Flavonoid intake and risk of chronic diseases[1,2]

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ABSTRACT

Background: Flavonoids are effective antioxidants and may protect against several chronic diseases.

Objective: The association between flavonoid intake and risk of several chronic diseases was studied.

Design: The total dietary intakes of 10 054 men and women during the year preceding the baseline examination were determined with a dietary history method. Flavonoid intakes were estimated, mainly on the basis of the flavonoid concentrations in Finnish foods. The incident cases of the diseases considered were identified from different national public health registers.

Results: Persons with higher quercetin intakes had lower mortality from ischemic heart disease. The relative risk (RR) between the highest and lowest quartiles was 0.79 (95% CI: 0.63, 0.99: P for trend = 0.02). The incidence of cerebrovascular disease was lower at higher kaempferol (0.70; 0.56, 0.86; $P = 0.003$), naringenin (0.79; 0.64, 0.98; $P = 0.06$), and hesperetin (0.80; 0.64, 0.99; $P = 0.008$) intakes. Men with higher quercetin intakes had a lower lung cancer incidence (0.42; 0.25, 0.72; $P = 0.001$), and men with higher myricetin intakes had a lower prostate cancer risk (0.43; 0.22, 0.86; $P = 0.002$). Asthma incidence was lower at higher quercetin (0.76; 0.56, 1.01; $P = 0.005$), naringenin (0.69; 0.50, 0.94; $P = 0.06$), and hesperetin (0.64; 0.46, 0.88; $P = 0.03$) intakes. A trend toward a reduction in risk of type 2 diabetes was associated with higher quercetin (0.81; 0.64, 1.02; $P = 0.07$) and myricetin (0.79; 0.62, 1.00; $P = 0.07$) intakes.

Conclusion: The risk of some chronic diseases may be lower at higher dietary flavonoid intakes. *Am J Clin Nutr* 2002;76:560–8.

KEY WORDS Chronic disease, diet, flavonoids, flavonols, flavanones, flavones, prospective study, free radicals

INTRODUCTION

Free oxygen radicals may be involved in several pathologic conditions (1). Oxidation of LDLs is thought to play an important role in the development of atherosclerosis (2). Free oxygen radicals are apparently involved at different stages of cancer development (3). Free radicals may contribute to the autoimmune destruction of β cells, leading to diabetes (4), and may impair insulin action (5). Reactive oxygen species have also been proposed as mediators of inflammatory damage in asthma (6) and in joints in rheumatoid arthritis (7). Furthermore, it has been suggested that the oxidation of lens proteins by free radicals plays an important role in the process leading to cataract (8).

Flavonoids are products of plant metabolism and have different phenolic structures (9). They are effective antioxidants because of their free radical scavenging properties and because they are chelators of metal ions (10); thus, they may protect tissues against free oxygen radicals and lipid peroxidation. Flavonoids may also be activated by mechanisms that apparently are not directly dependent on their antioxidative properties. Under certain conditions they may also behave as prooxidants (11). A wide range of different biological activities, including antibacterial, antithrombotic, vasodilatory, antiinflammatory, and anticarcinogenic effects mediated by different mechanisms, are associated with flavonoid compounds (12). In vitro studies indicate considerable differences in the antioxidative potential of different flavonoid subgroups, depending on their chemical structures (11). Because of differences in their chemical structure, bioavailability, distribution, and metabolism (11), different flavonoid compounds may have different effects on human health.

Of the few prospective studies in humans that have predicted the effects of flavonoids on cardiovascular disease risk, some showed an inverse association (13–17), whereas others showed no association (18–21). Studies of cancer have also given contradictory results (15, 22, 23). Most of these previous studies investigated the effects of total intakes of selected flavonols and flavones, for which food-composition data were available.

In the present cohort study we extended the analyses beyond cardiovascular diseases and cancer to other chronic diseases associated with oxidative stress etiology. Flavanones were included in our analyses in addition to flavonols and flavones. To show potential differences in the effects of various flavonoids, we also investigated separately the effects of the major flavonoids quercetin, kaempferol, myricetin, naringenin, and hesperitin.

SUBJECTS AND METHODS

The Finnish Mobile Clinic Health Examination Survey performed multiphasic screening examinations in different regions of Finland during 1966–1972. A total of 62 440 persons participated (82.5% of those invited) (24). As part of that study, information

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on habitual food consumption was obtained from a random sample of 10 054 participants (25). All participants completed a premailed questionnaire, which was checked at the baseline examination. The questionnaire yielded information on residence, occupation, smoking, disease symptoms, and medication use. Body height and weight were measured at the baseline examination, and body mass index was calculated.

A dietary history method was used to collect data on habitual food consumption during the year preceding the interview. A questionnaire was used to guide the interview, which was conducted by trained personnel. The questionnaire listed > 100 food items and mixed dishes common in the diet of Finns during the time of the baseline study. Further details were given by the respondent during the interview. Consumption of foods was estimated per day, per week, per month, or per year according to the choice of the respondents. Food models made of plastic or rubber or samples of real food were used to aid in the estimation of the amount of food consumed. The consumption of individual food items consumed as such or eaten as part of a mixed dish was computed per day. Intakes of flavonoids and nutrients were evaluated for all food items. A nutrient-composition database was developed from information in the Finnish food-composition tables (26). The dietary survey method and the short-term and long-term reproducibility of the dietary data were described previously (27).

Intakes of flavonoids were estimated on the basis of recently analyzed data on the composition of flavonoids from domestic and imported foods consumed in Finland (28). A total of 77 samples of fruit, 89 of vegetables, 151 of berries, and 60 of beverages (including tea and wines) were collected from Finnish wholesale companies and supermarkets. Samples were collected to represent the most important plant foods consumed in Finland, on the basis of average food consumption data in 1997. In addition, berries with a suggested high flavonoid content were included in the study. The composition of 24 flavonoids was determined in 94 pooled samples. The method of Hertog et al (29), as modified by Mattila et al (30), was used. After extraction and hydrolyzation, flavonoids were separated and quantified with the use of HPLC apparatus equipped with a diode-array detector and an electrochemical coulometric array detector (ESA, Inc, Chelmsford, MA) (28). The column used was an Inertil (GL Sciences, Inc, Tokyo) ODS-3 (4.0 $\times$ 150 mm, 3 μm) with a C_{18} guard column. Individual flavonoids were identified on the basis of commercial flavonoid standards of HPLC purity.

For the flavonoid database used in the present study, the flavonoid contents of individual food items were calculated as the mean of different cultivars of domestic or imported varieties or both. The flavonoid values for jams and sweetened berry juices were adapted from analyses carried out in the Kuopio berry study (31). In addition, the flavonoid values of those vegetables not included in recent Finnish flavonoid analyses were obtained from studies conducted in the Netherlands (32, 33). In total, the flavonoid database included values of 4 flavonols (kaempferol, quercetin, myricetin, and isorhamnetin), 2 flavones (apigenin and luteolin), and 3 flavanones (hesperetin, naringenin, and eriodictyol). The intakes of apigenin, luteolin, isorhamnetin and eriodictyol were very low; thus, they were not reported separately but were accounted for in the total intake of flavonoids. Because consumption data for tea and wines were not available, intakes of catechins could not be estimated in the present study. Quercetin was mainly provided by apples and onions and kaempferol by white cabbage. Hesperitin and naringenin were derived from citrus fruit and myricetin from berries. The repeatability of the flavonoids considered was estimated on the basis of a subpopulation (17). The 4–8-mo repeatability of the daily consumption of all flavonoids combined was 0.53 (intraclass correlation coefficient) and varied for single flavonoids from 0.33 to 0.51. The corresponding coefficients for 4–7-y repeatability were 0.30 and from 0.11 to 0.31. The main sources of these flavonoids, covering 95% of intake, were oranges, apples, grapefruit, onions, white cabbage, berries, and juices.

The vitamin C contents of the food items were derived from Finnish food-composition tables (26). The amounts of β-carotene and various tocopherols and tocotrienols in the diet were based on analyses of Finnish foods (34, 35). The vitamin E activities of the various tocopherols and tocotrienols, in α-tocopherol equivalents, were estimated by using the factors of McLaughlin and Weihrauch (36). The vitamin intakes represent the amounts in raw foodstuffs. The fatty acid estimates are presented elsewhere (37). Energy intake was calculated on the basis of the amounts of protein, fat, and, available carbohydrate consumed.

The population at risk for a specific disease included persons free of that disease at the baseline examination. Mortality data from Statistics Finland were linked to the study population by using personal identification numbers (38). Coverage of the mortality register, based on death certificates, is complete, including emigrants who died abroad. The codes 410–414 of ICD-8 (International Classification of Diseases, 8th revision) were used for ischemic heart disease as the cause of death, and cerebrovascular disease was identified by codes 430–438. During the 28 y of follow-up (from 1967 to late 1994), a total of 2085 persons died—681 from ischemic heart disease.

Information regarding the incidence of cerebrovascular disease and cataract during the 28-y follow-up was obtained by linking data from the Finnish Hospital Discharge Register maintained by the National Board of Health to the dietary data (39). This national register covers all diagnoses for persons discharged from general hospitals in Finland. A total of 806 fatal or nonfatal cerebrovascular disease cases and 132 cataract cases occurred.

Information on cancer incidence during the follow-up was obtained by linking the nationwide Finnish Cancer Registry (40) to the dietary data. The primary site of the cancer was coded according to the ICD-7 (41). A total of 1093 new cancer cases were noted during a maximal followup of 30 y to late 1996.

In Finland, a proportion of the costs of drugs taken for certain chronic diseases is reimbursed. Eligibility for reimbursement requires a comprehensive medical certificate written by an attending physician. A nationwide central register of all patients receiving drug reimbursement is maintained by the Social Insurance Institution (42). Participants in the present study were linked to that register by using the individual social security code number assigned to each Finnish citizen. In the follow-up period lasting until late 1994, 382 cases of asthma, 526 of type 2 diabetes, and 90 of rheumatoid arthritis occurred. Certificates from attending physicians for patients with chronic inflammatory arthritis were reviewed to identify true incident cases of rheumatoid arthritis and their rheumatoid factor status by the time of diagnosis.

The Cox proportional hazards model was used to estimate the strength of association between the flavonoids and their major sources and the subsequent risk of chronic disease (43). Person-time for each participant was calculated from the date of the baseline examination to the date of occurrence of the disease considered, death, or the end of follow-up, whichever came first. Potential confounding factors were adjusted for by including them in the models. Five different models were used: *1*) the basic model,

TABLE 1
Subject characteristics and flavonoid intakes at baseline for the total population and by disease[1]

Variable	Total population (n = 10054)	Total mortality (n = 2085)	IHD mortality (n = 681)	Cerebrovascular disease (n = 806)	Cancer (n = 1093)	Rheumatoid arthritis (n = 90)	Diabetes (n = 526)	Cataract (n = 132)	Asthma (n = 382)
Sex (% male)	52.8	62.1	66.9	53.9	55.2	30.0	48.5	45.4	53.4
Age (y)	39.3 ± 15.8[2]	53.3 ± 12.8	54.0 ± 10.6	52.1 ± 12.7	50.3 ± 12.8	41.0 ± 11.7	49.2 ± 13.1	60.1 ± 10.8	41.6 ± 12.4
Hypertensive (%)	9.6	19.6	21.0	23.2	15.3	8.9	27.0	25.0	7.9
Smokers (%)	35.3	44.7	44.7	34.7	39.4	33.3	28.1	25.0	40.8
Serum cholesterol (mmol/L)	6.4 ± 1.5	6.9 ± 1.5	7.3 ± 1.6	6.9 ± 1.4	6.8 ± 1.4	6.6 ± 1.4	6.7 ± 1.4	6.9 ± 1.3	6.4 ± 1.4
BMI (kg/m^2)	24.8 ± 4.1	26.2 ± 4.2	26.6 ± 4.0	26.5 ± 4.2	26.0 ± 4.3	26.1 ± 5.9	29.0 ± 4.7	27.4 ± 5.0	25.5 ± 3.7
Diabetes (%)	1.8	4.1	5.5	3.6	2.1	1.1	0	10.6	1.8
Flavonoids (mg)									
Total[3]	24.2	18.3	17.5	19.6	20.6	24.2	21.8	21.1	20.4
Quercetin	3.3	2.8	2.7	2.9	2.8	3.6	3.0	2.7	2.9
Kaempferol	0.6	0.5	0.5	0.5	0.5	0.7	0.5	0.5	0.6
Myricetin	0.12	0.11	0.14	0.12	0.11	0.12	0.13	0.13	0.13
Naringenin	5.1	3.7	3.5	4.1	4.2	4.4	5.0	3.9	4.2
Hesperetin	15.1	11.1	10.6	11.8	12.8	15.3	13.2	13.8	12.5
Foodstuff (g)									
Apple	39.0	31.1	28.2	33.2	30.8	44.5	32.1	27.5	28.2
Onion	3.6	3.1	3.2	3.3	3.2	3.5	3.4	3.0	3.5
White cabbage	7.8	6.4	6.1	6.2	7.0	9.8	7.4	8.0	7.8
Orange	37.8	27.5	26.4	29.2	32.3	38.9	33.1	34.9	31.0
Grapefruit	1.5	0.9	0.9	1.4	1.3	0	2.3	0	1.0
Berries	16.0	15.4	15.5	15.8	14.7	19.4	13.9	16.2	17.0
Juices	25.0	22.7	21.9	23.8	21.9	31.8	26.7	22.5	27.8

[1] n = the number of persons. IHD, ischemic heart disease.
[2] $\bar{x}$ ± SD.
[3] Includes apigenin, luteolin, isorhamnetin, and eriodictyol (intake of each compound < 0.1 mg).

presented in Tables 2–6; *2*) the basic model excluding cases that occurred during the first 2 y of follow-up; *3*) the basic model based on a maximum follow-up of 15 y; *4*) the basic model further adjusted for intakes of energy, cholesterol, saturated fatty acids, fiber, vitamin E, vitamin C, and β-carotene; and *5*) the basic model in which quercetin, kaempferol, myricetin, and naringenin were simultaneously included. Interaction terms were also included in the basic model. The interactions between the different flavonoids and sex and all diseases considered were studied. The results of the different models that deviated considerably from those of the basic model are presented in Results. Relative risks were estimated for quartiles of intake by using the lowest quartile as the reference category. A test for trend was carried out by including the flavonoid quartile as a continuous variable in the model. The analyses were performed by using SAS 6.12 (SAS Institute Inc, Cary, NC).

RESULTS

The mean (± SD) total intake of flavonoids in the total study population was 24.2 ± 26.7 mg/d (quercetin, 3.3 ± 2.4 mg; kaempferol, 0.6 ± 0.7 mg; myricetin, 0.1 ± 0.2 mg; naringenin, 5.1 ± 8.8 mg; and hesperetin, 15.1 ± 18.8 mg; **Table 1**). The mean values for nondietary potential confounding factors and the mean intakes of the different flavonoids and foodstuffs rich in flavonoids varied by disease.

Total mortality

Persons with a higher total flavonoid intake tended to have a lower total mortality (**Table 2**). The relative risk (RR)—adjusted for age, sex, geographic area, occupation, blood pressure, smoking, serum cholesterol, body mass index, and diabetes—between the highest and lowest quartiles of intake was 0.92 (95% CI: 0.80, 1.04; P for trend = 0.11). This association was mainly due to quercetin (0.88; 0.78, 1.00; P = 0.03). The association tended to persist for quercetin after simultaneous adjustment for the different flavonoids (0.87; 0.73, 1.03; P = 0.07). Of the dietary sources rich in flavonoids, apple (0.87; 0.77, 0.99; P = 0.003), onion (0.89; 0.77, 1.03; P = 0.02), and orange (0.92; 0.81, 1.05; P = 0.15) intakes showed the strongest associations.

Mortality from ischemic heart disease

Ischemic heart disease mortality tended to be lower at higher quercetin and kaempferol intakes. The RRs of the disease at the highest and lowest quartiles of these flavonol intakes were 0.79 (0.63, 0.99; P = 0.02) and 0.82 (0.66, 1.02; P = 0.06), respectively, after adjustment for the common risk factors of cardiovascular disease (Table 2). Simultaneous adjustment for the different flavonoids gave a significant association for quercetin but not for kaempferol; the RRs were 0.74 (0.55, 0.99; P = 0.03) and 0.95 (0.72, 1.25; P = 0.64), respectively. Of the dietary sources rich in flavonoids, apple (0.75; 0.60, 0.94; P = 0.007) and onion (0.77; 0.59, 1.00; P = 0.02) intakes were significantly associated with a decrease in ischemic heart disease mortality.

Cerebrovascular disease

The incidence of cerebrovascular disease leading to hospitalization or death was lower at higher intakes of kaempferol (RR: 0.70; 95% CI: 0.56, 0.86; P = 0.003), hesperetin (0.80; 0.64, 0.99; P = 0.008), and naringenin (0.79; 0.64, 0.98; P = 0.006) after adjustment for common risk factors for cardiovascular disease (**Table 3**). Except for kaempferol, similar associations were observed for thrombotic and hemorrhagic stroke in men and women combined. The association with thrombotic stroke was stronger in men than in women (data not shown). An analysis of the simultaneous association between different

TABLE 2
Relative risks (and 95% CIs) of total mortality and mortality from ischemic heart disease (IHD) between quartiles of flavonoid intake[1]

Type of mortality and flavonoid	Quartile[2] 1 (lowest)	2	3	4 (highest)	*P* for trend
Total (*n* = 9131 at risk, 2085 cases)					
Quercetin	1	1.00 (0.90, 1.12)	0.92 (0.81, 1.04)	0.88 (0.78, 1.00)	0.03
Kaempferol	1	0.93 (0.83, 1.04)	0.93 (0.82, 1.05)	0.91 (0.80, 1.03)	0.12
Myricetin	1	1.01 (0.90, 1.14)	1.00 (0.89, 1.13)	1.05 (0.93, 1.19)	0.52
Hesperetin	1	0.96 (0.86, 1.07)	0.93 (0.82, 1.06)	0.94 (0.82, 1.07)	0.26
Naringenin	1	0.96 (0.86, 1.07)	0.92 (0.81, 1.05)	0.95 (0.83, 1.08)	0.29
Total	1	0.92 (0.82, 1.03)	0.90 (0.80, 1.01)	0.92 (0.80, 1.04)	0.11
IHD (*n* = 9131 at risk, 681 cases)					
Quercetin	1	0.93 (0.76, 1.13)	0.84 (0.68, 1.04)	0.79 (0.63, 0.99)	0.02
Kaempferol	1	0.80 (0.65, 0.98)	0.82 (0.66, 1.01)	0.82 (0.66, 1.02)	0.06
Myricetin	1	0.87 (0.70, 1.08)	1.11 (0.91, 1.36)	1.14 (0.92, 1.40)	0.11
Hesperetin	1	0.96 (0.79, 1.16)	0.89 (0.71, 1.12)	0.95 (0.76, 1.19)	0.48
Naringenin	1	0.97 (0.80, 1.18)	0.89 (0.71, 1.12)	0.98 (0.78, 1.22)	0.61
Total	1	0.99 (0.81, 1.20)	0.86 (0.69, 1.07)	0.93 (0.74, 1.17)	0.30

[1] Adjusted for sex, age, geographic area, occupation, blood pressure, smoking, serum cholesterol, BMI, and diabetes.

[2] Quercetin quartiles (mg/d): 1.5, 2.5, and 3.9 for men and 1.8, 2.9, and 4.7 for women; kaempferol quartiles: 0.1, 0.4, and 0.8 for men and 0.2, 0.5, and 0.9 for women; myricetin quartiles: 0, 0.06, and 0.11 for men and 0.03, 0.10, and 0.20 for women; hesperetin quartiles: 0, 6.8, and 15.4 for men and 3.2, 13.5, and 26.8 for women; naringenin quartiles: 0, 2.0, and 4.7 for men and 0.9, 3.9, and 7.7 for women; and quartiles of total flavonoids: 4.3, 12.0, and 26.9 for men and 8.5, 21.4, and 39.5 for women.

flavonoids and cerebrovascular disease incidence showed the strongest association to be for kaempferol (0.68; 0.52, 0.88; $P = 0.01$). Of the dietary sources rich in flavonoids, orange (0.79; 0.64, 0.98; $P = 0.02$), white cabbage (0.74; 0.60, 0.91; $P = 0.004$), and grapefruit (0.63; 0.36, 1.09; $P = 0.07$) intakes showed the strongest associations with cerebrovascular disease occurrence. Apple intake showed a significant association for thrombotic stroke (0.75; 0.57, 0.99; $P = 0.009$).

Cancer

The total cancer incidence was significantly lower at higher quercetin intakes (RR: 0.77; 95% CI: 0.65, 0.92; $P = 0.01$), mainly because of a lower lung cancer risk in men (0.42; 0.25, 0.72; $P = 0.001$) (**Table 4**). Prostate cancer risk was lower at higher myricetin intakes (0.43; 0.22, 0.86; $P = 0.002$), and breast cancer risk tended to be lower at higher quercetin intakes (0.62; 0.37,

TABLE 3
Relative risks (and 95% CIs) of cerebrovascular diseases between quartiles of flavonoid intake[1]

Type of cerebrovascular disease and flavonoid	Quartile[2] 1 (lowest)	2	3	4 (highest)	*P* for trend
All (*n* = 9131 at risk, 806 cases)					
Quercetin	1	0.89 (0.73, 1.07)	0.94 (0.78, 1.14)	0.86 (0.70, 1.05)	0.19
Kaempferol	1	0.94 (0.78, 1.13)	0.95 (0.79, 1.15)	0.70 (0.56, 0.86)	0.003
Myricetin	1	0.99 (0.82, 1.20)	0.88 (0.72, 1.06)	1.02 (0.84, 1.24)	0.77
Hesperetin	1	1.06 (0.89, 1.26)	0.79 (0.64, 0.98)	0.80 (0.64, 0.99)	0.008
Naringenin	1	1.08 (0.91, 1.28)	0.79 (0.64, 0.98)	0.79 (0.64, 0.98)	0.006
Total	1	1.14 (0.96, 1.37)	0.82 (0.67, 1.01)	0.79 (0.64, 0.98)	0.006
Thrombosis (*n* = 9131 at risk, 423 cases)					
Quercetin	1	0.77 (0.59, 1.01)	0.96 (0.74, 1.25)	0.80 (0.60, 1.05)	0.23
Kaempferol	1	1.01 (0.78, 1.29)	0.89 (0.68, 1.16)	0.63 (0.47, 0.85)	0.004
Myricetin	1	0.89 (0.68, 1.16)	0.75 (0.57, 0.98)	0.98 (0.75, 1.28)	0.43
Hesperetin	1	1.02 (0.81, 1.29)	0.72 (0.53, 0.97)	0.74 (0.55, 1.00)	0.01
Naringenin	1	1.04 (0.82, 1.32)	0.72 (0.53, 0.97)	0.73 (0.54, 0.98)	0.009
Total	1	1.08 (0.85, 1.37)	0.69 (0.52, 0.92)	0.73 (0.54, 0.98)	0.004
Hemorrhage (*n* = 9131 at risk, 91 cases)					
Quercetin	1	0.63 (0.35, 1.15)	0.88 (0.51, 1.53)	0.75 (0.42, 1.35)	0.47
Kaempferol	1	1.01 (0.59, 1.74)	0.69 (0.38, 1.28)	0.95 (0.53, 1.71)	0.57
Myricetin	1	0.89 (0.50, 1.56)	0.68 (0.37, 1.24)	1.00 (0.57, 1.75)	0.70
Hesperetin	1	0.82 (0.48, 1.39)	0.81 (0.44, 1.49)	0.62 (0.32, 1.18)	0.15
Naringenin	1	0.83 (0.49, 1.41)	0.86 (0.48, 1.56)	0.56 (0.29, 1.09)	0.11
Total	1	1.00 (0.59, 1.69)	0.87 (0.49, 1.54)	0.57 (0.29, 1.12)	0.11

[1] Adjusted for sex, age, geographic area, occupation, blood pressure, smoking, serum cholesterol, BMI, and diabetes.

[2] Quercetin quartiles (mg/d): 1.5, 2.5, and 3.9 for men and 1.8, 2.9, and 4.7 for women; kaempferol quartiles: 0.1, 0.4, and 0.8 for men and 0.2, 0.5, and 0.9 for women; myricetin quartiles: 0, 0.06, and 0.11 for men and 0.03, 0.10, and 0.20 for women; hesperetin quartiles: 0, 6.8, and 15.4 for men and 3.2, 13.5, and 26.8 for women; naringenin quartiles: 0, 2.0, and 4.7 for men and 0.9, 3.9, and 7.7 for women; and quartiles of total flavonoids: 4.3, 12.0, and 26.9 for men and 8.5, 21.4, and 39.5 for women.

TABLE 4
Relative risks (and 95% CIs) of cancer between quartiles of flavonoid intake[1]

Cancer site and flavonoid	Quartile[2] 1 (lowest)	2	3	4 (highest)	*P* for trend
All (*n* = 9865 at risk, 1093 cases)					
Quercetin	1	0.93 (0.79, 1.09)	0.97 (0.82, 1.14)	0.77 (0.65, 0.92)	0.01
Kaempferol	1	1.11 (0.95, 1.31)	1.06 (0.90, 1.25)	0.94 (0.78, 1.12)	0.51
Myricetin	1	1.08 (0.92, 1.27)	0.95 (0.81, 1.12)	0.99 (0.83, 1.17)	0.62
Hesperetin	1	1.08 (0.92, 1.25)	1.04 (0.87, 1.24)	0.96 (0.80, 1.15)	0.69
Naringenin	1	1.07 (0.92, 1.25)	1.02 (0.85, 1.22)	0.96 (0.80, 1.15)	0.67
Total	1	0.88 (0.75, 1.03)	0.98 (0.83, 1.15)	0.89 (0.74, 1.06)	0.33
Lung, in men (*n* = 5218 at risk, 169 cases)					
Quercetin	1	0.72 (0.49, 1.07)	0.72 (0.48, 1.09)	0.42 (0.25, 0.72)	0.001
Kaempferol	1	0.97 (0.65, 1.43)	0.80 (0.52, 1.24)	0.81 (0.51, 1.28)	0.26
Myricetin	1	1.06 (0.70, 1.60)	0.72 (0.46, 1.13)	1.20 (0.78, 1.83)	0.98
Hesperetin	1	0.77 (0.53, 1.11)	0.58 (0.35, 0.99)	0.74 (0.46, 1.18)	0.07
Naringenin	1	0.77 (0.53, 1.11)	0.67 (0.41, 1.09)	0.63 (0.40, 1.08)	0.04
Total	1	0.57 (0.38, 0.86)	0.63 (0.41, 0.97)	0.64 (0.39, 1.04)	0.02
Stomach (*n* = 9865 at risk, 74 cases)					
Quercetin	1	1.16 (0.63, 2.13)	1.23 (0.65, 2.34)	1.03 (0.52, 2.07)	0.82
Kaempferol	1	1.14 (0.63, 2.07)	0.79 (0.39, 1.58)	1.14 (0.59, 2.22)	0.98
Myricetin	1	0.85 (0.42, 1.72)	1.58 (0.89, 2.82)	1.16 (0.59, 2.26)	0.29
Hesperetin	1	1.05 (0.60, 1.86)	0.89 (0.44, 1.81)	0.88 (0.43, 1.80)	0.67
Naringenin	1	1.02 (0.58, 1.82)	0.88 (0.43, 1.80)	0.94 (0.47, 1.88)	0.78
Total	1	0.82 (0.44, 1.52)	0.93 (0.49, 1.78)	0.87 (0.44, 1.75)	0.73
Colorectum (*n* = 9865 at risk, 90 cases)					
Quercetin	1	0.84 (0.48, 1.49)	0.97 (0.56, 1.70)	0.62 (0.33, 1.17)	0.22
Kaempferol	1	1.61 (0.92, 2.82)	1.04 (0.55, 1.94)	1.13 (0.60, 2.12)	0.96
Myricetin	1	1.53 (0.86, 2.73)	1.40 (0.78, 2.50)	1.31 (0.71, 2.43)	0.39
Hesperetin	1	1.49 (0.87, 2.58)	1.56 (0.86, 2.84)	0.97 (0.50, 1.90)	0.84
Naringenin	1	1.57 (0.91, 2.70)	1.51 (0.83, 2.77)	0.93 (0.48, 1.82)	1.00
Total	1	1.24 (0.70, 2.18)	1.49 (0.85, 2.63)	0.84 (0.43, 1.64)	0.95
Urinary organs (*n* = 9865 at risk, 81 cases)					
Quercetin	1	1.42 (0.82, 2.47)	0.89 (0.46, 1.70)	0.87 (0.44, 1.72)	0.49
Kaempferol	1	1.06 (0.62, 1.82)	0.64 (0.33, 1.22)	0.67 (0.34, 1.31)	0.11
Myricetin	1	1.08 (0.62, 1.89)	0.65 (0.34, 1.24)	0.78 (0.41, 1.49)	0.23
Hesperetin	1	1.25 (0.71, 2.19)	1.49 (0.80, 2.76)	0.83 (0.40, 1.70)	0.94
Naringenin	1	1.26 (0.72, 2.22)	1.50 (0.81, 2.78)	0.81 (0.39, 1.66)	0.90
Total	1	0.95 (0.53, 1.70)	1.20 (0.67, 2.15)	0.69 (0.34, 1.41)	0.57
Prostate (*n* = 5218 at risk, 95 cases)					
Quercetin	1	1.21 (0.72, 2.02)	0.92 (0.52, 1.64)	0.76 (0.40, 1.42)	0.35
Kaempferol	1	1.12 (0.64, 1.96)	1.55 (0.88, 2.74)	1.03 (0.53, 2.02)	0.54
Myricetin	1	0.93 (0.55, 1.57)	0.51 (0.28, 0.91)	0.43 (0.22, 0.86)	0.002
Hesperetin	1	1.66 (0.99, 2.81)	1.36 (0.70, 2.62)	1.47 (0.80, 2.71)	0.26
Naringenin	1	1.68 (0.99, 2.84)	1.33 (0.69, 2.57)	1.48 (0.80, 2.73)	0.27
Total	1	0.73 (0.41, 1.28)	1.12 (0.64, 1.94)	1.11 (0.61, 2.01)	0.57
Breast, in women (*n* = 4647 at risk, 125 cases)					
Quercetin	1	0.50 (0.29, 0.86)	0.92 (0.58, 1.46)	0.62 (0.37, 1.03)	0.25
Kaempferol	1	0.71 (0.42, 1.18)	0.84 (0.51, 1.36)	0.87 (0.53, 1.41)	0.70
Myricetin	1	1.13 (0.70, 1.82)	0.87 (0.52, 1.47)	0.95 (0.57, 1.60)	0.63
Hesperetin	1	1.27 (0.79, 2.06)	1.09 (0.64, 1.85)	1.08 (0.63, 1.86)	0.93
Naringenin	1	1.29 (0.80, 2.10)	1.04 (0.60, 1.78)	1.14 (0.67, 1.94)	0.82
Total	1	1.27 (0.76, 2.13)	1.19 (0.70, 2.02)	1.23 (0.72, 2.10)	0.53

[1] Adjusted for sex, age, geographic area, occupation, smoking, and BMI.

[2] Quercetin quartiles: 1.5, 2.5, and 3.9 for men and 1.8, 2.9, and 4.7 for women; kaempferol quartiles: 0.1, 0.4, and 0.8 for men and 0.2, 0.5, and 0.9 for women; myricetin quartiles: 0, 0.06, and 0.11 for men and 0.03, 0.10, and 0.20 for women; hesperetin quartiles: 0, 6.8, and 15.4 for men and 3.2, 13.5, and 26.8 for women; naringenin quartiles: 0, 2.0, and 4.7 for men and 0.9, 3.9, and 7.7 for women; and quartiles of total flavonoids: 4.3, 12.0, and 26.9 for men and 8.5, 21.4, and 39.5 for women.

1.03; $P = 0.25$). However, no significant associations were observed between flavonoid intake and occurrence of cancers of the stomach, colorectum, or urinary organs. Adjustment for dietary sources strengthened the association between quercetin intake and breast cancer risk (0.54; 0.30, 0.95; $P = 0.14$). Simultaneous study of the different flavonoids did not notably change the association between myricetin intake and prostate cancer incidence but strengthened the association between quercetin and lung cancer

TABLE 5
Relative risks (and 95% CIs) of rheumatoid arthritis between quartiles of flavonoid intake[1]

Type of arthritis and flavonoid	Quartile[2] 1 (lowest)	2	3	4 (highest)	*P* for trend
All (*n* = 9283 at risk, 90 cases)					
Quercetin	1	3.52 (1.79, 6.94)	1.43 (0.65, 3.14)	2.64 (1.30, 5.36)	0.16
Kaempferol	1	1.58 (0.82, 3.05)	1.78 (0.93, 3.40)	1.91 (1.01, 3.62)	0.05
Myricetin	1	0.83 (0.46, 1.50)	1.27 (0.74, 2.17)	0.83 (0.44, 1.55)	1.00
Hesperetin	1	1.67 (0.97, 2.86)	0.79 (0.39, 1.59)	1.10 (0.59, 2.07)	0.61
Naringenin	1	1.72 (1.00, 2.96)	0.89 (0.45, 1.75)	0.99 (0.52, 1.88)	0.46
Total	1	1.86 (1.04, 3.33)	1.08 (0.56, 2.08)	1.18 (0.62, 2.26)	0.83
Rheumatoid factor–positive (*n* = 9283 at risk, 64 cases)					
Quercetin	1	3.76 (1.62, 8.73)	1.96 (0.78, 4.96)	2.94 (1.22, 7.05)	0.13
Kaempferol	1	1.73 (0.75, 3.96)	2.27 (1.02, 5.05)	2.49 (1.13, 5.49)	0.02
Myricetin	1	0.73 (0.36, 1.47)	1.26 (0.68, 2.33)	0.69 (0.32, 1.47)	0.75
Hesperetin	1	2.51 (1.25, 5.07)	1.31 (0.56, 3.05)	1.45 (0.64, 3.27)	0.92
Naringenin	1	2.59 (1.28, 5.22)	1.48 (0.65, 3.39)	1.28 (0.56, 2.93)	0.91
Total	1	3.48 (1.57, 7.70)	2.08 (0.88, 4.91)	1.76 (0.72, 4.30)	0.70
Rheumatoid factor–negative (*n* = 9283 at risk, 26 cases)					
Quercetin	1	3.12 (1.00, 9.74)	0.52 (0.09, 2.85)	2.12 (0.63, 7.15)	0.80
Kaempferol	1	1.36 (0.47, 3.96)	1.06 (0.34, 3.33)	1.05 (0.33, 3.29)	0.93
Myricetin	1	1.17 (0.39, 3.50)	1.32 (0.44, 3.95)	1.28 (0.41, 3.98)	0.62
Hesperetin	1	0.74 (0.29, 1.90)	0.24 (0.05, 1.10)	0.72 (0.25, 2.03)	0.26
Naringenin	1	0.77 (0.30, 1.98)	0.25 (0.05, 1.16)	0.67 (0.24, 1.90)	0.23
Total	1	0.59 (0.21, 1.64)	0.29 (0.08, 1.08)	0.71 (0.26, 1.91)	0.32

[1] Adjusted for sex and age.
[2] Quercetin quartiles (mg/d): 1.5, 2.5, and 3.9 for men and 1.8, 2.9, and 4.7 for women; kaempferol quartiles: 0.1, 0.4, and 0.8 for men and 0.2, 0.5, and 0.9 for women; myricetin quartiles: 0, 0.06, and 0.11 for men and 0.03, 0.10, and 0.20 for women; hesperetin quartiles: 0, 6.8, and 15.4 for men and 3.2, 13.5, and 26.8 for women; naringenin quartiles: 0, 2.0, and 4.7 for men and 0.9, 3.9, and 7.7 for women; and quartiles of total flavonoids: 4.3, 12.0, and 26.9 for men and 8.5, 21.4, and 39.5 for women.

(0.34; 0.18, 0.64; $P = 0.001$). The association was stronger in nonsmokers (0.13; 0.03, 0.57; $P = 0.005$) than in smokers (0.49; 0.28, 0.86; $P = 0.02$). Of the dietary sources rich in flavonoids, apple intake was strongly associated with a lower risk of lung cancer (0.40; 0.22, 0.74; $P = 0.001$).

Rheumatoid arthritis

A higher intake of kaempferol was related to a high risk of rheumatoid arthritis (RR: 1.91; 95% CI: 1.01, 3.62; $P = 0.05$) (**Table 5**). Although no significant trend was found for quercetin ($P = 0.16$), the relative risk between the highest and lowest quartiles of intake differed significantly from unity (2.64; 1.30, 5.36). The associations were mainly related to rheumatoid factor–positive disease. Of the dietary sources rich in flavonoids, intake of white cabbage was strongly associated with an increase in rheumatoid factor–positive disease (3.27; 1.69, 6.33; $P < 0.001$).

Type 2 diabetes

A lower risk of type 2 diabetes tended to be associated with higher quercetin (RR: 0.81; 95% CI: 0.64, 1.02; $P = 0.07$) and myricetin (0.79; 0.62, 1.00; $P = 0.07$) intakes (**Table 6**). Adjustment for cardiovascular disease risk factors (data not shown) or dietary sources did not alter the results. Of the dietary sources rich in flavonoids, apple and berry intakes showed the strongest associations: 0.73 (0.57, 0.92; $P = 0.003$) and 0.74 (0.58, 0.95; $P = 0.03$), respectively.

Cataract

Cataract incidence was not significantly lower at higher total flavonoid intakes. In contrast with the hypothesis studied, an elevated risk of cataract was noted in the highest quartile of hesperetin intake (RR: 1.66; 95%CI: 1.04, 2.66; $P = 0.13$). Adjustment for other dietary sources, however, lowered the risk (1.48; 0.81, 2.70; $P = 0.46$).

Asthma

The incidence of asthma was lower at higher total flavonoid intakes (RR: 065; 95% CI: 0.47, 0.90; $P = 0.04$). This association was due to quercetin (0.76; 0.56, 1.01; $P = 0.05$), hesperetin (0.64; 0.46, 0.88; $P = 0.03$), and naringenin (0.69; 0.50, 0.94; $P = 0.06$). Inclusion of all flavonoids in the same model resulted in nonsignificant associations for quercetin (0.70; 0.48, 1.04; $P = 0.09$) and naringenin (0.72; 0.52, 0.99; $P = 0.12$). The strongest associations were noted for apple (0.55; 0.40, 0.76; $P = 0.001$) and orange (0.71; 0.52, 0.98; $P = 0.09$) intakes.

Food sources of flavonoids

Of the main flavonoid sources, apple intake was associated with almost all of the chronic diseases considered (**Figure 1**). Apple intake was, after adjustment for intake of vegetables and fruit other than apples, inversely associated with occurrence of all cancers combined, lung cancer, asthma, type 2 diabetes, thrombotic stroke, total mortality and ischemic heart disease mortality. The only disease with a suggestively elevated risk at higher apple intakes was rheumatoid arthritis.

DISCUSSION

The results of our study suggest the presence of an inverse association between flavonoid intake and subsequent occurrence

TABLE 6
Relative risks (and 95% CIs) of other chronic diseases between quartiles of flavonoid intake[1]

Type of disease and flavonoid	Quartile[2] 1 (lowest)	2	3	4 (highest)	*P* for trend
Diabetes (*n* = 9878 at risk, 526 cases)					
Quercetin	1	0.69 (0.54, 0.87)	0.74 (0.58, 0.94)	0.81 (0.64, 1.02)	0.07
Kaempferol	1	0.97 (0.77, 1.23)	1.01 (0.80, 1.28)	0.92 (0.72, 1.18)	0.63
Myricetin	1	0.74 (0.58, 0.93)	0.85 (0.67, 1.06)	0.79 (0.62, 1.00)	0.07
Hesperetin	1	0.84 (0.67, 1.06)	0.82 (0.63, 1.05)	0.96 (0.76, 1.22)	0.56
Naringenin	1	0.84 (0.68, 1.06)	0.81 (0.63, 1.05)	0.98 (0.78, 1.24)	0.67
Total	1	0.85 (0.68, 1.08)	0.86 (0.68, 1.09)	0.98 (0.77, 1.24)	0.75
Cataract (*n* = 10022 at risk, 132 cases)					
Quercetin	1	1.03 (0.66, 1.61)	1.02 (0.63, 1.64)	0.94 (0.57, 1.56)	0.86
Kaempferol	1	1.41 (0.90, 2.22)	1.35 (0.83, 2.18)	1.16 (0.69, 1.95)	0.48
Myricetin	1	0.78 (0.48, 1.27)	0.84 (0.52, 1.36)	1.10 (0.69, 1.76)	0.85
Hesperetin	1	1.35 (0.87, 2.10)	0.88 (0.50, 1.54)	1.66 (1.04, 2.66)	0.13
Naringenin	1	1.39 (0.90, 2.16)	0.99 (0.58, 1.71)	1.53 (0.95, 2.46)	0.19
Total	1	1.21 (0.77, 1.90)	1.09 (0.66, 1.79)	1.36 (0.84, 2.21)	0.28
Asthma (*n* = 10039 at risk, 382 cases)					
Quercetin	1	0.98 (0.75, 1.29)	0.88 (0.66, 1.16)	0.76 (0.56, 1.01)	0.05
Kaempferol	1	1.01 (0.77, 1.33)	0.86 (0.65, 1.15)	0.86 (0.64, 1.14)	0.18
Myricetin	1	0.86 (0.65, 1.14)	0.91 (0.69, 1.21)	1.13 (0.86, 1.49)	0.42
Hesperetin	1	1.06 (0.82, 1.37)	1.15 (0.86, 1.52)	0.64 (0.46, 0.88)	0.03
Naringenin	1	1.06 (0.82, 1.38)	1.17 (0.88, 1.55)	0.69 (0.50, 0.94)	0.06
Total	1	1.01 (0.77, 1.33)	1.14 (0.87, 1.49)	0.65 (0.47, 0.90)	0.04

[1] Diabetes and asthma adjusted for sex and age; cataract adjusted for sex, age, and geographic area.

[2] Quercetin quartiles: 1.5, 2.5, and 3.9 for men and 1.8, 2.9, and 4.7 for women; kaempferol quartiles: 0.1, 0.4, and 0.8 for men and 0.2, 0.5, and 0.9 for women; myricetin quartiles: 0, 0.06, and 0.11 for men and 0.03, 0.10, and 0.20 for women; hesperetin quartiles: 0, 6.8, and 15.4 for men and 3.2, 13.5, and 26.8 for women; naringenin quartiles: 0, 2.0, and 4.7 for men and 0.9, 3.9, and 7.7 for women; and quartiles of total flavonoids: 4.3, 12.0, and 26.9 for men and 8.5, 21.4, and 39.5 for women.

of ischemic heart disease, cerebrovascular disease, lung and prostate cancer, type 2 diabetes, and asthma. The potential beneficial effects of flavonoids were mainly ascribed to quercetin, the most potent antioxidant (11) but also in some cases to kaempferol, myricetin, hesperitin, and naringenin. The lower risk found for ischemic heart disease mortality was concentrated in persons with higher intakes of apples and onions and accordingly to the flavonols quercetin (44) and kaempferol. Three former prospective studies on the combined effect of flavonols and flavones (13, 16, 17) gave similar findings. In contrast, 2 other studies failed to find any such associations in persons free of disease at baseline (18, 20).

In the present study, a lower incidence of cerebrovascular disease was associated with the intake of the flavonol kaempferol and of the flavonones naringenin and hesperitin but not of quercetin, in agreement with a previous finding (19). One previous small cohort study reported a strong inverse association between the sum of quercetin, myricetin, luteolin, and apigenin intakes and stroke incidence (14), whereas 2 other studies failed to find any association between flavonol and flavone intakes and stroke mortality (16, 21).

In a previous study, we found a lower risk of lung cancer at higher quercetin intakes (15). This finding agrees with the results of a study on flavonoids from vegetables and fruit (23) but differs from the results of another study on quercetin and total flavonoids (22). In the present study, we also found a lower risk of prostate cancer at higher myricetin intakes. No association between the intake of quercetin (15) or other flavonoids and the risk of cancers of the stomach, colorectum, or urinary organs was found in the present study or in a previous cohort study (22).

A reduced risk of type 2 diabetes was related to higher intakes of quercetin and myricetin, mainly because of the intakes of apples and berries. Asthma incidence was lower at higher intakes of quercetin, naringenin, and hesperetin. Accordingly, the strongest associations were between intakes of apples and orange. In general, cataract incidence was not associated with flavonoid intake. Unexpectedly, higher intakes of kaempferol were related

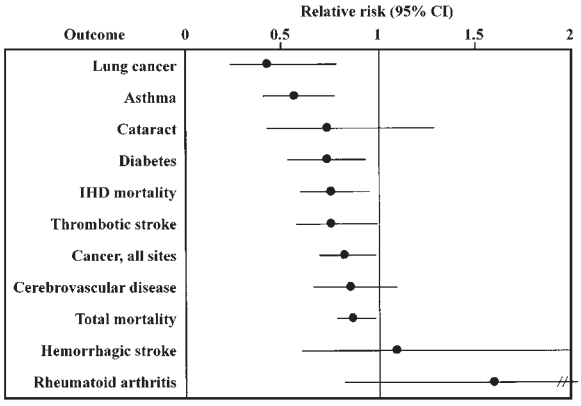

FIGURE 1. Relative risks (●) and 95% CIs (horizontal bars) of chronic diseases between the highest (>47 g/d) and lowest (0 g/d) quartiles of apple intake. The relative risks were adjusted for sex, age, disease-specific nondietary confounding factors, and intakes of vegetables and fruit other than apples. IHD, ischemic heart disease.

to an elevated risk of rheumatoid factor–positive rheumatoid arthritis. The highest risks were associated with the intake of white cabbage.

Our findings support the hypothesis that flavonols and flavonones protect against several chronic diseases. Several alternative explanations are possible for our findings, however. First, foodstuffs rich in flavonoids may contain other biologically active but still unknown compounds that may be what provides the protection (45). One such food is apples, the major source of quercetin in the present population. Apple intake predicted the occurrence of ischemic heart disease, lung cancer, type 2 diabetes, and asthma. Because apples are a relatively poor source of vitamin C and β-carotene, adjustment for these antioxidant vitamins did not notably alter the association. Adjustment for quercetin reduced the strength of the association between apple consumption and the incidence of lung cancer, suggesting that some other substance or substances in apples may have been responsible for the observed association. It is also possible that the association was due to some other fruit or vegetable, the consumption of which may be associated with the consumption of foodstuffs rich in flavonoids. Adjustment for other fruit and vegetables and for other main sources of flavonoids, however, did not materially alter the results of the present study. The inverse association between flavonoid intake and asthma risk may have resulted because children with a high risk of asthma were advised by clinicians to avoid citrus fruit in Finland. A lifestyle associated with a high intake of foodstuffs rich in flavonoids may also reduce the risk of chronic diseases.

Second, although the intakes of antioxidant vitamins and their main sources were adjusted for in the present study, it is possible that the relatively low short-term reliability of the intake estimates for micronutrients (27) did not allow for a sufficient adjustment to eliminate any resulting association due to them.

Third, in addition to vegetables and fruit, tea and red wine are major sources of flavonoids (46). Data on tea and red wine were not available in the present study and, therefore, flavonoids provided by these beverages could not be estimated. However, the tea consumption of Finns was low, because coffee was mainly consumed as a refreshment beverage at the time of baseline. The consumption of red wine is also low in Finland, because beer and liquors are preferred. The contribution of tea and red wine to flavonoid intake was thus small in the present population.

Fourth, preclinical disease may have affected dietary habits and, consequently, flavonoid intake at baseline, resulting in an artificial association. Exclusion of persons with disease at baseline and of persons who developed the disease during the first years of follow-up would diminish this type of bias. The results were not notably altered by the exclusion of persons who developed disease during the first 2 y of follow-up. Furthermore, the follow-up was of sufficient duration to show the sequential relation between dietary intake and subsequent disease occurrence. In contrast, the consumption of fruit and vegetables in Finland increased considerably during the long follow-up (47), indicating a change in flavonoid intakes. Such a change tends to weaken the representative value of the dietary measurement, accordingly altering the strength of the association. Although we found a relatively low long-term repeatability of the flavonoid estimates, the strength of the association appeared to be similar for a shorter follow-up period.

Fifth, the intake of flavonoids in the present population was exceptionally low, making it tempting to speculate that the antioxidative potential was not sufficient to provide protection against chronic disease under all circumstances. In accordance, we found a greater reduction in lung cancer risk among nonsmokers than among current smokers in agreement with the fact that smokers have a larger burden of oxidative stress.

Sixth, it cannot be excluded that the lack of significant association for some diseases may have been due to a small number of cases. Also, a lack of information on the diseases studied because of the emigration of some persons during the follow-up period may have caused a negligible bias. Finally, despite the use of flavonoid concentrations in Finnish foods, which apparently enabled accurate estimates of the flavonoid intake data, it is still possible that information on flavonoid intake is not an accurate measure of the flavonoids available in the human body. We must either await more information on the absorption of flavonoids (46) or use the available serologic markers until strong interpretations of the discovered associations can be made.

In summary, we found inverse relations between the dietary intake of some flavonoids and the incidence of several chronic diseases. These associations were mainly attributable to the consumption of apples, the main source of quercetin in the present population. Although our finding was independent of the intake of antioxidant vitamins, the potential importance of other biologically active compounds in fruit and vegetables on the relation cannot be excluded. Further prospective studies from populations with different flavonoid intakes should focus on the effects of effect-modifying and confounding factors, such as dietary patterns and lifestyle, until firm conclusions can be drawn about the role of flavonoids in the etiology of chronic diseases.

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