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Association of flavonoid-rich foods and flavonoids with risk of all-cause mortality

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Abstract

Flavonoids are bioactive compounds found in foods such as tea, red wine, fruits, 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 flavonoid-rich foods, and flavonoids, in preventing all-cause mortality remains uncertain. As such, we examined the association of intake of flavonoid-rich foods and flavonoids with subsequent mortality among 93,145 young and middle-aged women in the Nurses' Health Study II. During 1,838,946 person-years of follow-up, 1,808 participants died. When compared to non-consumers, frequent consumers of red wine, tea, peppers, blueberries, and strawberries were at reduced risk of all-cause mortality ($P<0.05$), with the strongest associations observed for red wine and tea; multivariable-adjusted hazard ratios (95%CI): 0.60 (0.49–0.74), and 0.73 (0.65–0.83), respectively. Conversely, frequent grapefruit consumers were at increased risk of all-cause mortality, compared to their non-grapefruit consuming counterparts ($P<0.05$). When compared to those in the lowest consumption quintile, participants in the highest quintile of total-flavonoid intake were at reduced risk of all-cause mortality in the age-adjusted model; 0.81 (0.71–0.93). However, this association was attenuated following multivariable-adjustment; 0.92 (0.80–1.06). Similar results were observed for

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AUTHOR CONTRIBUTIONS

All authors were responsible for either drafting of the work or revising it critically for important intellectual content, and provided final approval of the version to be published. KLI, AHE, EBR made substantial contributions to conception or design of the work, or the acquisition, analysis, or interpretation of data for the work.

CONFLICT OF INTEREST STATEMENT

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consumption of flavan-3-ols, proanthocyanins and anthocyanins. Flavonols, flavanones and flavones were not associated with all-cause mortality in any model. Despite null associations at the compound level and select foods, higher consumption of red wine, tea, peppers, blueberries and strawberries, was associated with reduced risk of total and cause-specific mortality. These findings support the rationale for making food-based dietary recommendations.

Keywords

Flavonoids; mortality; cancer; cardiovascular disease; red wine; tea

INTRODUCTION

Flavonoids represent a structurally diverse group of polyphenolic compounds which are synthesized during plant metabolism[1] and are present in many commonly consumed foods[2]. Particular fruits and vegetables, such as blueberries, apples, spinach and onions are considered rich sources of flavonoids. So too are beverages, such as tea and red wine[3].

Meta-analyses have shown that consumption of flavonoid-rich foods are associated with reduced risk of cause-specific mortalities such as those attributable to cancer, diabetes, and cardiovascular disease[4–7]. Much of the beneficial effects of these foods have been attributed to their high content of biologically active flavonoids, which have been shown to improve nitric oxide homeostasis and endothelial function, and reduce platelet aggregation and oxidative stress[8–13]. Flavonoids are also thought to play roles in inactivating carcinogens, inducing antiproliferation, cell cycle arrest and apoptosis, and inhibiting angiogenesis[14].

Despite this growing evidence for reduced risk of specific cancer and cardiovascular disease mortalities associated with consumption of flavonoid rich foods, the relationship of flavonoid-rich food and flavonoid compound intake with risk of all-cause mortality is less clear. Following the advent of the comprehensive United States Department of Agriculture (USDA) flavonoid-class food content database in 2007[15], the few studies exploring the relation of flavonoid intake with all-cause mortality have yielded inconsistent patterns of association, likely due to insufficient sample size, limited variation in intake, or incomplete food composition table[16–18].

The varying levels of flavonoid-class intake and different patterns of flavonoid-class intake across countries[19] have also likely contributed to the lack of clarity regarding the relationship between flavonoid-compound intake and risk of all-cause mortality in the population. Furthermore, the role that the whole-food, as distinct from the isolated food-constituent, plays in the relationship with all-cause mortality is yet to be elucidated. We have recently shown that a higher intake of total-flavonoids, as well as individual flavonoid classes, was associated with lower risk of cardiovascular, cancer and all-cause mortality in elderly, postmenopausal women[16]. Therefore, this study sought to explore the relationship between the consumption of flavonoid rich foods, and flavonoid-compounds, and the risk of all-cause mortality in a cohort of young and middle-aged US women.

PARTICIPANTS AND METHODS

Participants

In 1989, 116 430 women aged between 25 and 42 years, were enrolled into the Nurses' Health Study II. Baseline for this analysis was 1991, where 93 145 participants had complete dietary intake data and were free of previous myocardial infarction, angina, stroke and cancer. The institutional review board at Brigham and Women's Hospital reviewed and approved this study, and participants provided implied consent by virtue of questionnaire return.

Mortality ascertainment

Mortality incidence were identified through reports from family members and postal authorities, allowing ascertainment of an estimated 98% or more of all deaths[20]. Further mortality cases were identified through the National Death Index. Using data from death certificates and medical records, a physician blinded to exposure intake classified causes of mortality according to the eighth and ninth revisions of the International Classification of Diseases (ICD)[21, 22].

Deaths attributable to cardiovascular disease were defined using the ICD8 codes 390–458 (ICD9 390–459) and cancer mortalities were those with ICD8 codes ranging from 140 to 207 (ICD9 140–208). The other-cause mortality variable refers to all mortalities not attributable to CVD or cancer based on ICD8 codes.

Dietary intake assessment

At baseline (1991) and every subsequent 4 years until 2007, participants completed a semi-quantitative food-frequency questionnaire (FFQ). From this, habitual daily intake, in mg/d, of total-flavonoids and flavonoid-classes was estimated using previously described methods[23]. Flavonoid-classes in this analysis include: *i)* flavonols; *ii)* flavan-3-ols (including catechins and epicatechins, and excluding proanthocyanins); *iii)* proanthocyanins; *iv)* flavones; *v)* flavanones; and *vi)* anthocyanins. Frequency of consumption of flavonoid-rich foods were recorded as number of servings per day, week, or month[24].

As an indicator of adherence to a healthy dietary pattern, the Alternative Healthy Eating Index score was calculated using methods previously described[25].

In order to reflect long-term dietary intake, and to minimize effects of within-person variation, flavonoid exposure was considered the cumulative average of flavonoid intake, updated with every 4-year FFQ return. To account for potential alterations in dietary patterns following a major illness diagnosis, the primary flavonoid exposure was computed by suspending dietary intake updates following reported diagnoses of stroke, heart disease, angina, or cancer, although follow-up continued until death or the end of the study period at 2009.

Risk factor assessment

At baseline, and every two years thereafter, participants completed questionnaires on lifestyle, medical conditions, medications and family medical history.

Statistical Analysis

Analyses for habitual consumption of flavonoid-rich foods based on categories of consumption from the FFQ; ranging from non-consumers to frequent consumers, as defined as consuming the food more than once per week. Exposure of total-flavonoid or flavonoid-class consumption was divided into quintiles. Hazard ratios (HR) and 95% confidence intervals for risk of all-cause, and cause-specific, mortalities were estimated using age-adjusted and multivariable-adjusted Cox proportional-hazards models. P values for trend were calculated with the use of the Wald test of a score variable based on the median consumption level for each quintile of flavonoid consumption.

The multivariable-adjusted model included age, body mass index (BMI), smoking status, menopausal status, family history of diabetes/cancer/myocardial infarction, multivitamin supplement use, aspirin use, race, type 2 diabetes, hypercholesterolemia, hypertension, physical activity, alcohol consumption, and caloric intake. The multivariable plus diet-adjusted model incorporated the multivariable-adjusted model plus the Alternative Healthy Eating Index (minus alcohol) score[26].

For sensitivity analyses, baseline flavonoid intake and unrestricted cumulative average flavonoid intake, where updates continued until death or end of study irrespective of chronic disease diagnosis, were also computed. To address the concern that occult chronic diseases in the years that preceded diagnosis may have influenced dietary intake, we excluded the first 2 years of follow-up data and added a 2-year lag period between flavonoid-intake assessment and each follow-up period.

We conducted several additional sensitivity analyses to assess the robustness of the results. To minimize the influence of smoking or an extremely low or high body-mass index on the results, we excluded participants who had ever smoked or who had a BMI of less than 18.5 or more than 40 kg/m^2. We also excluded participants who had diabetes at baseline, and we suspended updating of dietary variables after a diagnosis of diabetes during study follow-up.

Analyses were performed with the SAS statistical package (version 9.3, SAS Institute). Statistical tests were two-sided, and P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Cohort characteristics

At baseline, the mean age of participants was 36.1 (±4.7) years, with a mean BMI of 24.6 (±5.3) kg/m^2. Over the 18-year (1 838 904 person-year) follow-up, there were 1 894 deaths. Cancer was the leading cause of mortality in this cohort, accounting for 47% (n=887) of all deaths. Cardiovascular disease contributed 10% (n=189) to all follow-up mortalities, and the remaining 818 (43%) mortalities comprised the other cause mortality group. The majority of other-cause mortalities were due to infections (n=182, ICD8 000–136), diseases of other endocrine glands (n=192, ICD8 250–258), and diseases of the nervous system (n=315, ICD8 320–358).

Mean daily total-flavonoid consumption was 379 (±374) mg. Proanthocayanins contribute 57%, and flavan-3-ols 28%, to total-flavonoid intake (Table 1).

Participants were similar in terms of baseline risk factors across all levels of total-flavonoid consumption. However, high flavonoid consumers were more physically active and were less likely to be current smokers at baseline (Table 2).

Flavonoid-rich foods and risk of all-cause, and cause specific, mortality

We explored potential whole-food contributors by analyzing foods rich in the flavonoid-classes (Figure 1). Frequent consumption of blueberries, strawberries, apples, peppers, red-wine and tea were all significantly inversely associated with risk of all-cause mortality in age-adjusted, multivariable-adjusted and multivariable-plus-diet- adjusted models. When compared to non-consumers, frequent tea and red wine consumption showed the greatest magnitude of reduction in risk. Conversely, when compared to infrequent consumers, risk of all-cause mortality was greater in participants with frequent grapefruit consumption. Continuing to update of intake irrespective of chronic disease diagnosis did not substantially impact results, and results were similar in all sensitivity analyses.

In cause-specific age and multivariable-adjusted analyses (Table 3), when compared to non-consumers, the benefit of frequent blueberry and strawberry consumption was restricted to cancer mortality, and the benefit of peppers restricted to mortalities from other-causes.

Although not associated with all-cause mortality, frequent orange-fruit consumers were at reduced risk of cancer and other-cause mortalities, respectively. Congruent with the all-cause mortality results, we observed that frequent grapefruit consumers were at increased risk of mortalities from other causes.

Both red wine and tea showed the greatest magnitude of benefit in the all-cause mortality analyses. Specifically, in the multivariable-adjusted model, when compared to the non-consumers, the relative risk (95% CI) of all-cause mortality for frequent consumers of red wine and tea (more than once per week) was 0.60 (0.49, 0.74), and 0.73 (0.65, 0.83), respectively. When looking at cause-specific mortalities, frequent consumption of red wine and tea was associated with reduced risk of both cancer and other-cause mortalities, in both age-adjusted and multivariable-adjusted models. Results were not significantly altered in sensitivity analyses.

Flavonoid compounds and risk of all-cause, and cause specific, mortality

In age-adjusted models, participants in the highest quintile of total-flavonoid consumption were 19% (7–29%) less likely to have died in the 18-year follow-up period, when compared to those in the lowest quintile (Table 4). Similar beneficial associations were observed with increased consumption of flavan-3-ols, flavonols, flavones, proanthocyanins and anthocyanins, however, relationships were attenuated and no longer statistically significant following multivariable-adjustment. Despite multivariable-adjustment substantially attenuating the relationships for proanthocyanins and anthocyanidins, no one factor in the multivariable-adjusted model was responsible for attenuation of the findings. Results were not significantly altered in sensitivity analyses.

We then examined the relation of individual flavonoid classes with cause-specific mortality. In age-adjusted models, when compared to the lowest quintile, participants in the highest quintile of anthocyanin intake were at lower risk of mortality from cancer, cardiovascular disease and other-causes. This beneficial association remained for cancer mortalities following multivariable-adjustment (Table 5). Flavan-3-ols and proanthocyanins followed a similar inverse pattern, whereas flavonols, flavanones and flavones showed no association in either the unadjusted or multivariable-adjusted models, with any of the mortality types.

DISCUSSION

This prospective cohort study of middle-aged US women found that participants with higher intakes of specific flavonoid-rich foods, namely blueberries, strawberries, peppers, red wine and tea, were associated with reduced risk of all-cause mortality. When exploring contributors to these relationships, the association with all-cause mortality appeared to be largely driven by mortalities from cancer, as well as other causes. These beneficial relations did not extend to the other flavonoid-rich foods, or intakes of flavonoid compounds.

Despite null associations at a compound level, numerous significant associations with all-cause mortality were observed for many flavonoid-rich foods. Our finding of a null association of total-flavonoid intake with risk of all-cause mortality in US women is congruent with the Iowa Womens' Health Study[17]. However, in our previous analysis in Australian women[16] we observed a strong relation between increased total-flavonoid intake and reduced risk of all-cause mortality. This incongruence in findings between studies, and the differences we observed in associations with compounds and whole foods, is likely explained by the complexity of flavonoid intake assessment and regional differences in the compositional variation in the whole food sources of dietary flavonoids[19], which in turn shapes the pattern of over 4,000 different flavonoid compounds consumed on a daily basis[27].

When looking at whole-food associations, we observed that increased consumption of blueberries, strawberries, peppers, red wine and tea was associated with reduced risk of all-cause mortality. These associations remained after adjusting for dietary pattern, suggesting that the relations are not explained by their contribution to a healthy dietary pattern. Furthermore, our results are supported by clinical trial data showing effects of these foods in improving endothelial function, nitric oxide status, blood pressure and platelet function, and by reducing oxidative stress and inflammation[29–33]. The strongest beneficial relation with all-cause mortality was observed with the frequency of red wine consumption, which remained even after adjusting for total alcohol consumption, which has been shown to be a strong predictor of all-cause mortality[34]. When looking at cause-specific mortalities, the strongest associations for with red wine were observed with reduced risk of cancer and other-cause mortalities, in both unadjusted and multivariate-adjusted models. The lack of beneficial association with cardiovascular disease may be due to the cohort characteristics itself, namely the low cardiovascular disease mortality rate in this middle aged female population.

In contrast to the beneficial whole foods listed above, which are rich sources of flavan-3-ols, proanthocyanins and anthocyanins, the foods rich in flavanones showed markedly different results. Oranges showed no association with all-cause mortality, and grapefruit had a small positive association with all-cause mortality. This inverse association may be due to the contribution of sugar-rich juices to total grapefruit intake. Furthermore, this detrimental association may also be explained by be due to the findings that grapefruit components have clinically significant interactions with drugs, which appear to be independent of their flavonoid content[35]. However, this hypotheses were unable to be explored in this cohort.

We observed that flavonoid-rich whole foods, and not flavonoid subclasses, showed the strongest associations with risk of all-cause mortality. Although not reaching statistical significance, many of the flavonoid subclasses followed similar trends to that of their predominant whole food constituents. For example, the positive and null associations of flavanone-rich grapefruit and oranges, respectively, were reflected in a non-significant trend in the multivariate-adjusted model whereby high flavanone consumers tended to have higher mortality rates. Conversely, the beneficial associations of anthocyanin-rich blueberries and strawberries was reflected in a no-significant observed trend high anthocyanin consumers tended to have lower mortality rates. The role of the whole-food in influencing relationships has not yet been fully elucidated, and results from the literature are conflicting. In understanding the strength of association differences at a whole food level as opposed to a compound level, it is important to note that flavonoid intake estimates are derived from intake data for many different individual food items, the majority of which were not included in our study, which only looked at foods which contribute substantially to flavonoid-class intake. The importance of whole foods, as opposed to isolated nutrients, are becoming increasingly recognized for public health guidelines and dietary recommendations[28].

Although results were not substantially altered by conducting sensitivity analyses, such as the lag analyses, it is important to note that causality of observed relationships cannot be established due to the observational nature of the study. Also, despite the inclusion of dietary and lifestyle factors into statistical models, residual or unmeasured confounders cannot be ruled out. Identification of causality is further limited by the complexity associated with assessing food composition and dietary intake including for flavonoids[36], which further highlights the importance of conducting both nutrient-based and whole-food based analyses.

In summary, in this prospective cohort study of female US nurses, we found a beneficial relationship between the dietary intake of select whole-food sources of flavonoids and risk of mortality. Specifically, frequent consumption of blueberries, strawberries, peppers, red wine and, was associated with reduced risk of all-cause mortality. These beneficial associations did not extend to total-flavonoids or flavonoid subclasses, and when considering the literature as a whole, future prospective association studies are warranted.

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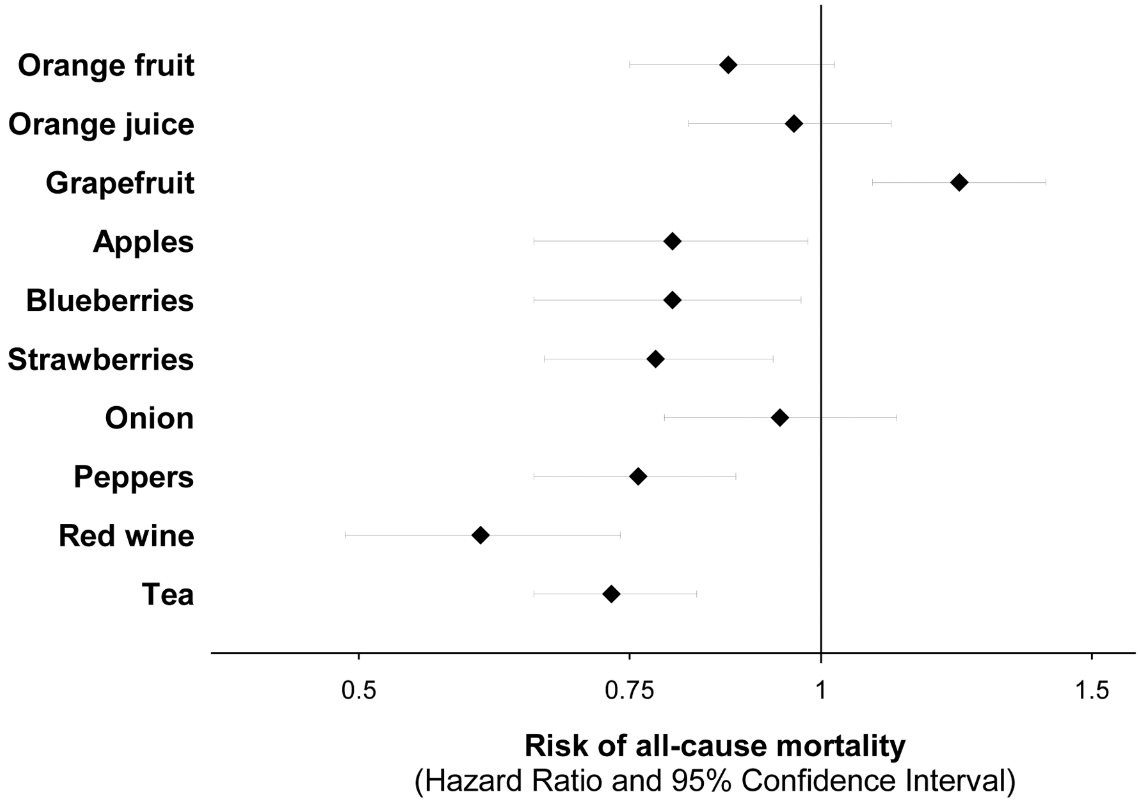

Figure 1:
Multivariable-adjusted risk of all-cause mortality by flavonoid-rich foods, comparing non-consumers (referent group) to frequent consumers (more than once per week). Multivariable adjusted model includes: age, body mass index, smoking status, menopausal status, family history of diabetes, cancer and myocardial infarction, multivitamin supplement use, Aspirin use, race, type 2 diabetes, hypercholesterolemia, hypertension, physical activity, caloric intake, alcohol consumption and the Alternative Healthy Eating Index (minus alcohol) score. The person years (non-consumers, frequent consumers) for each of the food items are as follows: Orange fruit (310336, 452010); Orange juice (231916, 916036); Grapefruit (725397, 329583); Apples (100840, 974249); Blueberries (868779, 110744); Strawberries (221774, 350689); Onions (168378, 499571); Peppers (320691, 501045); Tea (353257, 1067188); Red wine (1181732, 150932).

Table 1:

Baseline total-flavonoid and flavonoid-class consumption, and frequency of consumption of major whole food contributors[1]

	Level of consumption (mg/d)	Major whole food contributors
Total-flavonoids	379±374	**Tea**
		Apples
		Oranges[2]
Flavonoid-classes		
Flavonols	19 ± 13	**Tea**
		Onions
		Apples
Flavan-3-ols	61 ± 82	**Tea**
		Apples
		Blueberries
Proanthcyanins	257 ± 278	**Tea**
		Apples
		Strawberries
Flavones	2 ± 1	**Oranges**[2]
		Red wine
		Peppers
Flavanones	33 ± 33	**Oranges**[2]
		Grapefruit[2]
		Red wine
Anthocyanins	11 ± 14	**Blueberries**
		Strawberries
		Apples

[1]Results are energy-adjusted mean ± SD. n = 93,145.

[2]Includes both fresh fruit and juice products.

Table 2:

Baseline characteristics of the cohort stratified by quintiles of total-flavonoid consumption[1]

	Quintile 1 < 150 mg/d	Quintile 3 222 – < 329 mg/d	Quintile 5 ≥ 587 mg/d
Number	18 617	18 612	18 651
Demographic variables			
Age (years)[2]	36.0 ± 4.7	36.0 ± 4.7	36.5 ± 4.6
Body mass index (kg/m^2)	25.0 ± 5.7	24.4 ± 5.1	24.7 ± 5.3
Caucasian (%)	93.1	93.6	94.7
Current smoker (%)	18.1	9.9	11.3
Postmenopausal (%)	3.2	3.1	3.9
Physical activity (MET-hrs/wk)[3]	16.8 ± 24.2	22.6 ± 28.1	21.6 ± 28.8
Prevalent disease			
Type 2 diabetes (%)	1.0	1.0	1.0
Hypercholesterolemia (%)	11.3	10.1	10.9
Hypertension (%)	6.4	6.0	7.0
Family history of disease			
Diabetes (%)	17.2	16.0	17.4
Myocardial infarction (%)	22.7	20.7	22.2
Cancer(%)	22.7	22.9	22.2
Dietary intake and medications			
Current Aspirin use (%)	11.7	10.7	12.0
Current multivitamin use (%)	38.6	47.1	42.7
Calorie intake (Kcal/d)	1 703.2 ± 540.8	1 851.4 ± 548.5	1 735.4 ± 565.7
Alcohol intake (g/d)	3.1 ± 6.4	3.3 ± 5.9	2.6 ± 5.6
AHEI (score)[4]	40.8 ± 10.1	45.5 ± 10.4	44.9 ± 10.5

[1] Results are mean ± SD or percentage where appropriate. Values standardized to the age distribution of the study population. Flavonoid consumption is standardized to total-energy intake. n = 93,145;

[2] Value is not age adjusted;

[3] Met: metabolic equivalent;

[4] AHEI: Alternative Healthy Eating Index (excluding alcohol) score.

Table 3:

Multivariable-adjusted risk of mortality subtypes by flavonoid-rich foods, comparing non-consumers (referent group) to frequent consumers (more than once per week).[1]

	Cancer mortality[3] ≥ once per week	CVD mortality[4] ≥ once per week	Other-cause[4] ≥ once per week
Orange fruit consumption			
Age-adjusted	0.75 (0.60–0.95)	0.66 (0.41–1.07)	0.79 (0.64–0.97)
Multivariable-adjusted[2]	0.76 (0.60–0.98)	0.89 (0.54–1.48)	0.98 (0.78–1.24)
Orange juice consumption			
Age-adjusted	0.90 (0.72–1.13)	0.76 (0.48–1.21)	0.83 (0.68–1.03)
Multivariable-adjusted[2]	0.96 (0.76–1.21)	0.89 (0.55–1.43)	0.97 (0.78–1.21)
Grapefruit consumption			
Age-adjusted	1.01 (0.83–1.22)	0.72 (0.48–1.08)	1.19 (1.00–1.42)
Multivariable-adjusted[2]	1.07 (0.88–1.31)	0.92 (0.60–1.42)	1.47 (1.22–1.77)
Apple consumption			
Age-adjusted	0.63 (0.47–0.84)	0.74 (0.37–1.48)	0.60 (0.45–0.79)
Multivariable-adjusted[2]	0.68 (0.50–0.93)	1.19 (0.58–2.45)	0.84 (0.63–1.14)
Blueberry consumption			
Age-adjusted	0.67 (0.50–0.89)	0.41 (0.19–0.89)	0.77 (0.60–1.01)
Multivariable-adjusted[2]	0.64 (0.47–0.87)	0.64 (0.29–1.41)	1.00 (0.75–1.32)
Strawberry consumption			
Age-adjusted	0.69 (0.54–0.89)	0.49 (0.29–0.82)	0.65 (0.51–0.81)
Multivariable-adjusted[2]	0.73 (0.56–0.95)	0.72 (0.41–1.24)	0.86 (0.67–1.10)
Onion consumption			
Age-adjusted	0.84 (0.65–1.08)	0.92 (0.53–1.62)	1.00 (0.78–1.28)
Multivariable-adjusted[2]	0.83 (0.64–1.09)	0.95 (0.53–1.70)	1.05 (0.81–1.35)
Pepper consumption			
Age-adjusted	0.78 (0.63–0.96)	0.74 (0.47–1.17)	0.58 (0.47–0.71)
Multivariable-adjusted[2]	0.80 (0.64–1.01)	1.04 (0.64–1.71)	0.67 (0.54–0.84)
Red wine consumption			
Age-adjusted	0.60 (0.46–0.78)	0.43 (0.22–0.82)	0.57 (0.44–0.74)
Multivariable-adjusted[2]	0.53 (0.39–0.72)	0.74 (0.35–1.58)	0.65 (0.48–0.89)
Tea consumption			
Age-adjusted	0.67 (0.56–0.81)	0.62 (0.43–0.90)	0.71 (0.60–0.85)
Multivariable-adjusted[2]	0.68 (0.56–0.82)	0.70 (0.48–1.02)	0.79 (0.66–0.95)

[1] Results are HR (95% CI) and n(%) where appropriate. n = 93,145.

[2] Multivariable adjusted model includes: age, body mass index, smoking status, menopausal status, family history of diabetes, cancer and myocardial infarction, multivitamin supplement use, Aspirin use, race, type 2 diabetes, hypercholesterolemia, hypertension, physical activity, caloric intake, alcohol consumption and the Alternative Health Eating Index (minus alcohol) score.

[3]Total number of cancer mortalities: 887.

[4]Total number of cardiovascular disease (CVD) mortalities: 189.

[5]Total number of mortalities from other causes: 818

Table 4:

Association of quintiles of total-flavonoid and flavonoid-class consumption with risk of all-cause mortality[1]

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P for trend
Total-flavonoid intake (mg/d)	< 138	138 – <207	207 – < 308	308 – <518	≥ 518	
Person-years	355 151	368 485	370 364	372 609	372 295	
Deaths (n)	433	390	323	351	397	
Age-adjusted	1.00 (referent)	0.85 (0.74–0.97)	0.69 (0.60–0.80)	0.73 (0.63–0.84)	0.81 (0.71–0.93)	0.10
Multivariable-adjusted[2]	1.00 (referent)	0.96 (0.84–1.11)	0.81 (0.70–0.94)	0.86 (0.74–0.99)	0.92 (0.80–1.06)	0.59
Flavonol intake (mg/d)	< 9	9 – < 13	13 – < 17	17 – < 26	≥ 26	
Person-years	361 301	368 810	370 972	372 134	365 687	
Deaths (n)	398	347	345	356	448	
Age-adjusted	1.00 (referent)	0.83 (0.71–0.95)	0.82 (0.69–0.92)	0.80 (0.69–0.92)	1.00 (0.87–1.14)	**0.030**
Multivariable-adjusted[2]	1.00 (referent)	0.90 (0.78–1.05)	0.89 (0.77–1.04)	0.88 (0.76–1.03)	1.08 (0.94–1.25)	**0.006**
Flavan-3-ol intake (mg/d)	< 12	12 – < 19	19 – < 39	39 – < 86	≥ 86	
Person-years	352 706	366 094	372 429	373 445	374 230	
Deaths (n)	428	399	335	335	397	
Age-adjusted	1.00 (referent)	0.88 (0.77–1.01)	0.72 (0.62–0.83)	0.71 (0.62–0.82)	0.82 (0.72–0.94)	0.30
Multivariable-adjusted[2]	1.00 (referent)	0.99 (0.86–1.14)	0.81 (0.70–0.94)	0.79 (0.69–0.92)	0.90 (0.78–1.03)	0.30
Proanthcyanin intake (mg/d)	< 79	79 – < 126	126 – < 200	200 – < 356	≥ 356	
Person-years	352 476	367 583	372 126	373 157	373 562	
Deaths (n)	435	400	327	331	401	
Age-adjusted	1.00 (referent)	0.87 (0.76–1.00)	0.70 (0.61–0.81)	0.69 (0.60–0.80)	0.82 (0.72–0.94)	0.78
Multivariable-adjusted[2]	1.00 (referent)	0.98 (0.85–1.13)	0.81 (0.70–0.94)	0.80 (0.69–0.93)	0.92 (0.80–1.05)	0.42
Flavone intake (mg/d)	< 0.7	0.7 – < 1.1	1.1 – < 1.5	1.5 – < 2.2	≥ 2.2	
Person-years	362 321	371 169	371 600	371 692	362 121	
Deaths (n)	404	381	369	335	405	
Age-adjusted	1.00 (referent)	0.90 (0.78–1.03)	0.84 (0.73–0.97)	0.75 (0.65–0.86)	0.89 (0.77–1.02)	**0.007**
Multivariable-adjusted[2]	1.00 (referent)	1.00 (0.87–1.16)	1.00 (0.87–1.16)	0.92 (0.79–1.07)	1.11 (0.96–1.29)	0.96
Flavanone intake (mg/d)	< 9	9 – < 17	17 – < 30	30 – < 51	≥ 51	
Person-years	360 666	370 612	373 056	372 588	361 982	
Deaths (n)	373	378	389	380	374	
Age-adjusted	1.00 (referent)	0.98 (0.85–1.13)	0.98 (0.85–1.13)	0.94 (0.81–1.08)	0.92 (0.80–1.06)	0.75
Multivariable-adjusted[2]	1.00 (referent)	1.07 (0.93–1.24)	1.11 (0.96–1.28)	1.11 (0.96–1.28)	1.11 (0.97–1.30)	**0.015**
Anthocyanin intake (mg/d)	< 3	3 – < 5	5 – < 9	9 – < 17	≥ 17	
Person-years	354 483	368 366	374 278	373 382	368 395	
Deaths (n)	456	407	331	336	364	
Age-adjusted	1.00 (referent)	0.85 (0.74–0.97)	0.67 (0.58–0.77)	0.67 (0.58–0.77)	0.71 (0.62–0.82)	**<0.001**
Multivariable-adjusted[2]	1.00 (referent)	0.96 (0.84–1.10)	0.81 (0.70–0.94)	0.85 (0.73–0.99)	0.92 (0.79–1.08)	0.10

[1]Results are HR (95% CI) and n(%) where appropriate. n = 93,145.

[2]Multivariable adjusted model includes: age, body mass index, smoking status, menopausal status, family history of diabetes, cancer and myocardial infarction, multivitamin supplement use, Aspirin use, race, type 2 diabetes, hypercholesterolemia, hypertension, physical activity, caloric intake, alcohol consumption and the Alternative Health Eating Index (minus alcohol) score

Table 5:

Multivariable-adjusted risk of mortality subtypes by total flavonoid and flavonoid class, comparing participants in the lowest quintile of flavonoid intake (referent group) to those in the highest quintile.[1]

	Cancer mortality[3] Quintile 5	CVD mortality[4] Quintile 5	Other-cause[5] Quintile 5
Total flavonoid intake			
Age-adjusted	0.80 (0.64–0.98)	0.66 (0.43–1.02)	0.86 (0.71–1.05)
Multivariable-adjusted[2]	0.84 (0.67–1.04)	0.83 (0.53–1.29)	1.03 (0.84–1.26)
Flavonol intake			
Age-adjusted	0.98 (0.80–1.20)	0.76 (0.50–1.16)	1.08 (0.88–1.31)
Multivariable-adjusted[2]	0.99 (0.80–1.24)	0.91 (0.58–1.41)	1.22 (0.99–1.51)
Flavan-3-ol intake			
Age-adjusted	0.84 (0.68–1.04)	0.64 (0.42–0.98)	0.85 (0.70–1.04)
Multivariable-adjusted[2]	0.87 (0.70–1.08)	0.75 (0.49–1.16)	0.96 (0.78–1.17)
Proanthcyanin intake			
Age-adjusted	0.86 (0.70–1.06)	0.64 (0.41–0.99)	0.83 (0.68–1.00)
Multivariable-adjusted[2]	0.90 (0.72–1.11)	0.77 (0.49–1.20)	0.97 (0.79–1.18)
Flavone intake			
Age-adjusted	0.89 (0.72–1.10)	0.74 (0.48–1.16)	0.91 (0.75–1.12)
Multivariable-adjusted[2]	1.00 (0.80–1.06)	1.15 (0.72–1.83)	1.22 (0.99–1.51)
Flavanone intake			
Age-adjusted	0.91 (0.73–1.13)	0.81 (0.51–1.28)	0.95 (0.77–1.18)
Multivariable-adjusted[2]	1.03 (0.83–1.29)	1.10 (0.69–1.76)	1.21 (0.97–1.50)
Anthocyanin intake			
Age-adjusted	0.74 (0.59–0.91)	0.48 (0.30–0.78)	0.74 (0.61–0.90)
Multivariable-adjusted[2]	0.77 (0.61–0.98)	0.85 (0.50–1.43)	1.10 (0.88–1.37)

[1]Results are HR (95% CI) and n(%) where appropriate. n = 93,145).

[2]Multivariable adjusted model includes: age, body mass index, smoking status, menopausal status, family history of diabetes, cancer and myocardial infarction, multivitamin supplement use, Aspirin use, race, type 2 diabetes, hypercholesterolemia, hypertension, physical activity, caloric intake, alcohol consumption and the Alternative Health Eating Index (minus alcohol) score.

[3]Total number of cancer mortalities: 887.

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