Higher dietary flavone, flavonol, and catechin intakes are associated with less of an increase in BMI over time in women: a longitudinal analysis from the Netherlands Cohort Study

Higher dietary flavone, flavonol, and catechin intakes are associated with less of an increase in BMI over time in women: a longitudinal analysis from the Netherlands Cohort Study[1–3]

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ABSTRACT

Background: Dietary flavonoids are suggested to have antiobesity effects. Prospective evidence of an association between flavonoids and body mass index (BMI) is lacking in general populations.

Objective: We assessed this association between 3 flavonoid subgroups and BMI over a 14-y period in 4280 men and women aged 55–69 y at baseline from the Netherlands Cohort Study.

Design: Dietary intake was estimated at baseline (1986) by a validated food-frequency questionnaire. BMI was ascertained through self-reported height (in 1986) and weight (in 1986, 1992, and 2000). Analyses were based on sex-specific quintiles for the total intake of 6 catechins and of 3 flavonols/flavones. Linear mixed effect modeling was used to assess longitudinal associations in 3 adjusted models: age only, lifestyle (age, energy intake, physical activity, smoking status, alcohol intake, type 2 diabetes, and coffee consumption), and lifestyle and diet (vegetables, fruit, fiber, grains, sugar, dessert, and dieting habits).

Results: After adjustment for age and confounders, the BMI (kg/m^2) of women with the lowest intake of total flavonols/flavones and total catechins increased by 0.95 and 0.77, respectively, after 14 y. Women with the highest intake of total flavonols/flavones and total catechins experienced a significantly lower increase in BMI of 0.40 and 0.31, respectively (between group difference: $P < 0.05$). This difference remained after additional adjustment for dietary determinants and after stratification of median baseline BMI. In men, no significant differences in BMI change were observed over the quintiles of flavonoid intake after 14 y.

Conclusion: Our results suggest that flavonoid intake may contribute to maintaining body weight in the general female population. *Am J Clin Nutr* 2008;88:1341–52.

INTRODUCTION

It is well accepted that overweight and obesity are major contributors to the global burden of chronic disease and disability. According to the World Health Organization, an individual is considered overweight if his or her body mass index (BMI; in kg/m^2) is >25 and obese if his or her BMI exceeds 30 (1). It is of great importance to determine effective and safe mechanisms for maintaining a healthy body weight as the prevalence of overweight, and obesity continues to rise at an alarming rate.

The role of dietary intake and modification for weight maintenance has traditionally been described in terms of macronutrients and micronutrients; however, emerging evidence suggests that the flavonoids, a group of nonnutritive phytochemicals with diverse beneficial biochemical and antioxidant effects (2–9), may be a dietary factor that can also modulate body weight (9–24). Present in foods of plant origin such as fruit, vegetables, tea, wine, seeds, herbs, spices, and whole grains, >6000 naturally occurring flavonoids have been identified and classified into 6 major subgroups: catechins, flavonols, flavones, flavanones, anthocyanins, and isoflavones (25).

Short-term studies using green tea as a source of catechins have shown a reduction in body weight and body fat compared with baseline measurements in overweight individuals (15, 17–20, 23, 24). The major catechins found in the diet are (+)-catechin, (−)-epicatechin, (−)-epigallocatechin (EGC), (+)-gallocatechin (GC), (−)-epicatechin gallate (ECG), and (−)-epigallocatechin gallate (EGCG) (26). Animal studies have shown that catechins increase energy expenditure, increase glucose uptake in skeletal muscle, decrease glucose uptake in adipose tissue, and prevent obesity in a dose-response fashion (22, 27). Additionally, animal studies have shown an antiobesity effect of the major dietary flavonols (quercetin, myricetin, and kaempferol) and the major dietary flavones (luteolin and apigenin) through mechanisms such as influences on glucose uptake and fatty acid catabolism (16, 21). Recent molecular data suggests that other subclasses of flavonoids may have an effect on adipokine secretion and up-regulation of gene expression (9–11, 13).

Applying the findings of human studies to the general population is difficult because of the short duration of the interventions and because they included primarily overweight and obese

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[2] Supported by the Dutch Cancer Society and by a VENI Innovational Research Grant from the Netherlands Organization for Scientific Research—Earth and Life Sciences.

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Received February 26, 2008. Accepted for publication July 15, 2008.
doi: 10.3945/ajcn.2008.26058.

subjects (15, 17–20, 23, 24). The Netherlands Cohort Study on diet and cancer (NLCS) provided a unique opportunity to assess the association between flavonoid intake and BMI change over time in the general population. Because the majority of evidence suggesting an association between flavonoid intake and body weight currently exists for the catechin, flavonol, and flavone groups, we focused on only these 3 subclasses in the present study.

SUBJECTS AND METHODS

Subjects and study design

The NLCS is a prospective cohort study that was initiated in 1986 with the enrollment of 120 852 individuals in the Netherlands and with the purpose of investigating the association between diet and the development of cancer. The cohort included 58 279 men and 62 573 women between the ages of 55 and 69 y at baseline who completed a self-administered questionnaire on dietary habits, lifestyle, health, and demographic information. Municipal registries from throughout the Netherlands were used to constitute an efficient sampling frame reflective of the general population. Further details of the design of the NLCS were described in previous publications (28–30).

The NLCS is a case-cohort design with a subcohort of 5000 individuals randomly selected from the larger cohort on recruitment into the study. These individuals have been followed-up biennially from baseline in 1986 for migration and vital status to estimate person time at risk. Follow-up of the subcohort has also allowed for the additional accumulation of prospective data regarding a number of factors related to body weight and weight change. This subcohort was the study population used for the present study.

In our analysis, individuals who returned incomplete baseline dietary questionnaires, individuals with missing values for height or weight at baseline, and all prevalent cancer cases other than skin cancer at baseline were excluded. This resulted in an initial study population of 4280 individuals. Follow-up measurements specifically regarding BMI were recorded in the years 1992 and 2000, and data were available for 3787 and 2091 individuals, respectively, at these time points. The study protocol of the NLCS was approved by the Medical Ethics Committees of the University Hospital Maastricht and TNO Nutrition in February 1985 and July 1986, respectively.

Dietary assessment

The measurement instrument used to assess dietary flavonoid intake at baseline was a self-administered food-frequency questionnaire (FFQ) consisting of 150 food items (28–30). This dietary assessment was part of a larger questionnaire that also included questions regarding a number of lifestyle factors. The FFQ was aimed at habitual intake; therefore, dietary intake with a reference period of 1 y was assessed to account for seasonal variations in some foods, such as vegetables and fruit (28). For each item on the questionnaire, the frequency of consumption was asked on a scale consisting of 7 categories. The number of servings per consumption frequency was reported in natural units (eg, slice of bread) or household units (eg, spoonful) or the individual serving size in grams was asked. For some foods, the frequency categories were replaced by the number of serving units taken daily, weekly, or monthly. An open-ended question was included to account for any foods eaten regularly but not included in the questionnaire (30). Questionnaire data were key-entered twice and processed in a manner blinded with respect to case/subcohort status to minimize observer bias in the coding and interpretation of data. The questionnaire was shown to be valid and reliable and is described in greater detail elsewhere (28–30).

The major sources of dietary catechins and flavonol/flavone intake in our population are similar to other studies in the Dutch population. These include tea, apples, pears, chocolate, and broad beans for catechin intake (31, 32) and tea, onions, leek, apples, pears, and sweet peppers for flavonol/flavone intakes (33). Information regarding the flavonoid content in different foods and beverages on the questionnaire was required to enable the epidemiologic evaluation of these substances (32, 34–36). This was done individually for catechins, flavones, and flavonols for every item on the FFQ. To determine catechin concentrations, tables from Arts et al (31, 32) were used. These tables contain the catechin content of 24 different fruit and fruit varieties, 27 different types of vegetables and legumes, staple foods, processed foods, chocolate, 8 types of black tea, 18 types of red and white wine, apple juice, grape juice, iced tea, beer, chocolate milk, and coffee commonly consumed in the Netherlands. Furthermore, these products were sampled multiple times in different seasons and from different retail outlets (31, 32). Data by Hertog et al (34, 35), derived in a similar fashion, were used to determine the concentration of flavonols and flavones. Concentrations of each specific flavonoid are reported for each item on the FFQ in mg/100 g of fresh weight of edible portion of food and in mg/100 mL of beverage. The flavonoid content of each participant's diet was calculated by multiplying the reported consumption frequency and consumed quantity on the FFQ by the assigned flavonoid content of each food.

Ascertainment of BMI

Subjects were followed up biennially since the time of the baseline questionnaire. At these time points, additional self-administered questionnaires were mailed to all individuals given they were still alive and reachable at the same address. If necessary, new addresses were obtained and individuals were contacted there. Height (cm) was self-measured and reported on the baseline dietary questionnaire. Body weight (kg) was reported on questionnaires on 3 different occasions: at baseline in the autumn of 1986 and in the autumn of 1992 and 2000. In 1986 and 1992, the question was open-ended and phrased as "how much do you weigh now (kg)?" In 2000, subjects were asked "have you weighed yourself recently (yes/no)?" If the subjects answered "yes," they were directed to an open-ended question, "how much do you weigh (kg)?" At all 3 time points, the weight measurement was self-reported. BMI (in kg/m^2) was calculated for each time point by using the recorded weight at each time point divided by height squared at baseline.

Statistical analysis

Data were analyzed by using Stata (version 9.2; Statacorp, College Station, TX). All analyses were conducted separately for catechin and flavonol/flavone intakes and were stratified by sex, because sex was shown to act as an effect modifier (data not shown). Flavonol and flavone intakes were considered together because flavones contributed minimally to total flavonoid intake. Sex-specific quintiles of total catechins, total flavonols/flavones,

and specific catechin and flavonol compounds were assessed. Mean total flavonol/flavone intake and total catechin intake as well as other population characteristics were analyzed by using data from the baseline questionnaire. Pearson's correlation and one-factor analysis of variance was applied to determine the correlation between continuous variables and total flavonoid intake, and a chi-square test was used to assess the association between total flavonoid intake and categorical variables.

Linear mixed effect (LME) modeling was applied to assess the change in BMI over time and the longitudinal relation between flavonoid intake at baseline and BMI at baseline (1986), in 1992, and in 2000. The mixed model consists of 2 parts: fixed effects and random effects. Fixed effects describe population slopes for a set of considered covariates, which include exposures and confounders. Random effects describe individual variability in outcome and in changes over time. By considering individual random slopes, this model allowed us to examine the influence of covariates on the change in BMI over time (37). This model also accounts for the correlation between repeated measurements on the same subject and accounts for missing values at various time points (38).

For the LME model, a categorical time variable was created by using the values 0, 6, and 14; reflecting the time points (in y) of the BMI measurements from baseline. Two dummy variables indicating the 3 time points and 4 flavonoid intake dummy variables were entered into the model. Furthermore, interactions of the time dummies with the 4 flavonoid intake dummies (8 interaction terms) were included. A random slope for time at the individual level was obtained by using time as a continuous variable. Longitudinal information was derived by considering the regression coefficients of the time dummies and the regression coefficients of the flavonoid-time interaction terms. The coefficients of the time dummies reflect the change in BMI over time (6 and 14 y, respectively) in the lowest quintile. The coefficient of an interaction term gives the difference between the change in BMI in a quintile after 6 and 14 y and the change in BMI in the lowest quintile of flavonoid intake as the reference category.

In addition to an unadjusted and age adjusted model, we created an LME model adjusted for age plus confounding variables. These variables were identified as being associated with both BMI and flavonoid intake from the previous literature or were variables that, when entered in our model, resulted in a >10% change in the regression coefficients. These included age (y), total energy intake (kcal/d), coffee drinking (cups/d), physical activity (min/d), smoking status (current smoker, ex-smoker, and never smoker), alcohol intake (g/d), and the presence of type 2 diabetes (yes or no). Intervention research has shown a potential synergistic relation between caffeine and flavonoids (20); therefore, we performed an additional stratified analysis testing coffee drinking as a possible effect modifier.

We hypothesized that individuals with a high intake of dietary flavonoids would also have a healthier lifestyle and, as a result, less of an increase in BMI over time. Therefore, we created a fourth model additionally adjusted for fiber, fruit, vegetable, grain, desert, and sugar intakes (g/d) and dieting habits in the 5 y leading up to the baseline questionnaire (yes or no). Furthermore, we investigated whether an association was present over a range of BMI values or whether it would be present only in individuals who had the most weight to lose. Using median BMI at baseline (women: 24.64; men: 24.80) to classify individuals as having a low or high BMI, we conducted a stratified analysis adjusting for initial confounders and the extra dietary and lifestyle factors. Finally, although LME models should be robust to missing values, we conducted the initial analysis excluding individuals with missing BMI measurements at 1 or 2 time points ($n = 1992$ remaining) and excluding individuals who developed cancer between 1986 and 2000 ($n = 3496$ remaining). All models were tested for evidence of a linear trend by using the time-by-quintile interaction. Two-tailed P values <0.05 were considered statistically significant in all analyses.

RESULTS

Baseline population characteristics are presented in **Table 1**. Flavonoid intake was higher in women than in men for all investigated catechins and flavonols/flavones. Compared with women, men consumed more calories, drank more alcohol, and had a higher proportion of current and ex-smokers. For both men and women, higher flavonoid intake was associated with higher total energy intake, a smaller proportion of current smokers, and a higher level of physical activity. In men, higher intake was also associated with older age. The presence of type 2 diabetes did not differ across quintiles of intake in both sexes (data not shown). In both men and women, BMI increased slightly from baseline over time, although this increase was only significant in women (**Table 2**).

The course of BMI change over time in quintiles of total baseline flavonols/flavones and total catechin intake, adjusted for confounding variables, is depicted for men and women in **Figure 1** and **Figure 2**, respectively. Although BMI increased in each quintile of intake over time, women in the third, fourth, and fifth quintiles of total flavonol/flavone and total catechin intake had a significantly lower BMI increase than did women with the lowest intake. After 14 y, the BMI of women with the lowest intake of total flavonols/flavones and total catechins had increased by 0.95 and 0.77, respectively. In contrast, women with the highest intake of total flavonols/flavones and total catechins experienced a significantly lower BMI increase of 0.40 and 0.31, respectively (between-group difference for both: $P < 0.05$). The BMI of men also increased after 14 y in all quintiles of total intake, but this change was not different between intake groups. No significant linear trends were observed.

The association between BMI change and specific flavonoid compounds are presented in **Table 3**, adjusted for identified confounders. Results are presented by sex, according to quintiles of intake, and are interpreted as the change in BMI in each quintile at a given follow-up time point compared with baseline. Myricetin intake was associated with a lower BMI increase in women of the highest quintile after 6 y and after 14 y. Women in the highest quintiles of ECG, GC, EGC, and EGCG intake had a significantly lower increase in BMI than did women in the lowest quintile after 6 y. This association was still observed after 14 y and was additionally observed in women with the highest intakes of epicatechin.

To assess the influence of potential confounders, 4 different models were studied: unadjusted, age adjusted, adjusted for identified confounders, and adjusted for identified confounders plus additional dietary and lifestyle factors. Regression coefficients of the LME analyses for total dietary flavonol/flavone and total dietary catechin intake are presented in **Table 4** and **Table 5**. We observed similar associations between BMI change and total

TABLE 1
Baseline characteristics of the subcohort in the Netherlands Cohort Study

	Men (n = 2107)	Women (n = 2173)	Correlation with total flavonoid intake[1,2]	P value[3]
Demographics				
Age (y)	61.3 ± 4.2[4]	61.4 ± 4.3	0.10	0.00
Anthropometrics				
Height (m)	176.5 ± 6.7	165.2 ± 6.2	−0.03	0.05
Weight (kg)	77.7 ± 9.4	68.5 ± 10.3	−0.06	0.00
BMI (kg/m^2)	25.0 ± 2.6	25.1 ± 3.7	−0.05	0.01
Dietary factors				
Total energy intake (kcal)	2169 ± 507	1683 ± 397	0.06	0.00
Total catechins (mg/d)[5]	57.2 ± 36.9	67.0 ± 39.1	0.99	—
Catechin	4.4 ± 2.8	4.6 ± 2.4	0.65	—
Epicatechin	13.0 ± 7.2	15.0 ± 7.5	0.82	—
Epicatechin gallate	18.6 ± 13.9	22.3 ± 15.0	0.97	—
Gallocatechin	2.8 ± 2.0	3.3 ± 2.2	0.97	—
Epigallocatechin	4.6 ± 3.2	5.4 ± 3.4	0.97	—
Epigallocatechin gallate	13.8 ± 10.4	16.5 ± 11.1	0.97	—
Total flavonol/flavones (mg/d)[6]	26.4 ± 12.5	29.0 ± 12.7	0.89	—
Quercetin	18.2 ± 9.0	19.6 ± 8.9	0.73	—
Kaempferol	6.8 ± 3.9	7.8 ± 4.1	0.95	—
Myricetin	1.4 ± 0.96	1.6 ± 0.97	0.93	—
Self-reported illness				
Type 2 diabetes (%)	3.4	3.6	—	0.02
Lifestyle behaviors				
Smoking status (%)	—	—	—	0.00
Never	12.7	58.2	—	—
Former	51.5	20.6	—	—
Current	35.8	21.2	—	—
Alcohol intake (%)	—	—	—	0.01
0 g/d	14.6	32.3	—	—
0.1-4 g/d	21.1	35.8	—	—
5-14 g/d	26.8	19.0	—	—
15-29 g/d	22.6	9.4	—	—
≥30 g/d	14.9	3.6	—	—
Physical activity (%)	—	—	—	0.02
<30 min/d	18.0	24.4	—	—
30-60 min/d	31.1	31.2	—	—
60-90 min/d	19.0	22.7	—	—
>90 min/d	31.9	21.8	—	—

[1] Sum of total catechin and total flavonol/flavone intake.
[2] Reported as pairwise correlation coefficients (continuous variable).
[3] P values for continuous variables are from one-factor ANOVA, and P values for categorical variables are from a chi-square test.
[4] $\bar{x}$ ± SD (all such values).
[5] Sum of catechin, epicatechin, epicatechin gallate, gallocatechin, epigallocatechin, and epigallocatechin gallate.
[6] Sum of quercetin, kaempferol, myricetin (flavonols), luteolin, and apigenin (flavones).

intake in all models. Even after the data were adjusted for a number of additional lifestyle factors, women with the highest dietary flavonoid intake experienced a significantly lower increase in BMI over 14 y than did women with the lowest intake (0.50 and 0.44 less of an increase, respectively; $P < 0.05$). No significant linear trends were observed.

Results of the analysis stratified by median BMI at baseline are presented in **Table 6**. Total flavonol/flavone and total catechin intakes were associated with a lower BMI change in women with a BMI in the low range (<24.64) and women with a BMI in the high range (>24.64), although it was not always statistically significant. Stratification of subjects as coffee drinkers (>3 cups/d) or non-coffee drinkers (0 cups/d) suggested that coffee drinking was not an effect modifier in this population (data not shown). Our findings did not change when after subjects with missing BMI measurements at 1 or 2 time points or who developed cancer after 1986 were excluded (data not shown).

DISCUSSION

Although a number of studies have investigated the effect of flavonoid intake on body weight and BMI, the few observational data contributing to this evidence are only cross-sectional in nature (39–43). We observed, after 14 y, that women in all quintiles of flavonoid intake experienced an increase in BMI. However, women with the highest intake of total flavonols/flavones and total catechins had a significantly lower BMI increase over time than did women with the lowest intake. When body weight and height were substituted for BMI in the model, women

TABLE 2
Change in BMI from baseline over time for subcohort members of the Netherlands Cohort Study[1]

	BMI (kg/m^2)[2]	
Year	Men (n = 2107)[3]	Women (n = 2173)
1986	24.95 ± 0.04	25.07 ± 0.04
1992	25.00 ± 0.05	25.25 ± 0.07[4]
2000	25.03 ± 0.06	25.55 ± 0.08[4]

[1] All values are $\bar{x}$ ± SE.
[2] BMI derived from a linear mixed model including BMI and time.
[3] Number of subjects at baseline.
[4] Significantly different from baseline, $P < 0.05$.

with the highest intake of total flavonols/flavones and total catechins gained 1.00 and 0.95 kg less body weight, respectively. These observations may have important public health implications because even moderate elevations in BMI and body weight over a long period of time have been shown to increase disease risk (44–51).

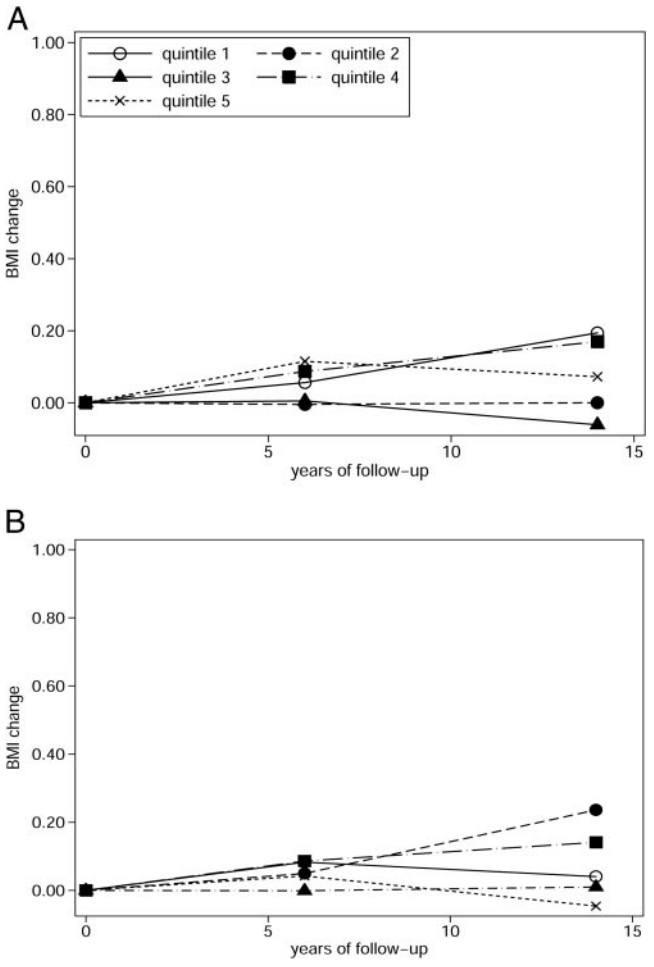

FIGURE 1. Change in BMI (kg/m^2) over 14 y for men in each quintile of total dietary flavonol/flavone intake (A; P for trend 0.06) and total dietary catechin intake (B; P for trend = 0.95). Graphs derived from linear mixed models adjusted for total energy intake, physical activity, smoking status, alcohol consumption, type 2 diabetes, coffee drinking, and age.

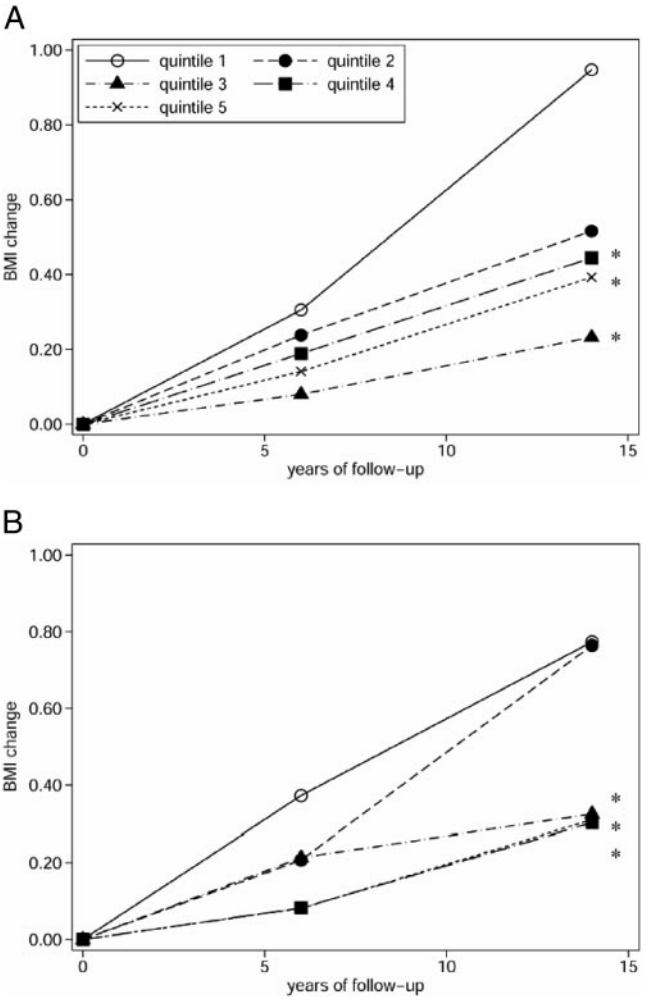

FIGURE 2. Change in BMI (kg/m^2) over 14 y for women in each quintile of total dietary flavonol/flavone intake (A; P for trend = 0.52) and total dietary catechin intake (B; P for trend = 0.08). Graphs derived from linear mixed models adjusted for total energy intake, physical activity, smoking status, alcohol consumption, type 2 diabetes, coffee drinking, and age. *Significantly lower BMI increase than in the lowest quintile, $P < 0.05$.

Our finding of a protective association between catechin intake and BMI in women is supported by human intervention studies using tea or tea extracts as a treatment for overweight and obesity. Tsuchida et al (15) reported that, compared with controls, subjects consuming high levels of catechins experienced a significant decrease in BMI (0.49) after a 12-wk randomized controlled trial. Treatment consisted of 588 mg catechins/d; similar doses were used in other successful intervention studies (18, 20). In our study, the mean total catechin intake in women in the highest quintile was 125 mg/d. Because this is a much lower concentration than what was used in intervention studies, it is interesting that we still observed significant inverse associations with BMI, even after adjusting for all confounders. Because diet assessed through the FFQ in our study reflects the diet of individuals for an entire year preceding baseline, and has been observed to be stable for ≥5 y (29), a much longer exposure time to these substances is expected compared with the controlled intervention studies described above.

The observation that there was a protective association between myricetin and BMI in women is intriguing. Myricetin

TABLE 3
Change in BMI from baseline (1986) over time associated with specific dietary flavonoid intakes by quintile (Q) of flavonoid intake for subcohort members of the Netherlands Cohort Study[1]

	Men (n = 2107)					Women (n = 2173)				
	Q of flavonoid intake[2]					Q of flavonoid intake[3]				
Flavonoid and year	1	2	3	4	5	1	2	3	4	5
Flavonol/flavones										
Quercetin										
1992	0.00 ± 0.09	0.04 ± 0.08	−0.02 ± 0.08	0.09 ± 0.08	0.14 ± 0.08	0.21 ± 0.10	0.23 ± 0.09	0.24 ± 0.09	0.05 ± 0.09	0.21 ± 0.09
2000	0.15 ± 0.12	0.15 ± 0.12	−0.11 ± 0.12	0.11 ± 0.12	0.08 ± 0.12	0.78 ± 0.17	0.63 ± 0.15	0.43 ± 0.15	0.33 ± 0.15[4]	0.36 ± 0.15
Kaempferol										
1992	0.09 ± 0.08	0.03 ± 0.08	0.08 ± 0.08	0.05 ± 0.08	0.01 ± 0.08	0.36 ± 0.09	0.18 ± 0.09	0.27 ± 0.09	0.04 ± 0.09[4]	0.11 ± 0.09
2000	0.12 ± 0.12	0.07 ± 0.12	0.11 ± 0.12	0.10 ± 0.12	−0.04 ± 0.12	0.69 ± 0.16	0.62 ± 0.16	0.44 ± 0.15	0.40 ± 0.15	0.32 ± 0.15
Myricetin										
1992	0.06 ± 0.08	0.01 ± 0.08	0.04 ± 0.08	−0.01 ± 0.08	0.16 ± 0.08	0.39 ± 0.09	0.17 ± 0.09	0.20 ± 0.09	0.12 ± 0.09[4]	0.08 ± 0.09[4]
2000	0.16 ± 0.12	0.02 ± 0.12	−0.03 ± 0.12	0.08 ± 0.12	0.15 ± 0.12	0.73 ± 0.16	0.65 ± 0.16	0.42 ± 0.16	0.47 ± 0.15	0.20 ± 0.15[4]
Catechins										
Catechin										
1992	0.03 ± 0.08	−0.02 ± 0.08	0.19 ± 0.08	0.02 ± 0.08	0.04 ± 0.08	0.25 ± 0.10	0.27 ± 0.09	0.25 ± 0.09	0.11 ± 0.09	0.10 ± 0.08
2000	0.14 ± 0.13	0.06 ± 0.12	0.04 ± 0.12	0.04 ± 0.12	0.09 ± 0.11	0.54 ± 0.17	0.59 ± 0.16	0.63 ± 0.15	0.40 ± 0.15	0.30 ± 0.15
Epicatechin										
1992	0.08 ± 0.08	0.03 ± 0.08	−0.02 ± 0.08	0.14 ± 0.08	0.02 ± 0.08	0.31 ± 0.09	0.25 ± 0.09	0.28 ± 0.09	0.06 ± 0.09	0.07 ± 0.09
2000	0.07 ± 0.12	0.22 ± 0.13	0.06 ± 0.12	0.07 ± 0.12	−0.02 ± 0.12	0.77 ± 0.18	0.49 ± 0.16	0.68 ± 0.15	0.33 ± 0.15[4]	0.24 ± 0.15[4]
ECG										
1992	0.16 ± 0.08	−0.02 ± 0.09	0.03 ± 0.08	0.05 ± 0.08	0.03 ± 0.08	0.36 ± 0.09	0.23 ± 0.09	0.22 ± 0.09	0.06 ± 0.09[4]	0.08 ± 0.09[4]
2000	0.16 ± 0.12	0.16 ± 0.12	0.07 ± 0.12	0.00 ± 0.12	−0.02 ± 0.12	0.83 ± 0.16	0.37 ± 0.15[4]	0.67 ± 0.15	0.30 ± 0.16[4]	0.30 ± 0.15[4]
GC										
1992	0.18 ± 0.09	0.02 ± 0.08	0.01 ± 0.09	−0.03 ± 0.07	0.11 ± 0.08	0.39 ± 0.09	0.24 ± 0.10	0.21 ± 0.09	0.05 ± 0.09[4]	0.08 ± 0.09[4]
2000	0.14 ± 0.14	0.15 ± 0.11	−0.01 ± 0.13	0.00 ± 0.11	0.08 ± 0.12	0.71 ± 0.16	0.85 ± 0.17	0.43 ± 0.14	0.25 ± 0.15[4]	0.30 ± 0.15
EGC										
1992	0.11 ± 0.08	0.00 ± 0.08	0.01 ± 0.8	0.09 ± 0.08	0.06 ± 0.08	0.41 ± 0.09	0.23 ± 0.09	0.16 ± 0.09	0.06 ± 0.09[4]	0.09 ± 0.09[4]
2000	0.12 ± 0.12	0.11 ± 0.12	−0.01 ± 0.12	0.19 ± 0.12	−0.06 ± 0.12	0.79 ± 0.16	0.73 ± 0.16	0.39 ± 0.15	0.27 ± 0.15[4]	0.30 ± 0.15[4]
EGCG										
1992	0.11 ± 0.07	0.01 ± 0.07	0.03 ± 0.10	−0.02 ± 0.09	0.11 ± 0.10	0.37 ± 0.09	0.23 ± 0.09	0.20 ± 0.10	0.05 ± 0.09[4]	0.08 ± 0.09
2000	0.14 ± 0.10	0.06 ± 0.11	0.17 ± 0.14	−0.04 ± 0.13	−0.01 ± 0.15	0.78 ± 0.16	0.63 ± 0.15	0.44 ± 0.17	0.28 ± 0.15[4]	0.29 ± 0.15[4]

[1] All values are $\bar{x}$ ± SE. Results were derived from a linear mixed model adjusted for age, baseline total energy intake (kcal/d), physical activity level (<30, 30-60, 60-90, and >90 min/d), smoking status (never smoker, ex-smoker, and current smoker), alcohol intake (0, 0.1-4, 5-14, 15-29, and ≥30 g/d), coffee consumption (cups/d), and type 2 diabetes (yes or no). ECG, epicatechin gallate; GC, gallocatechin; EGC, epigallocatechin; EGCG, epigallocatechin gallate.

[2] Range of flavonoid intakes (mg/d): Q1, ≤24.1; Q2, 24.2-44.3; Q3, 44.4-62.7; Q4, 62.8-84.3; Q5, 84.4-290.1.

[3] Range of flavonoid intakes (mg/d): Q1, ≤36.1; Q2, 36.3-51.6; Q3, 51.8-75.4; Q4, 75.5-95.8; Q5, 96.0-247.1.

[4] Significantly lower BMI increase than in the lowest quintile, as derived from the quintile-by-time interaction ($P < 0.05$).

TABLE 4
Change in BMI from baseline (1986) over time associated with total flavonol/flavone intakes by quintile (Q) of flavonoid intake for subcohort members of the Netherlands Cohort Study[1]

	Men					Women				
	Q of flavonoid intake[2]					Q of flavonoid intake[3]				
	1	2	3	4	5	1	2	3	4	5
Median intake (mg/d)	11.9	19.2	25.3	31.7	42.6	13.6	21.8	28.0	34.4	44.9
Model and year										
1) Unadjusted										
1992	0.06 ± 0.08[4]	0.00 ± 0.08	0.01 ± 0.08	0.08 ± 0.08	0.11 ± 0.08	0.29 ± 0.09	0.20 ± 0.09	0.09 ± 0.09	0.18 ± 0.09	0.13 ± 0.09
2000	0.21 ± 0.12	−0.02 ± 0.12	−0.03 ± 0.12	0.16 ± 0.12	0.09 ± 0.11	0.90 ± 0.16	0.46 ± 0.15	0.26 ± 0.15[5]	0.44 ± 0.15[5]	0.41 ± 0.15[5]
2) Age adjusted										
1992	0.06 ± 0.08	0.00 ± 0.08	0.01 ± 0.08	0.07 ± 0.08	0.11 ± 0.08	0.29 ± 0.09	0.20 ± 0.09	0.10 ± 0.09	0.18 ± 0.09	0.13 ± 0.09
2000	0.21 ± 0.12	−0.02 ± 0.12	−0.03 ± 0.12	0.16 ± 0.12	0.09 ± 0.11	0.90 ± 0.16	0.46 ± 0.15	0.26 ± 0.15	0.44 ± 0.15[5]	0.41 ± 0.15[5]
3) Adjusted for confounders										
1992	0.06 ± 0.08	0.00 ± 0.08	0.01 ± 0.08	0.09 ± 0.08	0.12 ± 0.08	0.31 ± 0.09	0.24 ± 0.09	0.08 ± 0.09	0.19 ± 0.09	0.14 ± 0.09
2000	0.19 ± 0.12	0.00 ± 0.12	−0.06 ± 0.12	0.17 ± 0.12	0.07 ± 0.12	0.95 ± 0.17	0.52 ± 0.16	0.23 ± 0.15[5]	0.44 ± 0.15[5]	0.39 ± 0.15[5]
4) Adjusted for confounders plus additional dietary and lifestyle factors										
1992	0.08 ± 0.09	−0.01 ± 0.08	0.03 ± 0.08	0.10 ± 0.09	0.13 ± 0.08	0.32 ± 0.10	0.27 ± 0.10	0.12 ± 0.10	0.19 ± 0.10	0.12 ± 0.09
2000	0.21 ± 0.13	−0.03 ± 0.12	−0.04 ± 0.12	0.15 ± 0.12	0.07 ± 0.12	0.91 ± 0.17	0.54 ± 0.16	0.25 ± 0.16[5]	0.42 ± 0.16[5]	0.41 ± 0.15[5]

[1] Results were derived from a linear mixed model *1*) unadjusted; *2*) age-adjusted; *3*) adjusted for age, total energy intake (kcal/d), physical activity (<30, 30-60, 60-90, and >90 min/d), smoking status (never smoker, ex-smoker, and current smoker), alcohol intake (0, 0.1-4, 5-14, 15-29, and ≥30 g/d), coffee drinking (cups/d), and type 2 diabetes (yes or no); and *4*) adjusted for the same variables in model 3 plus intake (g/d) of vegetables, fruit, fiber, grains, sugar, and desserts and dieting habits (yes or no to being on a diet in the past 5 y).

[2] Range of flavonoid intakes (mg/d): Q1, ≤24.1; Q2, 24.2-44.3; Q3, 44.4-62.7; Q4, 62.8-84.3; Q5, 84.4-290.1.

[3] Range of flavonoid intakes (mg/d): Q1, ≤36.1; Q2, 36.3-51.6; Q3, 51.8-75.4; Q4, 75.5-95.8; Q5, 96.0-247.1.

[4] $\bar{x}$ ± SE (all such values).

[5] Significantly lower BMI increase than in the lowest quintile, as derived from the quintile-by-time interaction ($P < 0.05$).

TABLE 5
Change in BMI from baseline (1986) over time associated with total catechin intakes by quintile (Q) of flavonoid intake for subcohort members in the Netherlands Cohort Study[1]

	Men					Women				
	Q of flavonoid intake[2]					Q of flavonoid intake[3]				
	1	2	3	4	5	1	2	3	4	5
Median intake (mg/d)	9.9	38.7	51.0	76.0	103.2	17.5	44.5	63.7	83.7	118.5
Model and year										
1) Unadjusted										
1992	0.08 ± 0.08[4]	0.06 ± 0.08	0.00 ± 0.08	0.08 ± 0.08	0.05 ± 0.08	0.38 ± 0.09	0.19 ± 0.09	0.19 ± 0.09	0.06 ± 0.09[5]	0.08 ± 0.09[5]
2000	0.03 ± 0.12	0.24 ± 0.12	0.00 ± 0.12	0.16 ± 0.12	−0.02 ± 0.12	0.75 ± 0.16	0.69 ± 0.15	0.31 ± 0.15[5]	0.28 ± 0.15[5]	0.38 ± 0.14[5]
2) Age adjusted										
1992	0.08 ± 0.08	0.06 ± 0.08	0.00 ± 0.08	0.08 ± 0.08	0.05 ± 0.08	0.38 ± 0.09	0.19 ± 0.09	0.19 ± 0.09	0.06 ± 0.09	0.08 ± 0.09
2000	0.03 ± 0.12	0.24 ± 0.12	0.00 ± 0.12	0.16 ± 0.12	−0.02 ± 0.12	0.75 ± 0.16	0.69 ± 0.15	0.31 ± 0.15[5]	0.28 ± 0.15[5]	0.38 ± 0.14[5]
3) Adjusted for confounders										
1992	0.08 ± 0.08	0.05 ± 0.08	0.00 ± 0.08	0.09 ± 0.08	0.04 ± 0.08	0.37 ± 0.09	0.21 ± 0.09	0.21 ± 0.09	0.08 ± 0.09[5]	0.08 ± 0.09[5]
2000	0.04 ± 0.12	0.24 ± 0.12	0.01 ± 0.12	0.14 ± 0.12	−0.05 ± 0.12	0.77 ± 0.16	0.76 ± 0.15	0.33 ± 0.16[5]	0.30 ± 0.15[5]	0.31 ± 0.15[5]
4) Adjusted for confounders plus additional dietary and lifestyle factors										
1992	0.11 ± 0.09	0.05 ± 0.08	0.02 ± 0.08	0.11 ± 0.08	0.04 ± 0.08	0.38 ± 0.10	0.25 ± 0.10	0.22 ± 0.10	0.09 ± 0.10[5]	0.07 ± 0.09[5]
2000	0.02 ± 0.13	0.23 ± 0.12	0.01 ± 0.12	0.15 ± 0.12	−0.05 ± 0.12	0.76 ± 0.17	0.78 ± 0.16	0.29 ± 0.16[5]	0.33 ± 0.16[5]	0.32 ± 0.15[5]

[1] Results were derived from a linear mixed model *1*) unadjusted; *2*) age-adjusted; *3*) adjusted for age, total energy intake (kcal/d), physical activity (<30, 30-60, 60-90, and >90 min/d), smoking status (never smoker, ex-smoker, and current smoker), alcohol intake (0, 0.1-4, 5-14, 15-29, and ≥30 g/d), coffee drinking (cups/d), and type 2 diabetes (yes or no); and *4*) adjusted for the same variables in model 3 plus intake of vegetables (g/d), fruit (g/d), fiber (g/d), grains (g/d), sugar (g/d), desserts (g/d), and dieting habits (yes or no to being on a diet in the past 5 y).

[2] Range of flavonoid intakes (mg/d): Q1, ≤24.1; Q2, 24.2-44.3; Q3, 44.4-62.7; Q4, 62.8-84.3; Q5, 84.4-290.1.

[3] Range of flavonoid intakes (mg/d): Q1, ≤36.1; Q2, 36.3-51.6; Q3, 51.8-75.4; Q4, 75.5-95.8; Q5, 96.0-247.1.

[4] $\bar{x}$ ± SE (all such values).

[5] Significantly lower BMI increase than in the lowest quintile, as derived from the quintile-by-time interaction ($P < 0.05$).

TABLE 6
Change in BMI from baseline (1986) over time associated with dietary flavonoid intakes by quintile (Q) of flavonoid intake for subcohort members of the Netherlands Cohort Study, stratified by median BMI at baseline[1]

	Men (n = 2107)					Women (n = 2173)				
	Q of flavonoid intake[2]					Q of flavonoid intake[3]				
Flavonoid and year	1	2	3	4	5	1	2	3	4	5
Total flavonol/flavones										
Low BMI										
1992	0.12 ± 0.11	0.08 ± 0.12	0.19 ± 0.12	0.29 ± 0.11	0.26 ± 0.11	0.34 ± 0.12	0.39 ± 0.13	0.25 ± 0.13	0.28 ± 0.12	0.15 ± 0.12
2000	0.34 ± 0.14	0.27 ± 0.15	0.21 ± 0.15	0.24 ± 0.14	0.18 ± 0.14	0.95 ± 0.21	0.80 ± 0.22	0.49 ± 0.20	0.52 ± 0.20	0.35 ± 0.19[4]
High BMI										
1992	0.02 ± 0.14	−0.11 ± 0.13	−0.13 ± 0.13	−0.13 ± 0.14	−0.04 ± 0.13	0.24 ± 0.16	0.17 ± 0.14	−0.01 ± 0.15	0.09 ± 0.15	0.09 ± 0.15
2000	0.05 ± 0.18	−0.34 ± 0.17	−0.26 ± 0.16	0.11 ± 0.18	−0.03 ± 0.16	0.87 ± 0.28	0.31 ± 0.25	0.02 ± 0.24[4]	0.29 ± 0.25	0.50 ± 0.25
Total catechins										
Low BMI										
1992	0.17 ± 0.12	0.08 ± 0.12	0.18 ± 0.12	0.31 ± 0.11	0.20 ± 0.11	0.41 ± 0.13	0.35 ± 0.12	0.30 ± 0.13	0.30 ± 0.12	0.08 ± 0.11
2000	0.25 ± 0.25	0.35 ± 0.15	0.16 ± 0.15	0.26 ± 0.14	0.21 ± 0.14	0.70 ± 0.22	1.05 ± 0.20	0.60 ± 0.21	0.44 ± 0.20	0.26 ± 0.19[4]
High BMI										
1992	0.05 ± 0.14	0.01 ± 0.13	−0.13 ± 0.13	−0.14 ± 0.13	−0.20 ± 0.13	0.35 ± 0.15	0.14 ± 0.15	0.14 ± 0.14	−0.12 ± 0.15[4]	0.05 ± 0.15
2000	−0.19 ± 0.17	0.11 ± 0.17	−0.13 ± 0.16	0.08 ± 0.17	−0.37 ± 0.17	0.84 ± 0.26	0.45 ± 0.26	−0.03 ± 0.25[4]	0.22 ± 0.25	0.40 ± 0.25

[1] All values are $\bar{x}$ ± SE. Results were derived from a linear mixed model adjusted for age, baseline total energy intake (kcal/d), physical activity level (<30, 30-60, 60-90, and >90 min/d), smoking status (never smoker, ex-smoker, and current smoker), alcohol intake (0, 0.1-4, 5-14, 15-29, and ≥30 g/d), coffee drinking (cups/d), type 2 diabetes (yes or no), dietary habits (yes or no to being on a diet in the past 5 y), and intake (g/d) of vegetables, fruit, fiber, grains, sugar, and dessert. Median BMI (in kg/m^2) was 24.8 for men and 24.6 for women. A low BMI was classified as less than the median value, and a high BMI was classified as greater than the median value.

[2] Range of flavonoid intakes (mg/d): Q1, ≤24.1; Q2, 24.2-44.3; Q3, 44.4-62.7; Q4, 62.8-84.3; Q5, 84.4-290.1.

[3] Range of flavonoid intakes (mg/d): Q1, ≤36.1; Q2, 36.3-51.6; Q3, 51.8-75.4; Q4, 75.5-95.8; Q5, 96.0-247.1.

[4] Significantly lower BMI increase than in the lowest quintile, as derived from the quintile-by-time interaction ($P < 0.05$).

contributes minimally to the percentage of total flavonols in the daily diet (52, 53). In our population, tea, onions, and leeks contributed most to myricetin intake (33). Despite limited evidence in the literature suggesting a direct association between myricetin and obesity, evidence indicates that myricetin can improve the metabolic profile (54, 55). Although a chance finding cannot be ruled out, further research regarding the relation between myricetin and body weight would be of interest.

It is well accepted that major modifiers of BMI change are energy restriction and physical activity. Although we adjusted our models for these variables, we also recognized that, because flavonoids are derived from healthy foods, individuals with the highest flavonoid intake likely had an overall healthier lifestyle than did those with the lowest intake, and this phenomenon may result in less of a BMI increase over time. When we attempted to control for further potential confounding in our model by accounting for intake of vegetables, fruit, grains, fiber, sugar, deserts, and dieting habits, our observations did not change. Although residual confounding cannot be ruled out entirely, our results suggest that there is an independent association between dietary flavonoid intake and BMI change in women.

There was a clear association between flavonoid intake and BMI change in women, but this was not the case in men. Descriptive analyses at baseline showed that over each quintile of intake, mean consumption of both total flavonols/flavones and catechins was higher in women than in men. This observation is supported by a previous study examining catechin intake in the general Dutch population, which estimated the average intake of the 6 major catechins as 50 mg/d, with a significantly higher intake in women than in men (60 compared with 40 mg/d, respectively) (36). It is possible that flavonoid consumption in men may not have been high enough for an association to be observed. Additionally, our analysis showed that, in general, BMI increased much less over time in men than in women.

Our study had many strengths. Although only baseline data on flavonoid intake and other dietary information were available, the FFQ used in the NLCS was shown to be reproducible over a period of ≥5 y (29). It is well established that flavonoid concentrations can vary according to growing season, transportation, and food processing, and these limitations can result in inaccurate reporting of flavonoid concentrations in composition databases. We attempted to control for this by using sources of high quality to calculate the flavonoid concentrations of food on the FFQ (31, 32, 34, 35). However, it should be noted that the concentrations we calculated may still have been influenced by these limitations. Human intervention studies have generally administered tea, or specific catechins isolated from tea, as a treatment for weight loss. It has been proposed that the results from several of these studies were attributable to caffeine or to a synergistic effect between caffeine and catechins rather than to catechins alone (20). We considered coffee drinking a proxy for caffeine in our adjustment and also observed no effect modification in an additional analysis stratified for low and high coffee drinkers. However, it should be acknowledged that we could not account for all sources of dietary caffeine, such as from tea and cocoa. We considered flavonoid intake from the whole diet, which accounts for a wide variety of food sources and allowed for a more complete estimate of total flavonoid intake. Finally, we accounted for a number of lifestyle and dietary factors suggested to be important when studying the health effects of flavonoids using epidemiologic data (25, 36).

Our results are questionable because of the use of self-reported weight and height to ascertain BMI in our population. Although the measurement of self-reported weight was not independently validated in the NLCS, many examples in the literature suggest that this method is a valid and reliable tool for assessing body weight and height in cohort studies. Analysis of large cohorts conducted in the Japanese, British, Swedish, and American working population have all concluded that self-reported weight and height are generally valid and reliable (56–59); however, there is a general tendency for women, especially overweight women, to underreport weight and for men to overreport height. An underestimation of weight and an overestimation of height will underestimate BMI and, as a result, will underestimate the prevalence of overweight and obesity (56–58). Although misclassification could not be ruled out, the associations we observed between dietary flavonoid intake and BMI may actually have been stronger than we reported if the overweight women in our study had underestimated their weight

The age group of our population was also a limitation. The subjects were ≥55 y of age at baseline and thus became elderly over the course of the 14 y of the study. For many subcohort members, only 1 or 2 weight measurements were available for analysis. To check for survivorship bias, we conducted an additional analysis using only those subjects who reported all 3 BMI measurements, and our results did not change. Because of the design of the NLCS, we were also able to reconduct the analysis after eliminating individuals who developed cancer at some time point between 1986 and 2000. We observed that the BMI change in women in the highest quintile remained significantly lower over the 14 y period than did BMI change in the women with the lowest intake.

The FFQ used in the NLCS only measured flavonoid intake as derived from food in the daily diet. In response to the growing public interest in dietary supplements, especially with respect to weight loss and weight maintenance, epidemiologic studies should consider the effect of individual flavonoid extracts and supplements on BMI in addition to dietary food sources, and intervention studies should study the safety of consuming high concentrations of supplements on a regular basis (60, 61). Finally, although the bioavailability of flavonoid subclasses such as the anthocyanidins are quite low (62, 63), future studies may consider investigating the association between these flavonoids and BMI change, because emerging evidence suggests that they may also possess mechanisms to modulate body weight.

In conclusion, our finding of a significant inverse association between dietary flavonoid intake and BMI increase in women suggests that, over time, flavonoid intake may be useful for weight maintenance, even in persons who are not obese. On a population level, it is relatively easy to increase one's flavonoid intake through the daily diet.

We are indebted to the participants of this study and thank the cancer registries (IKA, IKL, IKMN, IKN, IKO, IKR, IKST, IKW, IKZ, and VIKC) and the Netherlands Nationwide Registry Pathology (PALGA). We also thank S van de Crommert and J Nelissen for their assistance with data entry and data management; A Volovics and A Kester for statistical advice; L van Amelsvoort for sharing his expertise on longitudinal data analysis; L Schouten, C de Zwart, M Moll, W van Dijk, M Jansen, and A Pisters for assistance; and H van Montfort, T van Moergastel, L van den Bosch, and R Schmeitz for programming assistance.

The authors' responsibilities were as follows—LAEH: carried out the statistical analysis, interpreted the data, and helped draft the manuscript;

MPW, ICWA, and TA: assisted with the statistical analysis and data interpretation; MPW and ICWA: helped draft the manuscript, conceived the idea for the current research question, and critically revised the manuscript; PAvdB and RAG: conceived the study, participated in the design and coordination of the study, and critically revised the manuscript for important intellectual content; HAMB: developed the database of flavonoid composition of foods in the FFQ and critically revised the manuscript; and PCD: critically revised the manuscript. All authors approved the final version of the manuscript, and none of the authors had a conflict of interest.

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