grain intake and, occasionally, polyunsaturated fat intake.

We ran additional analyses by stratifying on baseline smoking status (ever-smoker or never-smoker), and obesity (obese: BMI ≥ 30 ; not obese: BMI < 30) to informally evaluate potential effect modification by these factors. Interaction terms between flavonoid intakes and each of these factors were also added to models 1, 3, and 4, and likelihood ratio chi-square tests were used to compare the main effects models to the models that included interaction effects and to formally test for statistical interactions. Because diabetic women may be more likely than nondiabetic women to change their diets, we conducted the primary analyses a second time after excluding women with self-reported type 2 diabetes mellitus at baseline ($n = 1772$) and compared these results with those from the total analytic cohort.

We evaluated the relation between the intake of select individual foods and CVD, CHD, and stroke mortality endpoints by using multivariate models similar to those described above. Individual flavonoid-containing foods were included for analysis if 1) the correlation between food intake and total flavonoid or flavonoid subclass intake was ≥ 0.5 ; 2) flavonoid intake from the food contributed to $\geq 1\%$ of total flavonoid intake in these data; or 3) the food was previously determined, in the scientific literature, to be associated with reduced CVD risks. Selected foods (percentage contribution to total flavonoid intake) included tea (26%), apples and pears (17%), bran added to food (9%), beans or lentils (9%), peaches (5%), oranges (5%), orange juice (5%), strawberries (4%), grapefruit (4%), other fruit juices (3%), chocolate (2%), blueberries (1%), red wine ($<1\%$), grapefruit juice ($<1\%$), grapes and raisins ($<1\%$), apple juice ($<1\%$), apple sauce ($<1\%$), tomatoes ($<1\%$), tomato juice ($<1\%$), broccoli ($<1\%$), celery ($<1\%$), Brussels sprouts ($<1\%$), string beans ($<1\%$), and kale or mustard greens ($<1\%$). Intakes were not divided into quintiles because of the large variability in the number of participants reporting consumption of the selected foods and the skewed distribution of the amounts consumed. Instead, we created categories of food intake— <1 time/wk, 1 time/wk, and >1 time/wk. In a few cases, there were so few consumers of a food that the categories were collapsed to nonconsumers (never or <1 time/mo) and consumers (≥ 1 times/mo) to allow for a sufficient sample size in each category. Food intake was initially adjusted for age and energy intake; additional multivariable models were run only for those foods that showed a significant association ($P < 0.05$) with the mortality endpoints.

We tested for evidence of a linear trend by evaluating the intake of total flavonoids and the subclasses (except anthocyanidins, for which the highest category test and the trend test are equivalent) as continuous variables with the quintiles coded to the median value of each quintile in separate proportional hazards regression models. We did not evaluate the dose response for individual foods because of the skewed distribution of intakes in the cohort.

All analyses, including Cox proportional hazards regression analyses, were conducted with the use of SPSS for WINDOWS software (version 7.0; SPSS Institute, Chicago, IL) and STATA software (version 7.0).

RESULTS

Previous reports from this cohort showed that recognized risk factors for CHD, reported at baseline—hypertension, type 2 diabetes mellitus, current smoking, low physical activity, higher BMI, and higher WHR—were associated with higher rates of CHD mortality (10, 33, 34). We calculated correlation coefficients to compare flavonoid intakes calculated by Sampson et al (31) and previously examined in the IWHs (10) with those derived in the current study. The dataset evaluated by Sampson et al included only 3 flavonols (quercetin, kaempferol, and myricetin) and the flavones luteolin and apigenin. Flavonol intakes based on the concentrations from the study by Sampson et al were highly correlated with the corresponding intakes in the current analysis (0.80–0.95) and with intakes of flavan-3-ols and proanthocyanidins derived in the current analysis (0.68–0.89), whereas flavone intakes showed a weaker correlation (0.31–0.47). Intakes of individual flavonols according to the concentrations determined by Sampson et al (31) were highly intercorrelated (0.77–0.84), whereas the correlation among flavones was

more modest ($r = 0.26$). In the current analysis, the flavan-3-ol monomers, flavonols, and proanthocyanidins were highly correlated with each other (0.75–0.81). Other variables in the current flavonoid dataset were less correlated.

The distribution of potential risk factors for CVD and stroke mortality according to total flavonoid intake level is shown in **Table 2**. The upper quintiles of flavonoid intake were associated with older age, lower BMI, lower WHR, greater physical activity, smaller proportions of current smokers, greater proportions of multivitamin users, education beyond high school, and current marriage. In addition, the upper quintiles were associated with greater intakes of whole grains, dietary fiber, vitamin C (without supplements), vitamin E (from any source), folate (from any source), and β -carotene (from any source) and lower intakes of alcohol, saturated fat, and cholesterol. The prevalence of type 2 diabetes mellitus and high blood pressure did not differ significantly across quintiles of total flavonoid intake.

Associations between intake of total flavonoids and flavonoid subclasses and mortality endpoints are shown in **Tables 3, 4, 5, and 6**. Because the results for models 2–5 did not appear to differ materially, we present only the results from model 1 (age- and energy-adjusted) and model 3 (multivariate-adjusted). After adjustment for age and energy, there was a significant inverse association between total mortality and each upper quintile of total flavonoids and each flavonoid subclass intake (Table 3). These associations approached 1.0 after adjustment for additional covariates, however, and only the associations with anthocyanidins and flavones remained significant in the multivariate models. No association was found between stroke mortality and any of the flavonoid classes; the tests for trend were not significant (Table 4). Intakes of total flavonoids (P for trend = 0.075), anthocyanidins, flavanones, flavones, and proanthocyanidins were inversely associated with CHD mortality in models after adjustment for age and energy, and anthocyanidins and flavanones remained significantly inversely associated after multivariate adjustment (Table 5). For total CVD mortality, significant inverse associations after adjustment for age and energy intake were observed for intake of total flavonoids, anthocyanidins, flavanones, flavones, and proanthocyanidins (Table 6). After multivariate adjustment, the relative risk for the upper category of anthocyanidins was attenuated but remained significant (P for trend = 0.032). The P values of the tests for trend for intake of flavanones were 0.001 after adjustment for age and energy, and 0.054 for the multivariate-adjusted model. The multivariate-adjusted relative risk in the “parsimonious” model for the highest versus lowest quintile was 0.77 (95% CI: 0.65, 0.92; P for trend = 0.002) (data not shown), whereas the corresponding RR in the multivariate model was 0.88 (0.77, 1.01) (see Table 6).

Most of the associations between the intakes of total flavonoids and subclasses and the mortality endpoints changed (ie, became closer to the null) and were no longer significant after adjustment for nondietary risk factors for CVD (model 3). We evaluated results from a “full” multivariate model (model 4), which included dietary factors associated with CVD. These dietary factors may have been correlated with the flavonoid and food variables, which were the independent variables of primary interest in the model; however, results from the models without these variables did not differ materially from results from the full model. The parsimonious model (model 5) did not include most of the dietary or nutrient variables from model 4, and again,

TABLE 2

Baseline characteristics by quintile (Q) of total flavonoid intake for 34 492 cardiovascular disease-free postmenopausal women (Iowa Women's Health Study, 1986)¹

	Total flavonoids (mg/d)					P for trend ²
	Q1 0.6–133.1 (n = 6898)	Q2 133.2–201.8 (n = 6899)	Q3 201.9–281.9 (n = 6898)	Q4 282.0–425.2 (n = 6899)	Q5 425.3–3524.4 (n = 6898)	
Continuous variables						
Baseline age (y)	61.1 ± 4.1 ³	61.4 ± 4.2	61.5 ± 4.2	61.8 ± 4.2	61.8 ± 4.2	<0.001
BMI (kg/m ²)	26.9 ± 5.2	27 ± 5.1	27 ± 5	27 ± 5	26.7 ± 5	0.014
WHR	0.8429 ± 0.0896	0.8368 ± 0.0844	0.8357 ± 0.0872	0.8349 ± 0.0817	0.8319 ± 0.0846	<0.001
Energy intake (kcal/d)	1468.5 ± 481.6	1684.2 ± 511.5	1826.6 ± 553.5	1960.4 ± 584.1	2064 ± 694	<0.001
Alcohol (g/d) ⁴	5.3 ± 10.8	4.1 ± 9	3.6 ± 8.4	3.2 ± 8	3.1 ± 8.2	<0.001
Whole-grain intake (servings/wk) ⁴	9.5 ± 7.5	10.5 ± 7.7	10.9 ± 7.7	11.7 ± 8.1	14.2 ± 10.8	<0.001
Dietary fiber (g/d) ⁴	16.3 ± 4	18.3 ± 4.5	19.8 ± 4.9	21.2 ± 5.2	23.2 ± 7.3	<0.001
Saturated fat (g/d) ⁴	26 ± 4.9	24.9 ± 4.8	24.1 ± 5.1	23.2 ± 5.4	22.2 ± 6.1	<0.001
Polyunsaturated fat (g/d) ⁴	12.3 ± 2.9	12.2 ± 3	12.1 ± 3.6	11.9 ± 3.4	11.8 ± 3.9	<0.001
Cholesterol (g/d) ⁴	285.6 ± 92.6	277.9 ± 84.2	274.9 ± 91.1	272.7 ± 104	261.2 ± 107	<0.001
Vitamin C without supplementation (mg/d) ⁴	114.3 ± 48	140.4 ± 53.2	157.5 ± 60.8	175.1 ± 72.1	185.2 ± 98	<0.001
Total vitamin E activity (IU/d) ⁴	51.6 ± 130.8	61.4 ± 141.8	65.2 ± 143.6	74 ± 154.6	83.8 ± 165.1	<0.001
Folate (μg/d) ⁴	364 ± 210	399.8 ± 215.9	426.1 ± 225.8	453.2 ± 236.7	491.6 ± 258.6	<0.001
Folate without supplementation (μg/d) ⁴	266.4 ± 79.1	292.5 ± 84.2	311.4 ± 95	330.7 ± 105.9	355.5 ± 122.6	<0.001
β-Carotene (IU/d) ⁴	7339.2 ± 5902.5	8439.1 ± 6148	9278.6 ± 6500.7	10554 ± 8442.8	11383.3 ± 9959.2	<0.001
Categorical variables						
Physical activity (%)						
Low	60	51	45	41	40	<0.001
Moderate	23	28	29	30	29	
High	17	21	26	29	31	
Smoking status (%)						
Never	55	64	69	71	69	<0.001
Past	20	19	19	18	20	
Current	25	16	13	11	11	
Pack-years (%)						
0	55	65	69	72	70	<0.001
1–19	14	14	14	13	14	
20–39	17	12	11	9	9	
≥40	14	9	7	6	7	
Estrogen use (%)						
Never	63	62	61	63	60	0.046
Past	27	27	28	26	28	
Current	10	11	11	11	12	
Diabetes (%)						
No	95	95	95	94	95	0.078
Yes	5	5	5	6	5	
Multivitamin use (%)						
No or don't know	70	67	66	64	62	<0.001
Yes	29	31	33	35	36	
Education (%)						
<High school	21	17	17	17	16	<0.001
High school	46	45	43	40	39	
>High school	33	38	41	43	45	
Baseline marital status (%)						
Not married	25	22	21	22	22	0.001
Married	75	78	79	78	78	
High blood pressure (%)						
No	65	63	63	63	65	0.501
Yes	34	35	35	36	34	
Not sure	2	1	2	1	1	
Aspirin frequency (%)						
Never	30	29	28	28	28	0.005
<1/wk	29	28	29	28	28	
1/wk	5	5	6	6	6	
2–5/wk	17	18	18	18	18	
≥6/wk	19	20	19	20	21	

¹ WHR, waist-to-hip ratio.² Likelihood ratio (chi-square test).³ $\bar{x} \pm SD$ (all such values).⁴ Adjusted for energy intake (kcal/d).

TABLE 3

Rate ratios (RR) of total mortality by quintile (Q) of flavonoid intake for 34 492 cardiovascular disease-free postmenopausal women (Iowa Women's Health Study)

	Flavonoid intake					<i>P</i> for trend ¹
	Q1	Q2	Q3	Q4	Q5	
Total flavonoids						
No. of deaths ²	1568 (106 568)	1416 (107 544)	1334 (108 183)	1365 (108 045)	1408 (107 736)	
Intake (mg/d)	95.8 (0.6–133.2) ³	167.5 (133.2–201.8)	238.9 (201.9–282)	336.5 (282–425.3)	603.3 (425.3–3524.4)	
RR (95% CI)						
Age- and energy-adjusted	1.00	0.85 (0.79, 0.92)	0.77 (0.72, 0.83)	0.76 (0.71, 0.82)	0.78 (0.72, 0.84)	<0.001
Multivariate-adjusted ⁴	1.00	0.95 (0.88, 1.02)	0.92 (0.85, 0.99)	0.94 (0.86, 1.01)	0.96 (0.89, 1.04)	0.716
Anthocyanidin⁵						
No. of deaths ²	2648 (182 302)	4443 (355 773)				
Intake (mg/d)	0	0.2 (0.01–1040)				
RR (95% CI)						
Age- and energy-adjusted	1.00	0.86 (0.81, 0.90)				<0.001
Multivariate-adjusted ⁵	1.00	0.90 (0.86, 0.95)				<0.001
Flavanones						
No. of deaths ²	1583 (106 815)	1426 (107 140)	1343 (107 991)	1311 (108 502)	1428 (107 627)	
Intake (mg/d)	7.6 (0–16.1)	26.6 (16.1–34)	40.4 (34–49.5)	59.9 (49.5–72.8)	93.7 (72.8–703.3)	
RR (95% CI)						
Age- and energy-adjusted	1.00	0.86 (0.80, 0.92)	0.79 (0.73, 0.85)	0.75 (0.70, 0.81)	0.81 (0.75, 0.87)	<0.001
Multivariate-adjusted ⁵	1.00	0.92 (0.85, 0.99)	0.90 (0.83, 0.97)	0.89 (0.83, 0.97)	0.93 (0.86, 1.01)	0.123
Flavones						
No. of deaths ²	1570 (106 616)	1476 (107 195)	1369 (108 126)	1342 (107 899)	1334 (108 239)	
Intake (mg/d)	0.1 (0–0.2)	0.3 (0.2–0.3)	0.4 (0.3–0.5)	0.8 (0.5–1)	1.5 (1–42.7)	
RR (95% CI)						
Age- and energy-adjusted	1.00	0.93 (0.86, 0.99)	0.85 (0.79, 0.91)	0.82 (0.76, 0.88)	0.79 (0.74, 0.86)	<0.001
Multivariate-adjusted ⁵	1.00	0.98 (0.91, 1.05)	0.92 (0.85, 0.99)	0.90 (0.83, 0.97)	0.88 (0.82, 0.96)	0.001
Flavonols						
No. of deaths ²	1560 (106 502)	1360 (108 023)	1333 (108 274)	1414 (107 755)	1424 (107 520)	
Intake (mg/d)	4.1 (0.2–5.4)	6.6 (5.4–7.7)	8.9 (7.7–10.3)	12.1 (10.3–14.6)	21 (14.6–125.4)	
RR (95% CI)						
Age- and energy-adjusted	1.00	0.85 (0.79, 0.91)	0.81 (0.75, 0.87)	0.85 (0.79, 0.91)	0.85 (0.79, 0.92)	0.019
Multivariate-adjusted ⁵	1.00	0.91 (0.84, 0.98)	0.90 (0.84, 0.98)	0.99 (0.92, 1.07)	0.95 (0.88, 1.03)	0.946
Isoflavones						
No. of deaths ²	1494 (107 286)	1368 (107 637)	1434 (107 975)	1366 (107 830)	1429 (107 346)	
Intake (mg/d)	0.1 (0–0.1)	0.1 (0.1–0.2)	0.3 (0.2–0.3)	0.3 (0.3–0.5)	0.8 (0.5–107.8)	
RR (95% CI)						
Age- and energy-adjusted	1.00	0.88 (0.81, 0.94)	0.92 (0.85, 0.99)	0.86 (0.79, 0.92)	0.90 (0.84, 0.97)	0.198
Multivariate-adjusted ⁵	1.00	0.96 (0.89, 1.03)	1.02 (0.94, 1.10)	0.99 (0.92, 1.07)	1.01 (0.93, 1.10)	0.455
Flavan-3-ols or monomers						
No. of deaths ²	1605 (106 389)	1408 (107 465)	1299 (108 171)	1309 (108 677)	1470 (107 372)	
Intake (mg/d)	4.2 (0–6.8)	10 (6.8–15.1)	20.4 (15.1–29.4)	75.7 (29.4–135.7)	181.6 (135.7–1049.8)	
RR (95% CI)						
Age- and energy-adjusted	1.00	0.83 (0.77, 0.89)	0.76 (0.70, 0.82)	0.75 (0.69, 0.81)	0.85 (0.79, 0.92)	0.262
Multivariate-adjusted ⁵	1.00	0.93 (0.86, 1.00)	0.87 (0.81, 0.94)	0.88 (0.81, 0.95)	0.98 (0.91, 1.06)	0.206
Proanthocyanidins						
No. of deaths ²	1548 (106 627)	1443 (107 483)	1349 (108 006)	1376 (107 895)	1375 (108 064)	
Intake (mg/d)	61.9 (0–89.5)	116.8 (89.5–143.9)	175.2 (143.9–212.3)	262.9 (212.3–343.2)	524 (343.2–3225.6)	
RR (95% CI)						
Age- and energy-adjusted	1.00	0.89 (0.83, 0.96)	0.80 (0.75, 0.87)	0.79 (0.73, 0.85)	0.78 (0.72, 0.84)	<0.001
Multivariate-adjusted ⁵	1.00	0.98 (0.91, 1.05)	0.94 (0.87, 1.01)	0.96 (0.89, 1.04)	0.94 (0.87, 1.02)	0.213

¹ Test for trend conducted with the median value for each quintile.² Person-years of follow-up in parentheses.³ Median; range in parentheses (all such values).⁴ Adjusted for age, energy intake, marital status, education, blood pressure, diabetes, BMI, waist-to-hip ratio, physical activity, smoking, and estrogen use.⁵ Zero intake versus >0.

results did not differ materially from those from the other multivariate models.

We found no material differences between results based on the full cohort and results from a subcohort restricted to women who

did not report a history of type 2 diabetes mellitus at baseline. In addition, the pattern of results was generally similar for never-smokers and ever-smokers and for obese and nonobese women. An exception to this was in analyses of flavanones, in which



TABLE 4

Rate ratios (RR) of stroke mortality by quintile (Q) of flavonoid intake for 34 492 cardiovascular disease-free postmenopausal women (Iowa Women's Health Study)

	Flavonoid intake					<i>P</i> for trend ¹
	Q1	Q2	Q3	Q4	Q5	
Total flavonoids						
No. of deaths from stroke ²	99 (106 568)	92 (107 544)	98 (108 183)	83 (108 045)	97 (107 736)	
Intake (mg/d)	95.8 (0.6–133.2) ³	167.5 (133.2–201.8)	238.9 (201.9–282)	336.5 (282–425.3)	603.3 (425.3–3524.4)	
RR (95% CI)						
Age- and energy-adjusted	1.00	0.87 (0.66, 1.16)	0.89 (0.67, 1.18)	0.71 (0.53, 0.97)	0.83 (0.62, 1.12)	0.281
Multivariate-adjusted ⁴	1.00	0.90 (0.67, 1.21)	0.94 (0.70, 1.27)	0.77 (0.56, 1.07)	0.94 (0.69, 1.29)	0.796
Anthocyanidins⁵						
No. of deaths from stroke ²	167 (182 302)	302 (355 773)				
Intake (mg/d)	0	0.2 (0.01–1040)				
RR (95% CI)						
Age- and energy-adjusted	1.00	0.93 (0.77, 1.13)				0.481
Multivariate-adjusted ⁴	1.00	1.01 (0.83, 1.24)				0.896
Flavanones						
No. of deaths from stroke ²	97 (106 815)	94 (107 140)	88 (107 991)	92 (108 502)	98 (107 627)	
Intake (mg/d)	7.6 (0–16.1)	26.6 (16.1–34)	40.4 (34–49.5)	59.9 (49.5–72.8)	93.7 (72.8–703.3)	
RR (95% CI)						
Age- and energy-adjusted	1.00	0.91 (0.68, 1.20)	0.83 (0.62, 1.11)	0.84 (0.63, 1.12)	0.88 (0.66, 1.17)	0.417
Multivariate-adjusted ⁴	1.00	0.91 (0.68, 1.22)	0.86 (0.64, 1.17)	0.94 (0.70, 1.27)	0.94 (0.69, 1.27)	0.846
Flavones						
No. of deaths from stroke ²	105 (106 616)	99 (107 195)	88 (108 126)	83 (107 899)	94 (108 239)	
Intake (mg/d)	0.1 (0–0.2)	0.3 (0.2–0.3)	0.4 (0.3–0.5)	0.8 (0.5–1)	1.5 (1–42.7)	
RR (95% CI)						
Age- and energy-adjusted	1.00	0.93 (0.71, 1.23)	0.83 (0.62, 1.10)	0.77 (0.57, 1.02)	0.85 (0.64, 1.13)	0.269
Multivariate-adjusted ⁴	1.00	0.94 (0.71, 1.26)	0.85 (0.63, 1.15)	0.83 (0.61, 1.13)	0.92 (0.68, 1.25)	0.664
Flavonols						
No. of deaths from stroke ²	111 (106 502)	88 (108 023)	82 (108 274)	86 (107 755)	102 (107 520)	
Intake (mg/d)	4.1 (0.2–5.4)	6.6 (5.4–7.7)	8.9 (7.7–10.3)	12.1 (10.3–14.6)	21 (14.6–125.4)	
RR (95% CI)						
Age- and energy-adjusted	1.00	0.79 (0.59, 1.04)	0.71 (0.53, 0.94)	0.73 (0.55, 0.98)	0.88 (0.66, 1.17)	0.879
Multivariate-adjusted ⁴	1.00	0.83 (0.62, 1.11)	0.76 (0.56, 1.03)	0.83 (0.61, 1.13)	0.92 (0.67, 1.24)	0.984
Isoflavones						
No. of deaths from stroke ²	89 (107 286)	88 (107 637)	100 (107 975)	94 (107 830)	98 (107 346)	
Intake (mg/d)	0.1 (0–0.1)	0.1 (0.1–0.2)	0.3 (0.2–0.3)	0.3 (0.3–0.5)	0.8 (0.5–107.8)	
RR (95% CI)						
Age- and energy-adjusted	1.00	0.94 (0.70, 1.27)	1.08 (0.81, 1.44)	1.01 (0.75, 1.36)	1.08 (0.80, 1.46)	0.508
Multivariate-adjusted ⁴	1.00	1.09 (0.80, 1.48)	1.21 (0.89, 1.63)	1.18 (0.86, 1.61)	1.23 (0.89, 1.69)	0.27
Flavan-3-ols or monomers						
No. of deaths from stroke ²	106 (106 389)	90 (107 465)	75 (108 171)	101 (108 677)	97 (107 372)	
Intake (mg/d)	4.2 (0–6.8)	10 (6.8–15.1)	20.4 (15.1–29.4)	75.7 (29.4–135.7)	181.6 (135.7–1049.8)	
RR (95% CI)						
Age- and energy-adjusted	1.00	0.81 (0.61, 1.08)	0.66 (0.49, 0.90)	0.88 (0.66, 1.16)	0.85 (0.64, 1.13)	0.837
Multivariate-adjusted ⁴	1.00	0.95 (0.71, 1.27)	0.76 (0.56, 1.05)	0.99 (0.74, 1.34)	0.95 (0.71, 1.28)	0.724
Proanthocyanidins						
No. of deaths from stroke ²	95 (106 627)	97 (107 483)	91 (108 006)	87 (107 895)	99 (108 064)	
Intake (mg/d)	61.9 (0–89.5)	116.8 (89.5–143.9)	175.2 (143.9–212.3)	262.9 (212.3–343.2)	524 (343.2–3225.6)	
RR (95% CI)						
Age- and energy-adjusted	1.00	0.98 (0.74, 1.30)	0.89 (0.66, 1.19)	0.80 (0.59, 1.08)	0.90 (0.67, 1.22)	0.511
Multivariate-adjusted ⁴	1.00	1.05 (0.78, 1.40)	0.97 (0.71, 1.32)	0.90 (0.65, 1.23)	1.02 (0.74, 1.39)	0.983

¹ Test for trend conducted with the median value for each quintile.

² Person-years of follow-up in parentheses.

³ Median; range in parentheses (all such values).

⁴ Adjusted for age, energy intake, marital status, education, blood pressure, diabetes, BMI, waist-to-hip ratio, activity, smoking, and estrogen use.

⁵ Zero intake versus >0.

inverse associations between intake and mortality due to CVD (*P* for interaction = 0.03 for model 1), CHD (*P* for interaction = 0.02 and 0.03 for models 1 and 4, respectively), and all causes (*P* for interaction = 0.0007, 0.002, and 0.0004 for models 1, 3, and

4, respectively) were observed among ever-smokers, but not among never-smokers. In addition, rate ratios for total mortality comparing the highest versus lowest quintiles of flavonols were significantly reduced for ever-smokers, but not



TABLE 5

Rate ratios (RR) of coronary heart disease (CHD) mortality by quintile (Q) of flavonoid intake for 34 492 cardiovascular disease-free postmenopausal women (Iowa Women's Health Study)

	Flavonoid intake					<i>P</i> for trend ¹
	Q1	Q2	Q3	Q4	Q5	
Total flavonoids						
No. of deaths from CHD ²	300 (106 568)	258 (107 544)	247 (108 183)	249 (108 045)	275 (107 736)	
Intake (mg/d)	95.8 (0.6–133.2) ³	167.5 (133.2–201.8)	238.9 (201.9–282)	336.5 (282–425.3)	603.3 (425.3–3524.4)	
RR (95% CI)						
Age- and energy-adjusted	1.00	0.81 (0.69, 0.96)	0.74 (0.63, 0.88)	0.72 (0.60, 0.86)	0.79 (0.66, 0.94)	0.075
Multivariate-adjusted ⁴	1.00	0.87 (0.73, 1.03)	0.85 (0.71, 1.02)	0.85 (0.70, 1.02)	0.94 (0.78, 1.13)	0.980
Anthocyanidins⁵						
No. of deaths from CHD ²	513 (182 302)	816 (355 773)				
Intake (mg/d)	0	0.2 (0.01–104.0)				
RR (95% CI)						
Age- and energy-adjusted	1.00	0.81 (0.73, 0.91)				<0.001
Multivariate-adjusted ⁴	1.00	0.88 (0.78, 0.99)				0.031
Flavanones						
No. of deaths from CHD ²	296 (106 815)	282 (107 140)	246 (107 991)	255 (108 502)	250 (107 627)	
Intake (mg/d)	7.6 (0–16.1)	26.6 (16.1–34)	40.4 (34–49.5)	59.9 (49.5–72.8)	93.7 (72.8–703.3)	
RR (95% CI)						
Age- and energy-adjusted	1.00	0.90 (0.76, 1.06)	0.77 (0.65, 0.91)	0.77 (0.65, 0.91)	0.74 (0.63, 0.88)	<0.001
Multivariate-adjusted ⁴	1.00	0.91 (0.77, 1.08)	0.83 (0.70, 0.99)	0.86 (0.72, 1.02)	0.78 (0.65, 0.94)	0.010
Flavones						
No. of deaths from CHD ²	269 (106 616)	284 (107 195)	271 (108 126)	254 (107 899)	251 (108 239)	
Intake (mg/d)	0.1 (0–0.2)	0.3 (0.2–0.3)	0.4 (0.3–0.5)	0.8 (0.5–1)	1.5 (1–42.7)	
RR (95% CI)						
Age- and energy-adjusted	1.00	1.04 (0.88, 1.23)	0.99 (0.84, 1.18)	0.91 (0.77, 1.09)	0.88 (0.74, 1.05)	0.047
Multivariate-adjusted ⁴	1.00	1.10 (0.92, 1.31)	1.10 (0.92, 1.31)	0.98 (0.82, 1.18)	0.95 (0.78, 1.14)	0.147
Flavonols						
No. of deaths from CHD ²	280 (106 502)	267 (108 023)	233 (108 274)	274 (107 755)	275 (107 520)	
Intake (mg/d)	4.1 (0.2–5.4)	6.6 (5.4–7.7)	8.9 (7.7–10.3)	12.1 (10.3–14.6)	21 (14.6–125.4)	
RR (95% CI)						
Age- and energy-adjusted	1.00	0.94 (0.79, 1.11)	0.80 (0.67, 0.95)	0.93 (0.78, 1.11)	0.94 (0.79, 1.13)	0.937
Multivariate-adjusted ⁴	1.00	0.95 (0.80, 1.13)	0.85 (0.71, 1.02)	1.03 (0.86, 1.23)	0.95 (0.79, 1.14)	0.965
Isoflavones						
No. of deaths from CHD ²	298 (107 286)	238 (107 637)	265 (107 975)	250 (107 830)	278 (107 346)	
Intake (mg/d)	0.1 (0–0.1)	0.1 (0.1–0.2)	0.3 (0.2–0.3)	0.3 (0.3–0.5)	0.8 (0.5–107.8)	
RR (95% CI)						
Age- and energy-adjusted	1.00	0.76 (0.64, 0.90)	0.85 (0.72, 1.01)	0.79 (0.66, 0.94)	0.89 (0.75, 1.06)	0.995
Multivariate-adjusted ⁴	1.00	0.84 (0.70, 1.00)	0.95 (0.80, 1.13)	0.94 (0.78, 1.12)	1.00 (0.83, 1.19)	0.425
Flavan-3-ols or monomers						
No. of deaths from CHD ²	300 (106 389)	233 (107 465)	252 (108 171)	253 (108 677)	291 (107 372)	
Intake (mg/d)	4.2 (0–6.8)	10 (6.8–15.1)	20.4 (15.1–29.4)	75.7 (29.4–135.7)	181.6 (135.7–1049.8)	
RR (95% CI)						
Age- and energy-adjusted	1.00	0.74 (0.62, 0.88)	0.79 (0.67, 0.94)	0.78 (0.65, 0.92)	0.91 (0.77, 1.07)	0.400
Multivariate-adjusted ⁴	1.00	0.82 (0.69, 0.99)	0.89 (0.74, 1.06)	0.91 (0.76, 1.09)	1.02 (0.86, 1.21)	0.113
Proanthocyanidins						
No. of deaths from CHD ²	291 (106 627)	264 (107 483)	249 (108 006)	268 (107 895)	257 (108 064)	
Intake (mg/d)	61.9 (0–89.5)	116.8 (89.5–143.9)	175.2 (143.9–212.3)	262.9 (212.3–343.2)	524 (343.2–3225.6)	
RR (95% CI)						
Age- and energy-adjusted	1.00	0.87 (0.74, 1.03)	0.79 (0.67, 0.94)	0.81 (0.68, 0.97)	0.77 (0.65, 0.92)	0.021
Multivariate-adjusted ⁴	1.00	0.94 (0.79, 1.12)	0.91 (0.76, 1.09)	0.94 (0.79, 1.13)	0.91 (0.76, 1.10)	0.489

¹ Test for trend conducted with the median value for each quintile.

² Person-years of follow-up in parentheses.

³ Median; range in parentheses (all such values).

⁴ Adjusted for age, energy intake, marital status, education, blood pressure, diabetes, BMI, waist-to-hip ratio, physical activity, smoking, and estrogen use.

⁵ Zero intake versus >0.

for never-smokers (*P* for interaction = 0.003, 0.002, and 0.002 for models 1, 3, and 4, respectively).

Consumption of the following foods or beverages from the FFQ was inversely associated with stroke mortality after adjustment for age and total energy intake (*P* for trend: <0.001–

0.021): apples and pears, red wine, bran (added to food), and chocolate (**Table 7**). Only intake of bran (added to food) remained statistically significant after multivariate adjustment (*P* for trend = 0.013). In the analyses of CHD mortality and foods (**Table 8**), the age- and energy-adjusted relative



TABLE 6

Rate ratios (RR) of cardiovascular disease (CVD) mortality by quintile (Q) of flavonoid intake for 34 492 CVD-free postmenopausal women (Iowa Women's Health Study)

	Flavonoid intake					<i>P</i> for trend ¹
	Q1	Q2	Q3	Q4	Q5	
Total flavonoids						
No. of deaths from CVD ²	515 (106 568)	463 (107 544)	440 (108 183)	434 (108 045)	464 (107 736)	
Intake (mg/d)	95.8 (0.6–133.2) ³	167.5 (133.2–201.8)	238.9 (201.9–282)	336.5 (282–425.3)	603.3 (425.3–3524.4)	
RR (95% CI)						
Age- and energy-adjusted	1.00	0.85 (0.75, 0.97)	0.78 (0.68, 0.89)	0.74 (0.65, 0.84)	0.79 (0.69, 0.90)	0.005
Multivariate-adjusted ⁴	1.00	0.90 (0.79, 1.03)	0.88 (0.77, 1.01)	0.86 (0.75, 0.99)	0.93 (0.81, 1.07)	0.628
Anthocyanidins⁵						
No. of deaths from CVD ²	876 (182 302)	1440 (355 773)				
Intake (mg/d)	0	0.2 (0.01–1040)				
RR (95% CI)						
Age- and energy-adjusted	1.00	0.85 (0.78, 0.92)				<0.001
Multivariate-adjusted ⁴	1.00	0.91 (0.83, 0.99)				0.032
Flavanones						
No. of deaths from CVD ²	500 (106 815)	475 (107 140)	458 (107 991)	420 (108 502)	463 (107 627)	
Intake (mg/d)	7.6 (0–16.1)	26.6 (16.1–34)	40.4 (34–49.5)	59.9 (49.5–72.8)	93.7 (72.8–703.3)	
RR (95% CI)						
Age- and energy-adjusted	1.00	0.90 (0.79, 1.02)	0.85 (0.75, 0.96)	0.76 (0.67, 0.86)	0.83 (0.73, 0.94)	0.001
Multivariate-adjusted ⁴	1.00	0.91 (0.80, 1.04)	0.91 (0.8, 1.04)	0.84 (0.73, 0.97)	0.88 (0.77, 1.01)	0.054
Flavones						
No. of deaths from CVD ²	488 (106 616)	497 (107 195)	462 (108 126)	417 (107 899)	452 (108 239)	
Intake (mg/d)	0.1 (0–0.2)	0.3 (0.2–0.3)	0.4 (0.3–0.5)	0.8 (0.5–1)	1.5 (1–42.7)	
RR (95% CI)						
Age- and energy-adjusted	1.00	1.01 (0.89, 1.14)	0.94 (0.83, 1.07)	0.83 (0.73, 0.95)	0.89 (0.78, 1.01)	0.015
Multivariate-adjusted ⁴	1.00	1.05 (0.92, 1.20)	1.02 (0.89, 1.17)	0.91 (0.79, 1.04)	0.95 (0.83, 1.10)	0.136
Flavonols						
No. of deaths from CVD ²	520 (106 502)	444 (108 023)	416 (108 274)	470 (107 755)	466 (107 520)	
Intake (mg/d)	4.1 (0.2–5.4)	6.6 (5.4–7.7)	8.9 (7.7–10.3)	12.1 (10.3–14.6)	21 (14.6–125.4)	
RR (95% CI)						
Age- and energy-adjusted	1.00	0.85 (0.75, 0.96)	0.77 (0.68, 0.88)	0.87 (0.76, 0.99)	0.87 (0.76, 0.99)	0.379
Multivariate-adjusted ⁴	1.00	0.87 (0.76, 0.99)	0.84 (0.73, 0.96)	0.97 (0.85, 1.11)	0.91 (0.79, 1.05)	0.779
Isoflavones						
No. of deaths from CVD ²	493 (107 286)	431 (107 637)	481 (107 975)	438 (107 830)	473 (107 346)	
Intake (mg/d)	0.1 (0–0.1)	0.1 (0.1–0.2)	0.3 (0.2–0.3)	0.3 (0.3–0.5)	0.8 (0.5–107.8)	
RR (95% CI)						
Age- and energy-adjusted	1.00	0.84 (0.74, 0.96)	0.94 (0.83, 1.07)	0.85, (0.74–0.97)	0.93 (0.82, 1.07)	0.926
Multivariate-adjusted ⁴	1.00	0.91 (0.80, 1.05)	1.05 (0.92, 1.20)	0.99 (0.86, 1.14)	1.05 (0.91, 1.21)	0.210
Flavan-3-ols or monomers						
No. of deaths from CVD ²	536 (106 389)	421 (107 465)	432 (108 171)	446 (108 677)	481 (107 372)	
Intake (mg/d)	4.2 (0–6.8)	10 (6.8–15.1)	20.4 (15.1–29.4)	75.7 (29.4–135.7)	181.6 (135.7–1049.8)	
RR (95% CI)						
Age- and energy-adjusted	1.00	0.75 (0.66, 0.86)	0.76 (0.67, 0.87)	0.77 (0.68, 0.88)	0.85 (0.75, 0.96)	0.885
Multivariate-adjusted ⁴	1.00	0.84 (0.74, 0.97)	0.85 (0.75, 0.98)	0.89 (0.78, 1.02)	0.95 (0.83, 1.09)	0.395
Proanthocyanidins						
No. of deaths from CVD ²	500 (106 627)	479 (107 483)	435 (108 006)	456 (107 895)	446 (108 064)	
Intake (mg/d)	61.9 (0–89.5)	116.8 (89.5–143.9)	175.2 (143.9–212.3)	262.9 (212.3–343.2)	524 (343.2–3225.6)	
RR (95% CI)						
Age- and energy-adjusted	1.00	0.92 (0.81, 1.05)	0.81 (0.71, 0.92)	0.81 (0.71, 0.93)	0.79 (0.69, 0.90)	0.002
Multivariate-adjusted ⁴	1.00	0.99 (0.87, 1.13)	0.92 (0.80, 1.06)	0.94 (0.82, 1.08)	0.93 (0.81, 1.07)	0.332

¹ Test for trend conducted with the median value for each quintile.

² Person-years of follow-up in parentheses.

³ Median; range in parentheses (all such values).

⁴ Adjusted for age, energy intake, marital status, education, blood pressure, diabetes, BMI, waist-to-hip ratio, physical activity, smoking, and estrogen use.

⁵ Zero intake versus >0.

risks were significantly decreased (*P* for trend: <0.001–0.033) in women reporting consumption of apples and pears, oranges, grapefruit, blueberries, red wine, celery, strawberries, Brussels sprouts, bran (added to food), chocolate, and other fruit juices.

Apples and pears, grapefruit, and red wine remained significantly inversely associated with CHD mortality in the multivariate-adjusted and parsimonious models. With the exception of broccoli (*P* for trend = 0.065) and tomatoes, all of the food



TABLE 7Rate ratios (RR) of stroke mortality by category of food intake for 34 492 cardiovascular disease-free postmenopausal women (Iowa Women's Health Study)¹

	Category of food intake			<i>P</i> for trend ²
	1	2	3	
Apples and pears				
No. of deaths from stroke ³	141 (133 008)	86 (107 446)	242 (297 621)	
Servings (no./wk)	<1.00	1.00	>1.00	
RR (95% CI)				
Age- and energy-adjusted	1.00	0.74 (0.57, 0.97)	0.73 (0.59, 0.90)	0.018
Multivariate-adjusted ⁴	1.00	0.85 (0.64, 1.12)	0.85 (0.68, 1.07)	0.284
Orange juice				
No. of deaths from stroke ³	192 (209 930)	39 (61 583)	238 (266 562)	
Servings (no./wk)	<1.00	1.00	>1.00	
RR (95% CI)				
Age- and energy-adjusted	1.00	0.68 (0.48, 0.96)	0.93 (0.77, 1.13)	0.888
Multivariate-adjusted ³	1.00	0.68 (0.47, 0.98)	0.91 (0.75, 1.12)	0.756
Red wine				
No. of deaths from stroke ³	391 (419 239)	78 (118 835)		
Servings (no./wk)	0	>0		
RR (95% CI)				
Age- and energy-adjusted	1.00	0.75 (0.59, 0.96)		0.021
Multivariate-adjusted ³	1.00	0.81 (0.62, 1.05)		0.109
Bran (added to food)				
No. of deaths from stroke ³	405 (436 997)	64 (101 078)		
Servings (no./wk)	0	>0		
RR (95% CI)				
Age- and energy-adjusted	1.00	0.61 (0.47, 0.79)		<0.001
Multivariate-adjusted ³	1.00	0.70 (0.53, 0.93)		0.013
Chocolate				
No. of deaths from stroke ³	251 (248 687)	218 (289 388)		
Servings (no./wk)	0	>0		
RR (95% CI)				
Age- and energy-adjusted	1.00	0.78 (0.65, 0.94)		0.01
Multivariate-adjusted ³	1.00	0.85 (0.70, 1.03)		0.098

¹ Categories of food intake: 1, <1 time/wk; 2, 1 time/wk; and 3, >1 time/wk.² Test for trend conducted with the median value for each quintile.³ Person-years of follow-up in parentheses.⁴ Adjusted for age, energy intake, marital status, education, blood pressure, diabetes, BMI, waist-to-hip ratio, physical activity, smoking, and estrogen use.

or beverage items shown in **Table 9** were significantly and inversely associated with total CVD mortality after adjustment for age and energy intake. Apples and pears, red wine, strawberries, bran (added to food), and chocolate (*P* for trend = 0.062) remained significantly associated with a reduced risk of CVD death in the multivariate models. We did not evaluate dose-response patterns for many of the food variables because of the skewed distribution of intake and variable number of consumers in the cohort.

DISCUSSION

This prospective study of postmenopausal women, with 16 y of follow-up, is, to our knowledge, the first study that has reported on total flavonoids and on 7 subclasses of flavonoids. We found that dietary intakes of flavanones and anthocyanidins were associated with a decreased risk of death due to CHD, CVD, and all causes combined after multivariate adjustment. We found no association between the intake of total flavonoids or any of the subclasses and stroke mortality. In the analyses of foods, apple and pear and red wine intakes were associated with reduced CHD

and total CVD mortality. Grapefruit, a major source of flavanones, was associated with a lower risk of CHD mortality.

The IWHs previously reported decreased risk for mortality due to CHD but not stroke with greater flavonol and flavone (and broccoli) intakes (10). In a subsequent analysis of this cohort, inverse associations were observed between CHD mortality and intakes of catechins and epicatechins (flavan-3-ols), apples, and wine (11). In contrast with the earlier report (10), in the current study we did not observe a significant inverse association between broccoli intake and CHD mortality. Our findings of decreased CHD and CVD mortality associated with increased intake of apples and pears and red wine are consistent with previous reports from the cohort in the current study (10, 11) and other studies (8, 9, 12, 16), although these associations were sometimes weak. Rimm et al (17) found no association between apple consumption and CHD mortality.

Several studies have reported decreased CHD mortality associated with increased intake of flavonols or one of its major sources, tea (or both) (12, 14, 35). We did not observe a significant reduction in risk of CHD mortality with the intake of tea or

TABLE 8

Rate ratios (RR) of coronary heart disease (CHD) mortality by category of food intake for 34 492 cardiovascular disease-free postmenopausal women (Iowa Women's Health Study)¹

	Category of food intake			P for trend ²
	1	2	3	
Apples and pears				
No. of deaths from CHD ³	392 (133 008)	258 (107 446)	679 (297 621)	
Servings/wk	<1.00	1.00	>1.00	
RR (95% CI)				
Age- and energy-adjusted	1.00	0.80 (0.68, 0.94)	0.74 (0.65, 0.84)	<0.001
Multivariate-adjusted ⁴	1.00	0.88 (0.75, 1.04)	0.85 (0.75, 0.98)	0.049
Oranges				
No. of deaths from CHD ³	634 (243 516)	256 (102 958)	439 (191 600)	
Servings/wk	<1.00	1.00	>1.00	
RR (95% CI)				
Age- and energy-adjusted	1.00	0.98 (0.85, 1.14)	0.88 (0.78, 0.99)	0.033
Multivariate-adjusted ⁴	1.00	1.08 (0.93, 1.26)	0.96 (0.84, 1.09)	0.446
Grapefruit				
No. of deaths from CHD ³	836 (316 726)	195 (86 878)	298 (134 471)	
Servings/wk	<1.00	1.00	>1.00	
RR (95% CI)				
Age- and energy-adjusted	1.00	0.80 (0.69, 0.94)	0.77 (0.67, 0.88)	<0.001
Multivariate-adjusted ⁴	1.00	0.90 (0.77, 1.06)	0.85 (0.74, 0.98)	0.02
Blueberries				
No. of deaths from CHD ³	1160 (456 840)	169 (81 235)		
Servings/wk	0	>0		
RR (95% CI)				
Age- and energy-adjusted	1.00	0.81 (0.69, 0.95)		0.011
Multivariate-adjusted ⁴	1.00	0.89 (0.75, 1.06)		0.179
Red wine				
No. of deaths from CHD ³	1119 (419 239)	210 (118 835)		
Servings wk	0	>0		
RR (95% CI)				
Age- and energy-adjusted	1.00	0.69 (0.60, 0.80)		<0.001
Multivariate-adjusted ⁴	1.00	0.79 (0.68, 0.93)		0.004
Celery				
No. of deaths from CHD ³	598 (230 778)	293 (119 833)	438 (187 464)	
Servings wk	<1.00	1.00	>1.00	
RR (95% CI)				
Age- and energy-adjusted	1.00	0.93 (0.81, 1.07)	0.86 (0.76, 0.98)	0.026
Multivariate-adjusted ⁴	1.00	1.02 (0.88, 1.18)	0.92 (0.81, 1.05)	0.17
Strawberries				
No. of deaths from CHD ³	370 (132 994)	959 (405 080)		
Servings wk	0	>0		
RR (95% CI)				
Age- and energy-adjusted	1.00	0.84 (0.74, 0.95)		0.005
Multivariate-adjusted ⁴	1.00	0.95 (0.83, 1.08)		0.402
Brussels sprouts				
No. of deaths from CHD ³	904 (377 038)	425 (161 036)		
Servings wk	0	>0		
RR (95% CI)				
Age- and energy-adjusted	1.00	1.14 (1.02, 1.28)		0.024
Multivariate-adjusted ⁴	1.00	1.09 (0.97, 1.23)		0.143
Bran (added to food)				
No. of deaths from CHD ³	1112 (436 997)	217 (101 078)		
Servings wk	0	>0		
RR (95% CI)				
Age- and energy-adjusted	1.00	0.77 (0.67, 0.89)		<0.001
Multivariate-adjusted ⁴	1.00	0.91 (0.78, 1.06)		0.238
Chocolate				
No. of deaths from CHD ³	667 (248 687)	662 (289 388)		
Servings wk	0	>0		
RR (95% CI)				
Age- and energy-adjusted	1.00	0.88 (0.79, 0.98)		0.023
Multivariate-adjusted ⁴	1.00	0.98 (0.88, 1.10)		0.775
Other fruit juices				
No. of deaths from CHD ³	786 (305 738)	543 (232 337)		
Servings wk	0	>0		
RR (95% CI)				
Age- and energy-adjusted	1.00	0.88 (0.79, 0.99)		0.031
Multivariate-adjusted ⁴	1.00	0.97 (0.86, 1.09)		0.564

¹ Categories of food intake; 1, <1 time/wk; 2, 1 time/wk; 3, >1 time/wk.

² Test for trend conducted with the median value for each quintile.

³ Person-years of follow-up in parentheses.

⁴ Adjusted for age, energy intake, marital status, education, blood pressure, diabetes, BMI, waist-to-hip ratio, physical activity, smoking, and estrogen use.

TABLE 9Rate ratios (RR) of cardiovascular disease (CVD) mortality by category of food intake for 34 492 CVD-free postmenopausal women (Iowa Women's Health Study)¹

	Category of food intake			<i>P</i> for trend ²
	1	2	3	
Apples and pears				
No. of deaths from CVD ³	679 (133 008)	450 (107 446)	1,187 (297 621)	
Servings wk	<1.00	1.00	>1.00	
RR (95% CI)				
Age- and energy-adjusted	1.00	0.81 (0.72, 0.91)	0.75 (0.68, 0.82)	<0.001
Multivariate-adjusted ⁴	1.00	0.90 (0.79, 1.01)	0.87 (0.78, 0.96)	0.019
Oranges				
No. of deaths from CVD ³	1104 (243 516)	431 (102 958)	781 (191 600)	
Servings wk	<1.00	1.00	>1.00	
RR (95% CI)				
Age- and energy-adjusted	1.00	0.95 (0.85, 1.07)	0.90 (0.82, 0.99)	0.031
Multivariate-adjusted ⁴	1.00	1.05 (0.93, 1.18)	0.99 (0.90, 1.09)	0.761
Grapefruit				
No. of deaths from CVD ³	1418 (316 726)	337 (86 878)	561 (134 471)	
Servings/wk	<1.00	1.00	>1.00	
RR (95% CI)				
Age- and energy-adjusted	1.00	0.82 (0.73, 0.92)	0.85 (0.77, 0.94)	0.001
Multivariate-adjusted ⁴	1.00	0.90 (0.80, 1.02)	0.93 (0.84, 1.03)	0.144
Blueberries				
No. of deaths from CVD ³	2011 (456 840)	305 (81 235)		
Servings/wk	0	>0		
RR (95% CI)				
Age- and energy-adjusted	1.00	0.85 (0.75, 0.96)		0.008
Multivariate-adjusted ⁴	1.00	0.93 (0.82, 1.06)		0.264
Broccoli				
No. of deaths from CVD ³	1199 (260 148)	702 (175 063)	415 (102 864)	
Servings/wk	<1.00	1.00	>1.00	
RR (95% CI)				
Age- and energy-adjusted	1.00	0.88 (0.80, 0.97)	0.89 (0.79, 1.00)	0.065
Multivariate-adjusted ⁴	1.00	0.94 (0.85, 1.03)	0.95 (0.85, 1.07)	0.506
Red wine				
No. of deaths from CVD ³	1942 (419 239)	374 (118 835)		
Servings/wk	0	>0		
RR (95% CI)				
Age- and energy-adjusted	1.00	0.71 (0.64, 0.80)		<0.001
Multivariate-adjusted ⁴	1.00	0.80 (0.71, 0.90)		<0.001
Celery				
No. of deaths from CVD ³	1055 (230 778)	504 (119 833)	757 (187 464)	
Servings/wk	<1.00	1.00	>1.00	
RR (95% CI)				
Age- and energy-adjusted	1.00	0.91 (0.82, 1.01)	0.85 (0.77, 0.93)	0.002
Multivariate-adjusted ⁴	1.00	0.97 (0.87, 1.08)	0.91 (0.83, 1.01)	0.085
Tea				
No. of deaths from CVD ³	1033 (229 082)	1283 (308 993)		
Servings/wk	0	>0		
RR (95% CI)				
Age- and energy-adjusted	1.00	0.90 (0.83, 0.98)		0.011
Multivariate-adjusted ⁴	1.00	0.97 (0.89, 1.06)		0.462
Grapes and raisins				
No. of deaths from CVD ³	1701 (386 242)	389 (97 429)	226 (54 404)	
Servings/wk	<1.00	1.00	>1.00	
RR (95% CI)				
Age- and energy-adjusted	1.00	0.86 (0.77, 0.97)	0.85 (0.74, 0.98)	0.007
Multivariate-adjusted ⁴	1.00	0.96 (0.85, 1.07)	0.94 (0.81, 1.09)	0.316
Strawberries				
No. of deaths from CVD ³	662 (132 994)	1654 (405 080)		
Servings/wk	0	>0		
RR (95% CI)				
Age- and energy-adjusted	1.00	0.82 (0.74, 0.89)		<0.001
Multivariate-adjusted ⁴	1.00	0.91 (0.82, 1.00)		0.046

(Continued)



TABLE 9 (Continued)

	Category of food intake			P for trend ²
	1	2	3	
Tomatoes				
No. of deaths from CVD ³	700 (148 088)	744 (192 919)	872 (197 068)	
Servings/wk	<1.00	1.00	>1.00	
RR (95% CI)				
Age- and energy-adjusted	1.00	0.82 (0.74, 0.91)	0.94 (0.85, 1.04)	0.649
Multivariate-adjusted ⁴	1.00	0.83 (0.74, 0.92)	0.93 (0.83, 1.03)	0.998
Bran (added to food)				
No. of deaths from CVD ³	1952 (436 997)	364 (101 078)		
Servings/wk	0	>0		
RR (95% CI)				
Age- and energy-adjusted	1.00	0.74 (0.66, 0.82)		<0.001
Multivariate-adjusted ⁴	1.00	0.86 (0.76, 0.97)		0.014
Chocolate				
No. of deaths from CVD ³	1198 (248 687)	1118 (289 388)		
Servings/wk	0	>0		
RR (95% CI)				
Age- and energy-adjusted	1.00	0.83 (0.77, 0.91)	<0.001	
Multivariate-adjusted ⁴	1.00	0.92 (0.84, 1.00)	0.062	

¹ Categories of food intake: 1, <1 time/wk; 2, 1 time/wk; 3, >1 time/wk.

² Test for trend conducted with the median value for each quintile.

³ Person-years of follow-up in parentheses.

⁴ Adjusted for age, energy intake, marital status, education, blood pressure, diabetes, BMI, waist-to-hip ratio, physical activity, smoking, and estrogen use.

flavan-3-ols, nor was the inverse association for these variables and total CVD mortality significant after multivariate adjustment. Two previous studies reported no evidence of a cardioprotective effect of tea (15, 17). A recent report from the Zutphen Elderly Study (36) presented inverse associations between cocoa intake and blood pressure and between CVD and all-cause mortality in men. We observed a borderline significant inverse association between chocolate intake and CVD mortality after multivariate adjustment.

The extent to which our results differed from those of some previous studies may be related to differences in dietary patterns of the cohorts, differences in the foods assessed in the FFQs, differences in the databases used to estimate flavonoid intake, or differences in the cutoffs used to categorize the consumption levels. There were also some internal inconsistencies in our data. For example, patterns of relative risks were not always monotonic. This finding could be due to chance variation or could indicate that the relation between dietary intake of flavonoids and the mortality outcomes investigated is not strictly linear. Significant interactions observed for ever-smokers and never-smokers could represent a biological interaction or could be related to other CVD risk factors that differ between smokers and non-smokers.

Strengths of the current study include its prospective design, large size, and virtually complete follow-up of the cohort for mortality and cause of death. Several limitations of the study and of the USDA databases must, however, be considered. We relied on dietary intake from an FFQ administered at one point in time and did not have updated information. Thus, misclassification of dietary exposure occurs to the extent that women's diets have changed over the follow-up period. In addition, the potential for a misclassification exists because of misreporting of usual diet. Flavonoid concentrations may be underestimated because of items missing from the questionnaire, such as onions, whole

grains, and certain types of berries, which are high in flavonoids. The questionnaire did include an item about blueberry intake. Information on relevant biomarkers of intake, particularly multiple measures over time, would enhance the ability to assess and classify exposure and may also provide insights into mechanisms.

The USDA databases are a compilation of data available in the literature on the flavonoid content of foods. Studies that did not use procedures allowing for good separation of flavonoid compounds were deemed unacceptable by the USDA and were not included in the databases. Nonetheless, the included studies differed with respect to several factors, including overall quality. The USDA assigned each study a rating based on the sampling plan, sample handling, number of samples, analytic method, and analytic quality; however, we did not exclude any of the data in the 3 USDA databases. The published studies had limited data from the United States, often were based on single samples, and often focused on single compounds. Because food and beverage preparation practices vary across countries, comparison across studies may not be possible. This is particularly true for tea, because brewing time practices, which affect the flavonoid content, vary across countries (21). An updated and expanded USDA flavonoid content database, including data from nationally representative US samples of 59 fruit, vegetables, and nuts, was released in January 2007 (37), when this manuscript was in press. Isoflavones and proanthocyanidins were not updated in this latest database.

The flavonoid databases provide limited data from which to understand the effect that processing (eg, drying or baking) has on the flavonoid concentration in foods, expressed as the ratio of flavonoid content in a processed food to that in the unprocessed food. In some cases, when the flavonoid content of the unprocessed food was unavailable, we calculated default processing factors by using those foods that had, for example, flavonoid data

for the raw form and the dried form. However, we do not know the between-food variability in processing.

It is also important to note that the intake estimates presented in the current study are based on the mean concentration of flavonoids in food and do not take into account the large variability in flavonoid content that is seen in many foods. Nevertheless, people eat various foods from various sources, and mean flavonoid content may be the most appropriate measure in epidemiologic studies.

An important limitation inherent in this type of research is multiple comparisons. Because several types of flavonoids and a variety of food sources exist, and because 4 outcome variables were used, many tests were performed. The primary a priori hypothesis was that each flavonoid would be associated with CVD death, and CHD death and stroke death are considered particular examples of that association. The same hypothesis was evaluated for flavonoid-containing foods; here an important caveat is that, given the varied nature of diet, each food contributes little to the overall diet, relative risks for any one food are expected to be less than (but not much less than) 1.0, and statistical power is likely to be low. Examination of total mortality was based on the assumptions that CVD death would play a major role in that endpoint and that flavonoids also protect against some noncardiovascular diseases. Thus *P* values in the current study must be viewed with caution; "significance" is most securely taken for observations in this study that are consistent with observations in other studies of diet and disease.

This study contributes important information about the relation between the intakes of total flavonoids and 7 subclasses and CVD mortality endpoints. These results alone cannot be considered conclusive, however, because of limitations of the observational study design and of the dietary intake information. Results from this study suggest that the intake of certain subclasses of flavonoids may be associated with lower CHD and total CVD mortality in postmenopausal women. Furthermore, consumption of some foods that are high in flavonoid content or that are among the main sources of flavonoids in the diet of these study participants may have similar associations. The study of potential cardioprotective effects of the intakes of flavanones and anthocyanidins should be replicated in other large prospective studies with comprehensive information about the dietary intake of sources of flavonoids.

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CGS and LMB mapped the foods in the food-frequency questionnaire to the foods in the flavonoid databases and conducted the statistical analyses; C-PH processed the original data and prepared the Iowa Women's Health Study dataset that was used for the analysis; DRJ, PJM, C-PH, LMB, and LH contributed to the design of the study and data analysis; LMB and PJM interpreted the results of the data analysis; PJM and CGS wrote the draft of the manuscript; and LH, C-PH, LMB, JAN, PJM, DRJ, and CGS contributed to the revision of the manuscript. None of the authors had any personal or financial conflict of interest.

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