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Flavonoid intake and incident hypertension in women[1]

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ABSTRACT

Background: Intake of flavonoid-containing food has been shown to have a beneficial effect on blood pressure in short-term randomized trials. There are limited data on total flavonoid and flavonoid-subclass consumption over a long period of time and the corresponding incidence of hypertension.

Objective: We aimed to evaluate the relation between flavonoid subclasses and total flavonoid intakes and incidence of hypertension.

Design: In a prospective cohort of 40,574 disease-free French women who responded to a validated dietary questionnaire, we observed 9350 incident cases of hypertension between 1993 and 2008. Cases were identified through self-reports of diagnosed or treated hypertension. Multivariate Cox regression models were adjusted for age, family history of hypertension, body mass index, physical activity, smoking, diabetes, hypercholesterolemia, hormone therapy, and alcohol, caffeine, magnesium, potassium, omega-3 (n–3), and processed meat intakes.

Results: Women in the highest quintile of flavonol intake had a 10% lower rate of hypertension than women in the lowest quintile (HR: 0.90; 95% CI: 0.84, 0.97; *P*-trend = 0.031). Similarly, there was a 9% lower rate for women in the highest category of intake than for women in the lowest category of intake for both anthocyanins and proanthocyanidin polymers [HRs: 0.91 (95% CI: 0.84, 0.97; *P*-trend = 0.0075) and 0.91 (95% CI: 0.85, 0.97; *P*-trend = 0.0051), respectively]. An inverse association for total flavonoid intake was observed with a similar magnitude.

Conclusion: In this large prospective cohort of French middle-aged women, participants with greater flavonol, anthocyanin, and polymeric flavonoid intakes and greater total flavonoid intake were less likely to develop hypertension. *Am J Clin Nutr* doi: 10.3945/ajcn.115.109249.

Keywords: cohort, diet, flavonoids, hypertension, prospective

INTRODUCTION

Fruit and vegetable consumption has been consistently associated with lower incidences of coronary artery disease (1), stroke (2), and cardiovascular mortality (3) in prospective studies. Short-term randomized trials (4, 5) have shown that high intakes of fruit and vegetables can decrease blood pressure modestly. Observational data have supported the possibility that diets that are high in fruit and vegetables may result in a lower increase in blood pressure over a longer period than can diets that are low in these foods (6). Clinical trials of flavonoid-containing foods have shown an overall beneficial effect on blood pressure (7). However, population-based evaluations on the relation of different flavonoid subclasses and incident hypertension have been limited to a single study (8). In this prospective study, an inverse association between anthocyanin, which is a flavonoid subclass, and hypertension was observed in US adults. However, a limited distribution of certain flavonoid-containing foods in this population may hinder the exploration of the impact of flavonoid subclasses on risk of hypertension.

An understanding of the relative impact of different phytochemicals on risk of hypertension may be useful to guide dietary recommendations and personal food choices. An evaluation of the relation of flavonoid subclasses and hypertension in a population in whom the consumption of flavonoid-rich foods and drinks, such as chocolate and wine, is common may provide additional insights because of a wider distribution of the exposure. Therefore, we investigated the relation between flavonoid subclasses and total flavonoid intakes and incidence of hypertension in a large prospective cohort of women.

METHODS

Study population

In 1990, 98,995 women, who were born between 1925 and 1950 were living in France, responded to a mailed questionnaire

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on reproductive characteristics, lifestyles, and newly diagnosed diseases (9). Women were part of a mutual health insurance plan for teachers and their spouses and accepted to take part in the prospective study E3N[7] [Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale (MGEN)], which is the French component of the European Prospective Investigation into Cancer and Nutrition (EPIC) (10). All E3N participants signed an informed consent form that complied with the French National Commission for Computerized Data and Individual Freedom. Study participants were mailed follow-up questionnaires in 1992, 1993, 1994, 1997, 2000, 2002, 2005, and 2008, and the average follow-up in each questionnaire cycle was 83%. Only 3% of participants (n = 3160) did not respond to any questionnaires after baseline. Information from the mutual health insurance plan was used for mortality follow-up, and vital status was unknown for only 740 participants (0.75%).

Between 1993 and 1995, 74,520 participants responded to a follow-up questionnaire that included a previously validated 208-item self-administered diet-history questionnaire (11). We excluded participants without risk-factor information before 1993 (n = 2793), with no follow-up after 1993 (n = 848), and with unrealistic energy consumption (n = 1381) that was defined by the first and 99th percentiles of the ratio of energy intake to the basal metabolic rate computed on the basis of age, height, and weight (12). We also excluded women who reported a diagnosis of cancer (n = 4253), cardiovascular disease (n = 449), or hypertension (n = 24,222) on the 1993 questionnaire. The final study population was 40,574 women.

Assessment of flavonoid intake

The first part of the dietary questionnaire was divided into 8 sections for each meal as follows: breakfast, lunch, midafternoon meal (goûter), dinner, and 4 other minor eating occasions (midmorning and late night snacks and lunch and dinner aperitifs) (http://www.e3n.fr/images/Questionnaires_pdf/Questionnaire_3_alimentaire.pdf). Women were asked to report the frequency of consumption of a given list of foods and food groups (e.g., fruit, meat, and cheese). Eleven categories of the frequency of consumption were available (never or <1 time/mo, 1, 2, or 3 times/mo, and 1, 2, 3, 4, 5, 6, or 7 times/wk). Habitually consumed portion sizes were reported by participants for beverages and food groups with the aid a brochure with colored photographs that was sent along with the questionnaire. Examples of 3 portion sizes were provided for each food group. Five portion-size categories were possible because participants could report the regular use of a portion size that was smaller than the smallest portion portrayed or larger than the largest portion portrayed. For beverages, we provided examples of different sizes of cups and glasses along with corresponding volumes in milliliters. The second part of the questionnaire contained qualitative questions on the consumption frequency of specific food items within one of the generic food groups used in the first part (e.g., for fruit, participants could report consumption of ≤15 specific fruit). We provided 4 response categories for each item as follows: never consumed or <1 time/mo; and least, moderately, and most consumed. Information from both parts of the questionnaire was used to estimate the habitual frequency of consumption of specific foods.

We calculated energy and nutrient intakes by multiplying the frequency of consumption of each food by the nutrient content of the food and summing over food items. We used the Center for Information on Quality of Foods nutrient database on food products produced and consumed in France (13). Flavonoid intake was estimated with the use of the Phenol-Explorer database (14). We estimated intakes of the following 6 flavonoid subclasses: flavonols (quercetin, kaempferol, myricetin, isohamnetin, morin, patuletin, jaceidin, spinacetin, and methoxynobiletin), flavones (luteolin, apigenin, diosmetin, sinensetin, nobiletin, tangeretin, and tetramethylscutellarein), flavanones (eriodictyol, hesperetin, naringenin, poncirin, didymin, prenylnaringenin, geranylnaringenin, and isoxanthohumol), anthocyanins (cyanidin, delphinidin, malvidin, pelargonidin, petunidin, and peonidin), flavanol monomers (catechins and epicatechins), and flavonoid oligomers and polymers (including proanthocyanidins and theaflavins). We added flavonoid subclass intakes to estimate total flavonoid intakes. We used estimates that were determined with the use of chromatography according the Phenol-Explorer database (most often, reversed phase HPLC was used) except for proanthocyanidins, for which content data obtained by normal phase HPLC were used (15).

The validity and reproducibility of the dietary questionnaire was evaluated in a sample of 119 women who were similar to the total study participants. These 119 women completed 2 diet-history questionnaires and 12 monthly 24-h dietary recalls over a 1-y period (11). Our results showed a slight overestimation of intakes of some foods and nutrients by our questionnaire than shown with the 24-h recalls; however, this difference did not seem to affect the ranking of individuals. Correlation coefficients between the dietary questionnaire and twelve 24-h recalls for important flavonoid-containing beverages and foods were 0.78, 0.74, 0.53, and 0.37 for tea, wine, oranges, and plain chocolate, respectively.

Hypertension assessment

We asked participants to report the presence of hypertension, the date of diagnosis, and the use of antihypertensive treatment at baseline in 1993 and in all subsequent questionnaires (1994, 1997, 2000, 2002, 2005, and 2008). Most participants reported the month and year of diagnosis (69%). When the month of diagnosis was not reported (14% of cases), we imputed the date as June of the year of diagnosis. We estimated that the median time between the date of diagnosis and the date of response to the first questionnaire after the diagnosis was 12 mo. Thus, for 17% of cases for which the date of diagnosis was missing, we assigned the date of diagnosis to be 12 mo before the date participants responded to the questionnaire in which hypertension was first reported. Most cohort participants (97.6%) were active members of the MGEN health insurance plan, which provided us with a drug-reimbursement database starting in January 2004. For cases identified after 2004, we used either the self-reported date of diagnosis or the first date of drug reimbursement for antihypertensive medications [diuretics, β-blockers, calcium, and angiotensin-converting enzyme inhibitors (Anatomical Therapeutic

[7] Abbreviations used: E3N, Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale; MET, metabolic equivalent; MGEN, Mutuelle Générale de l'Education Nationale.

Chemical Classification System codes C02, C03, C07, C08, and C09, respectively)] with whatever happened first as the date of diagnosis.

We assessed the validity of self-reported hypertension within the E3N cohort with the use of information on the MGEN health insurance plan drug-claims database. In women who were alive in January 2004 and up to their response to the last questionnaire in 2008, we observed a positive predictive value of 82% of self-reported hypertension compared with the self-report to a drug reimbursement corresponding to any of the previously specified codes.

Assessment of other covariates

For baseline covariates, whenever possible, we used information primarily from the 1992 questionnaire before the 1993 dietary assessment. For diabetes, we used self-reports, supplementary questionnaires, and the drug-reimbursement database (16). Treated hypercholesterolemia, a family history of hypertension, and smoking were based on self-reports. Menopausal status was determined with the use of information on last menstruation, the presence of hot flushes, and a history of hysterectomy, ovariectomy, and menopausal hormonal treatments. Self-reported height and weight were used to calculate BMI (in kg/m^2), which was defined as weight divided by the square of height. In this cohort, self-reported anthropometric measures were reliable. In a validation study in 152 E3N participants, the correlation coefficient between self-reported height and measured height was 0.89, and the correlation coefficient for weight 0.94 (17). We assessed usual physical activity with a questionnaire in 1993 that included items on weekly hours spent walking, cycling, performing light and heavy household chores, and recreational activities (e.g., swimming and tennis) and the daily number of flights of stairs climbed. Participants reported average physical activity hours per week during the summer and winter. We estimated metabolic equivalents (METs) per week by multiplying the yearly average METs for each item on the basis of values from the Compendium of Physical Activities (18) by the reported activity duration. This questionnaire performed well in a previous study (19). Habitual intakes of alcohol, caffeine, magnesium, potassium, omega-3 fatty acids, and processed red meat consumption were estimated from the dietary questionnaire in 1993 as previously described.

Statistical analysis

We categorized flavonoid subclasses and total flavonoid intakes in quintiles and evaluated nutrients as indicator variables with the lowest category as the referent. We used the median value for each category as a continuous variable to test for a trend and energy-adjusted nutrients with the use of the residual method (20). We calculated the person-time from the date of completion of the dietary questionnaire to the date of diagnosis, death, or 25 June 2008, whichever occurred earlier. HRs and 95% CIs were estimated from Cox regression models with the time on study as the time scale (SAS 9.3; SAS Institute Inc.). For multivariable models, we first adjusted for age, family history of hypertension, BMI (as a continuous variable), physical activity on METs per week (quintiles), smoking (never, former occasional, former regular, current occasional, and current regular), diabetes, hypercholesterolemia, and hormone therapy (premenopausal, ever, or never). In an additional multivariate model, we further adjusted for intakes of alcohol, caffeine, magnesium, potassium, ω-3, and processed meat (all in quintiles). We also evaluated the relation between major contributors of total flavonoid intake and incident hypertension. A previous study showed that the association between flavonoids and hypertension may be stronger in younger individuals (8); therefore, we repeated analyses in individuals who were ≤60 y old.

RESULTS

Age-adjusted baseline characteristics in 1993 of participants according to quintiles of total flavonoid intake are shown in **Table 1**. Compared with women with low flavonoid intake, women with higher intake were older, had a higher educational level, and were more likely to use menopausal hormone therapy and to have ever smoked. As expected, there was a direct relation between alcohol intake and fruit and vegetable consumption and dietary flavonoids. Women in the highest category of flavonoid intake had lower consumption of processed red meat and caffeine than women in the lowest category of intake.

Mean ± SD flavonoid intake was 575 ± 302 mg/d (10th percentile: 255 mg/d; 90th percentile: 969 mg/d), and polymeric flavonoids were the most-commonly consumed flavonoid subclass, whereas flavanones were the least commonly consumed flavonoids. Mean intake of polymers was 263 ± 166 mg/d (10th percentile: 109 mg/d; 90th percentile: 460 mg/d), of flavonols was 61 ± 34 mg/d (10th percentile: 26 mg/d; 90th percentile: 105 mg/d), of flavones was 7.9 ± 5 mg/d (10th percentile: 2; 90th percentile: 14), of flavanones was 41 ± 31 mg/d (10th percentile: 9 mg/d; 90th percentile: 80 mg/d), of anthocyanins was 71 ± 43 mg/d (10th percentile: 25 mg/d; 90th percentile: 126 mg/d), and of flavanol monomers was 130 ± 145 mg/d (10th percentile:19 mg/d; 90th percentile: 324 mg/d). The main foods that contributed to total flavonoid intake were tea, plain chocolate, plums, and wine (**Table 2**). Flavonols were mostly provided by spinach and tea. Anthocyanins were provided by cherries and wine, and polymers were provided by plain chocolate and plums.

In a population of French women with a mean age of 52 y (range: 45–58 y) after an average 13.8 y of follow-up and 493,893 person-years, we identified 9350 incident cases of hypertension (18.9 cases/1000 person-years). The incidence in participants in the highest category of flavonoid intake was 20 cases/1000 person-years, whereas the hypertension incidence in women in the lowest category of intake was 17.9 cases/1000 person-years. Age- and energy-adjusted estimates showed an inverse relation between all flavonoid subclasses and incident hypertension. The HR estimates for comparison of the highest quintile of intake with the lowest quintile of intake ranged from 0.87 to 0.92. Results were slightly attenuated after adjustment for several risk factors for hypertension that may also be related to flavonoid consumption and the diet. An inverse association remained for flavonols, anthocyanins, and polymers. When extreme quintiles of intake were compared, a 10% lower rate of hypertension was observed for flavonols (HR: 0.90; 95% CI: 0.84, 0.97; *P*-trend = 0.031), and similarly, a 9% lower rate of hypertension was observed for both anthocyanins and polymers [HRs: 0.91 (95% CI: 0.84, 0.97; *P*-trend = 0.0075) and 0.91 (95% CI: 0.85, 0.97; *P*-trend = 0.0051), respectively]. We observed a linear inverse association between total flavonoid intake and incident hypertension, and women in the highest category of total flavonoid intake had a 9% lower rate of hypertension than that

TABLE 1
Age-adjusted baseline characteristics according to quintiles of total flavonoid intake (E3N cohort, France, 1993)[1]

	Total flavonoid intake, quintiles				
	1	2	3	4	5
Intake,[2] mg/d	255	390	516	674	968
Cases, *n*	1951	1868	1922	1825	1784
Person-years	97,436	99,347	98,440	99,203	99,467
Age,[3] y	50.8	51.4	51.8	51.9	52.2
Risk factors					
BMI, kg/m^2	22.3 ± 2.92[4]	22.3 ± 2.73	22.2 ± 2.66	22.2± 2.58	22.0 ± 2.53
Diabetes, %	0.5	0.5	0.5	0.4	0.5
Treated hypercholesterolemia, %	5.0	4.9	4.7	4.2	4.6
Smoking, %					
Never	55.9	53.8	52.4	50.6	47.9
Former occasional	10.1	11.5	11.9	12.4	12.4
Former regular	19.3	21.6	22.0	22.9	25.1
Current occasional	4.5	4.8	4.8	5.7	5.8
Current regular	10.1	8.4	8.9	8.3	8.8
Premenopausal, %	59.4	59.4	59.1	59.7	58.8
Current MHT, %	20.3	21.4	22.6	21.6	23.2
Physical activity, METs/wk	52.2 ± 28.9	54.4 ± 29.7	54.9 ± 29.7	55.1 ± 29.5	54.3 ± 29.4
Postgraduate education, %	85.6	89.2	90.8	91.9	93.2
Family history of hypertension, %	27.1	29.3	29.5	28.9	28.5
Dietary factors					
Total energy intake, kcal/d	2102 ± 556	2146 ± 532	2154 ± 530	2142 ± 522	2090 ± 521
Alcohol, g/d	8.2 ± 10.0	11.2 ± 12.5	12.4± 14.1	12.8± 14.9	12.4 ± 15.5
Caffeine intake, mg/d	222 ± 164	208 ± 150	202 ± 150	190 ± 140	192 ± 135
Potassium, g/d	3.6 ± 0.8	3.8 ± 0.8	3.8 ± 0.8	3.8 ± 0.8	3.9 ± 0.8
Magnesium, mg/d	446 ± 130	446 ± 120	442 ± 124	426 ± 121	411 ± 120
ω-3 fatty acids, g/d	1.5 ± 0.4	1.5 ± 0.4	1.5 ± 0.4	1.5 ± 0.4	1.5 ± 0.4
Processed meat, g/d	28.3 ± 19.5	26.9 ± 18.0	26.1 ± 17.5	25.5 ± 17.7	24.0 ± 17.8
Fruit and vegetables, g/d	340 ± 149	438 ± 167	490 ± 193	530 ± 217	585 ± 258
Flavonoid classes, mg/d					
Flavonols	35 ± 15.6	45 ± 17.2	55 ± 19.4	69 ± 24.5	100 ± 40.3
Flavones	5 ± 3.5	7 ± 4.2	8 ± 4.7	9 ± 5.1	10 ± 5.7
Flavanones	24 ± 19.5	37 ± 24.7	43 ± 28.7	48 ± 31.9	53 ± 37.1
Flavanol monomers	27 ± 21.7	56 ± 42.9	95± 67.7	158 ± 97.5	316 ± 191.6
Anthocyanins	39 ± 19.9	62 ± 25.4	75 ± 34.3	84 ± 42.4	94 ± 52.6
Polymers	114 ± 40.71	183 ± 47.6	241 ± 69.0	310 ± 99.2	468 ± 211.5

[1]E3N, Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale; MET, metabolic equivalent; MHT, menopausal hormone therapy.
[2]All values are medians.
[3]All values are means.
[4]Mean ± SD (all such values).

of women in the lowest category (HR for comparison of extreme quintiles = 0.91; 95% CI: 0.85, 0.97; *P*-trend = 0.0207) (**Table 3**).

We repeated analyses in individuals ≤60 y of age because of the possibility that cumulative damage may exceed the capacity for flavonoids to exert a beneficial effect on the circulatory system. We showed no clear evidence of a stronger association between flavonoids and hypertension in younger women (**Table 4**). In women aged ≤60 y, the HR comparison of extreme quintiles of flavonol intake was 0.91 (95% CI: 0.82, 1.00). For anthocyanins, this HR was 0.94 (95% CI: 0.85, 1.04), and for polymer, this HR was 0.91 (95% CI: 0.84, 1.00). For total flavonoid intake, the HR estimate for comparison of extreme quintiles of intake was similar to what we observed for all women.

The 4 main contributors of flavonoid intake were tea, plain chocolate, plums, and wine. The consumption of plums was associated with a lower rate of hypertension. Women in the highest category of plum consumption had a 14% lower rate of hypertension than that of women in the lowest category (HR: 0.86; 95% CI: 0.81, 0.93; *P*-trend <0.0001). We showed no evidence of a linear inverse association between tea, chocolate,

TABLE 2
Major contributors to dietary intake of 6 flavonoid subclasses and total flavonoids

	Main food contributors (%)
Flavonols	Spinach (29), tea (29), wine (7), soup (7)
Flavones	Orange (19), fruit juices (15), artichokes (13)
Flavanones	Orange (48), fruit juices (37), grapefruit (12)
Anthocyanins	Cherries (40), wine (20), strawberries/ raspberries (17), plums (11), grapes (9)
Flavanol monomers	Tea (74), wine (6)
Polymers	Plain chocolate (35), plums (14), apples (10), tea (8), strawberries/raspberries (7)
Total flavonoids	Tea (23), plain chocolate (18), plums (8), wine (8)

TABLE 3
Hypertension according to quintile of flavonoid intake in all women[1]

	Quintile of intake					
	1	2	3	4	5	*P*-trend
Flavonols						
Cases, *n*	1958	1858	1878	1879	1777	—
Person-years	98,115	98,591	98,731	98,871	99,587	—
Age and energy adjusted	Referent	0.92 (0.87, 0.98)[2]	0.92 (0.86, 0.98)	0.92 (0.86, 0.98)	0.87 (0.81, 0.92)	<0.0001
Multivariable	Referent	0.91 (0.86, 0.97)	0.90 (0.84, 0.96)	0.91 (0.85, 0.97)	0.87 (0.82, 0.93)	0.0004
Diet	Referent	0.92 (0.86, 0.98)	0.91 (0.85, 0.97)	0.93 (0.87, 0.99)	0.90 (0.84, 0.97)	0.0310
Flavones						
Cases, *n*	1945	1836	1876	1837	1856	—
Person-years	98,521	99,259	99,088	98,858	98,167	—
Age and energy adjusted	Referent	0.93 (0.87, 0.99)	0.94 (0.88, 1.00)	0.91 (0.85, 0.97)	0.92 (0.86, 0.99)	0.0149
Multivariable	Referent	0.92 (0.86, 0.98)	0.93 (0.87, 0.99)	0.89 (0.84, 0.95)	0.90 (0.85, 0.96)	0.0031
Diet	Referent	0.93 (0.87, 0.99)	0.94 (0.88, 1.01)	0.91 (0.85, 0.97)	0.93 (0.87, 0.99)	0.0749
Flavanones						
Cases, *n*	1947	1797	1887	1852	1867	—
Person-years	98,140	99,439	99,167	98,942	98,207	—
Age and energy adjusted	Referent	0.90 (0.84, 0.96)	0.93 (0.87, 0.99)	0.90 (0.85, 0.96)	0.91 (0.85, 0.97)	0.0207
Multivariable	Referent	0.89 (0.84, 0.95)	0.92 (0.86, 0.98)	0.89 (0.83, 0.95)	0.90 (0.85, 0.96)	0.0172
Diet	Referent	0.90 (0.84, 0.96)	0.93 (0.87, 0.99)	0.90 (0.85, 0.97)	0.93 (0.87, 1.00)	0.2222
Anthocyanins						
Cases, *n*	1878	1856	1826	1871	1919	—
Person-years	98,199	99,110	99,558	98,910	98,118	—
Age and energy adjusted	Referent	0.96 (0.90, 1.02)	0.92 (0.86, 0.98)	0.93 (0.87, 0.99)	0.92 (0.87, 0.99)	0.0200
Multivariable	Referent	0.96 (0.90, 1.02)	0.90 (0.85, 0.96)	0.91 (0.86, 0.97)	0.90 (0.84, 0.96)	0.0013
Diet	Referent	0.96 (0.90, 1.03)	0.91 (0.85, 0.97)	0.91 (0.85, 0.98)	0.91 (0.84, 0.97)	0.0075
Flavanol monomers						
Cases, *n*	1958	1924	1869	1832	1767	—
Person-years	97,623	98,801	98,500	99,344	99,626	—
Age and energy adjusted	Referent	0.94 (0.89, 1.00)	0.92 (0.86, 0.98)	0.90 (0.84, 0.95)	0.87 (0.82, 0.93)	<0.0001
Multivariable	Referent	0.95 (0.89, 1.01)	0.94 (0.88, 1.00)	0.93 (0.87, 0.99)	0.93 (0.87, 0.99)	0.1241
Diet	Referent	0.95 (0.89, 1.01)	0.94 (0.88, 1.00)	0.94 (0.88, 1.00)	0.96 (0.90, 1.04)	0.7239
Polymers						
Cases, *n*	1954	1876	1876	1815	1829	—
Person-years	97,198	98,733	99,062	99,247	99,655	—
Age and energy adjusted	Referent	0.93 (0.87, 0.99)	0.92 (0.86, 0.98)	0.88 (0.82, 0.94)	0.88 (0.82, 0.94)	<0.0001
Multivariable	Referent	0.94 (0.89, 1.01)	0.93 (0.87, 0.99)	0.89 (0.83, 0.95)	0.90 (0.84, 0.96)	0.0008
Diet	Referent	0.95 (0.89, 1.01)	0.94 (0.88, 1.00)	0.91 (0.85, 0.97)	0.91 (0.85, 0.97)	0.0051
Total flavonoids						
Cases, *n*	1951	1868	1922	1825	1784	—
Person-years	97,436	99,347	98,440	99,203	99,467	—
Age and energy adjusted	Referent	0.92 (0.86, 0.98)	0.94 (0.88, 1.00)	0.88 (0.83, 0.94)	0.85 (0.80, 0.91)	0.0001
Multivariable	Referent	0.92 (0.86, 0.97)	0.94 (0.88, 1.00)	0.90 (0.85, 0.96)	0.88 (0.83, 0.94)	0.007
Diet	Referent	0.92 (0.86, 0.98)	0.95 (0.89, 1.02)	0.92 (0.86, 0.98)	0.91 (0.85, 0.97)	0.0207

[1]Multivariable analyses were adjusted for education, family history of hypertension, diabetes, hypercholesterolemia, BMI (continuous), smoking (never, former occasional, former regular, current occasional, or current regular), physical activity metabolic equivalents per week (quintiles), and hormone therapy (premenopausal, ever, or never). Diet was further adjusted for intakes of alcohol, processed meat, caffeine, magnesium, potassium, and ω-3 (quintiles).

[2]HR; 95% CI in parentheses (all such values).

and wine consumption and incident hypertension. The multivariable adjusted HR for comparison of the highest to the lowest categories of intake was 1.00 (95% CI: 0.94, 1.08; *P*-trend= 0.70) for tea, 0.97 (95% CI: 0.91, 1.03; *P*-trend = 0.32) for plain chocolate, and 0.88 (95% CI: 0.77, 1.01; *P*-trend = 0.58) for wine.

DISCUSSION

In this large prospective study, middle-aged women with greater flavonol, anthocyanin, and polymeric flavonoid intakes were less likely to develop hypertension over a 14-y follow-up period. We combined intakes from all flavonoid subclasses and observed an inverse association between total flavonoid intake and incident hypertension. Higher consumption of plums, which are a flavonoid-rich food, has been associated with a lower incidence of hypertension.

Evidence from a large number of short-term trials in humans has suggested that flavonoids and, in particular, flavanol monomers and procyanidin may have a beneficial effect on blood pressure in humans (7). Intake of flavonol-rich cocoa increases circulating nitric oxide species and enhances flow-mediated vasodilation, and epicatechin, which is the major cocoa flavan-3-ol, appears to have very similar effects to those observed for cocoa (21). Conversely, evidence for the potential mechanism by

TABLE 4
Hypertension according to quintile of flavonoid intake in women ≤60 y old[1]

	Quintile of flavonoids					
	1	2	3	4	5	*P*-trend
Flavonols	Referent	0.91 (0.84, 0.99)	0.92 (0.84, 1.00)	0.93 (0.85, 1.02)	0.91 (0.82, 1.00)	0.1387
Flavones	Referent	0.93 (0.86, 1.02)	0.97 (0.89, 1.05)	0.88 (0.81, 0.97)	0.96 (0.87, 1.05)	0.3261
Flavanones	Referent	0.92 (0.84, 1.00)	0.93 (0.86, 1.02)	0.93 (0.85, 1.01)	0.94 (0.85, 1.03)	0.3675
Anthocyanins	Referent	1.00 (0.92, 1.08)	0.90 (0.83, 0.99)	0.95 (0.86, 1.04)	0.94 (0.85, 1.04)	0.1602
Flavanol monomers	Referent	0.97 (0.89, 1.06)	0.95 (0.87, 1.04)	0.97 (0.89, 1.06)	0.98 (0.89, 1.07)	0.8508
Polymers	Referent	0.98 (0.90, 1.06)	0.99 (0.91, 1.08)	0.90 (0.83, 0.99)	0.91 (0.84, 1.00)	0.0159
Total flavonoids	Referent	0.92 (0.85, 1.00)	1.00 (0.92, 1.09)	0.95 (0.87, 1.04)	0.89 (0.82, 0.98)	0.0657

[1]All values are HRs; 95% CIs in parentheses. The analysis was adjusted for education, family history of hypertension, diabetes, hypercholesterolemia, BMI (continuous), smoking (never, former occasional, former regular, current occasional, or current regular), physical activity metabolic equivalents per week (quintiles), hormone therapy (premenopausal, ever, or never), and intakes of alcohol, processed meat, caffeine, magnesium, potassium, and ω-3 (all in quintiles).

which procyanidin would affect blood pressure is limited but could be related to the inhibition of the angiotensin-converting enzyme (22). A recent review of prospective studies that evaluated flavonoids and cardiovascular disease concluded there was some evidence that flavonoids could lower risk of coronary artery disease (23). It was difficult to make strong conclusions because of the between-study heterogeneity on the flavonoid subclasses and the cardiovascular outcomes evaluated. A recent prospective study with the added advantage of a repeated dietary evaluation, which may have lowered the exposure misclassification, showed that anthocyanin intake was associated with a 32% lower rate of myocardial infarction than that associated with extreme categories of intake (24). In the Nurses' Health Study, which includes older women and repeated dietary measurements, no association was observed for flavonoid intake and total stroke (25).

Information on the relation of flavonoid intake and incident hypertension has been limited to a pooled evaluation from 3 cohort studies in the United States (8). In this analysis, which was based on nearly 157,000 women and men with repeated dietary assessments, higher anthocyanin intake was inversely associated with the incidence of hypertension. Participants in the highest category of intake for this flavonoid subclass had an 8% lower incidence of hypertension than that of participants in in the lowest category. This observation is consistent with our results. However, in contrast to this report, in our population, high intakes of total flavonoid and the 2 additional subclasses flavonols and flavanol polymers were also associated with incident hypertension. There appears to be wide variation in the estimated intakes of flavonoids across populations (26–28) and even within similar populations (i.e., European populations). We estimated that the mean total flavonoid intake in our population was ~50% higher than those reported in these 3 North American prospective studies. We may have been able to detect associations for different flavonoid subclasses because of a wider distribution of the exposure in our population. For example, the mean intake for the highest category of flavonol intake that was reported in the Nurses' Health Study II was 36.2 mg/d, whereas the mean intake in our study was 61 mg/d. Alternatively, the contributors for flavonoids may differ between populations, and these foods may contain other active constituents apart from flavonoids. In our analyses of the main contributors to flavonoids, we showed that plums were inversely associated with hypertension. Plain chocolate and flavanol monomers, for which there is ample evidence of potential beneficial effects on blood pressure (29), were not associated with incident hypertension. Mean chocolate intake in our study appeared to be much higher than that observed in a study in Spain with null results on chocolate intake and incident hypertension (median intake in the highest category of intake in our study was 27 g/d in our study compared with 18 g/d in the Spanish study) (30). In contrast, although it was difficult to compare, the distribution of chocolate intake appeared to be similar to that observed in the Zutphen study, which observed an association between cocoa intake and blood pressure (31). Differences in the type of chocolate or labeled cocoa percentages, which may not reflect the true flavonoid content (32) of commonly consumed chocolate, may explain these differences.

The prospective design, limited loss to follow-up, and a large number of cases were important strengths of this analysis. Nevertheless, there were some limitations to consider. As with any observational study, we could not exclude the possibility of unmeasured confounding by dietary factors before baseline, lifestyles and behaviors, and genes or residual confounding by poorly measured factors. This possibility was particularly relevant when the strength of the association was modest. We were able to adjust for family history of hypertension, physical activity, adiposity, alcohol, smoking, and diet, which are all well-known risk factors for hypertension, and we did not observe important changes in the estimates after multivariable adjustment. The misclassification of flavonoid intake was unavoidable. Errors in the reporting of food consumption are common, and the dietary assessment included a limited number of foods, and important flavonoid-containing foods may have been missed (33). In addition, we used a flavonoid database that is incomplete, and depending on the food, estimates of flavonoid intake are often based on a limited number of publications. Also, unlike other authors (34), we were unable to assess the validity of the estimation of flavonoid intake. However, our questionnaire validly assessed intakes of major food contributors to flavonoid intake and may have appropriately ranked individuals. A misclassification of exposure was also possible because we assessed diet only at baseline, and women may have changed their diets during follow-up. We evaluated the relation of flavonoid classes with hypertension,

and because of the differences in structure and chemical properties, the biological effects of individual compounds may have been masked. However, because of the correlation of many of these compound, such an evaluation was challenging. The use of reliable biomarkers of different flavonoids in epidemiologic studies holds promise (35). However, besides the cost, rapid absorption, and elimination of these compounds, biomarker measures may not reflect long-term exposure. Flavonoid-containing foods have antioxidants and nitrates. We could not exclude the possibility that the observed association was due to the effects of other phytochemicals. Self-reports of medical conditions are also subject to misclassification. We identified cases of hypertension through questionnaire data, and a misclassification of the outcome was a possibility. When we assessed the validity of the self-reports of hypertension with the use of a drug-claims database, we observed an 82% positive predictive value for self-reported hypertension. However, nonmedical treatment is common, and it is possible that the use of the claims database may have underestimated the validity of the self-report. This misclassification was likely to be nondifferential because it was unlikely related to flavonoid intake; thus if a misclassification was present, it would have resulted in the attenuation of observed associations.

In conclusion, as flavonoid databases evolve and more biomarkers for flavonoid intake are developed, future studies will be able to assess flavonoid intake more accurately. Dietary recommendations and personal food choices should be guided by robust evidence on the effect of different phytochemicals on health. More evidence of the role of flavonoid intake and hypertension is necessary.

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