Inverse association of tea and flavonoid intakes with incident myocardial infarction: the Rotterdam Study[1–3]

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ABSTRACT

Background: Dietary flavonoids may protect against cardiovascular disease, but evidence is still conflicting. Tea is the major source of flavonoids in Western populations.

Objective: The association of tea and flavonoid intake with incident myocardial infarction was examined in the general Dutch population.

Design: A longitudinal analysis was performed with the use of data from the Rotterdam Study—a population-based study of men and women aged ≥55 y. Diet was assessed at baseline (1990–1993) with a validated semiquantitative food-frequency questionnaire. The analysis included 4807 subjects with no history of myocardial infarction, who were followed until 31 December 1997. Data were analyzed in a Cox regression model, with adjustment for age, sex, body mass index, smoking status, pack-years of cigarette smoking, education level, and daily intakes of alcohol, coffee, polyunsaturated fat, saturated fat, fiber, vitamin E, and total energy.

Results: During 5.6 y of follow-up, a total of 146 first myocardial infarctions occurred, 30 of which were fatal. The relative risk (RR) of incident myocardial infarction was lower in tea drinkers with a daily intake >375 mL (RR: 0.57; 95% CI: 0.33, 0.98) than in nontea drinkers. The inverse association with tea drinking was stronger for fatal events (0.30; 0.09, 0.94) than for nonfatal events (0.68; 0.37, 1.26). The intake of dietary flavonoids (quercetin + kaempferol + myricetin) was significantly inversely associated only with fatal myocardial infarction (0.35; 0.13, 0.98) in upper compared with lower tertiles of intake.

Conclusions: An increased intake of tea and flavonoids may contribute to the primary prevention of ischemic heart disease. *Am J Clin Nutr* 2002;75:880–6.

KEY WORDS Tea, flavonoids, myocardial infarction, ischemic heart disease, population-based study, the Rotterdam Study, Netherlands

INTRODUCTION

Epidemiologic studies have reported a reduced risk of ischemic heart disease in subjects with a high flavonoid intake through tea and other dietary sources (1–3), but findings are still conflicting (4, 5). The potential protective effect of flavonoids has been attributed to antioxidant (6–11), antithrombogenic (12–14), and antiinflammatory (15, 16) properties. Recent animal experiments suggest that flavonoids may also improve vascular function (17–19). In a previous cross-sectional analysis of data from the Rotterdam Study, we observed an inverse association of tea intake with aortic atherosclerosis (20). The present longitudinal study addresses the relation between tea intake and risk of first incident myocardial infarction in this population-based cohort of men and women aged ≥55 y.

SUBJECTS AND METHODS

The Rotterdam Study

The Rotterdam Study is a prospective study to assess the occurrence of chronic diseases in an aging population and to clarify the determinants of the diseases (21). The cohort comprises 7983 men and women aged ≥55 y (78% of the eligible population) who live in a defined district of Rotterdam. From August 1990 until June 1993, baseline data on current and past health, medication use, and risk indicators for chronic diseases were collected during a home interview by a trained research assistant. The participants were subsequently invited to the study center for a clinical examination and an assessment of diet.

Clinical examination

Height and weight were measured while the subjects were wearing indoor clothing and no shoes. Body mass index was computed as weight (in kg) divided by height squared (in m). Sitting systolic and diastolic blood pressures were measured twice with a random-zero sphygmomanometer by a trained research assistant after the subjects had rested for 5 min. The mean of the 2 blood pressure measurements was used in the analysis. A standard electrocardiogram was obtained, which was interpreted by using MEANS (Modular ECG Analysis System; 22). The subjects were

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considered to have diabetes mellitus if they reported using antidiabetes medication or if their nonfasting random or postload blood glucose concentrations were ≥11.1 mmol/L. Serum total cholesterol concentrations (mmol/L) were measured with the use of an automated enzymatic procedure (23). HDL cholesterol was measured similarly, after precipitation of the non-HDL fraction.

Dietary assessment

The participants indicated on a checklist all of the foods and beverages that they consumed more than once a month during the preceding year. The completed checklist formed the basis of an interview at the study center by a trained dietitian, who used a validated, semiquantitative food-frequency questionnaire (24). In two-thirds of the dietary interviews, a computerized version of the questionnaire was used, which included data checks. Participants quantified their habitual tea intake as the number of cups ingested per day, week, or month. One cup of tea was considered to equal 125 mL. Only the intake of black tea was assessed because this type of tea is predominantly consumed in the Netherlands. Intakes of total energy, macronutrients, and a large number of micronutrients were calculated from the food data with the use of Dutch food-composition tables (25). The total intake (mg/d) of the flavonols quercetin, kaempferol, and myricetin was computed with the use of published tables by Hertog et al (26, 27). Tea is a major source of flavonoids, <10% of which are flavonols (28, 29).

Follow-up procedures

The present analysis is based on follow-up data collected from baseline (1990–1993) until 31 December 1997. Information on the vital status of the participants was obtained at regular intervals from the municipal population registry. Informed consent for collection of follow-up data from the participants' general practitioners was obtained for 7751 participants of the Rotterdam Study (97%). Fatal and nonfatal events were reported by the general practitioners in the research area (covering 85% of the cohort) by means of a computerized system. All reported events were verified by research physicians who collected information from the patients' medical records at the general practitioners' offices. The information also included copies of discharge letters for hospital admissions of interest. The fatal and nonfatal events were coded independently by 2 research physicians according to the *International Statistical Classification of Diseases and Related Health Problems,* 10th revision (ICD-10) (30). If there was disagreement between reviewers, consensus was reached in a separate session. A medical expert in the field subsequently reviewed the coded events and his or her decision was considered definite if there were discrepancies. Myocardial infarctions included fatal and nonfatal incident events with an ICD-10 code I21. In the case of recurrent myocardial infarctions during follow-up, the first event was used in the analysis. A myocardial infarction was considered fatal if death occurred within 28 d after the onset of symptoms.

Study population

A total of 6521 independently living subjects attended the study center at baseline (82% of the Rotterdam Study cohort) and were eligible for a dietary interview. Diet could not be assessed in 271 participants of the pilot phase of the Rotterdam Study. Additionally, 122 subjects suspected of dementia were not interviewed because of expected difficulties in dietary recall, nor were a random group of 481 subjects because of logistic reasons. The dietitian considered 212 dietary reports unreliable, which were ultimately excluded. Dietary data were thus available for 5435 subjects, who had given informed consent for collection of follow-up data. We excluded 628 subjects with a self-reported history of myocardial infarction, which was verified with an electrocardiogram, who might intentionally have changed their diet. Thus, a total of 4807 subjects comprised the present analysis.

Data analysis

Data were analyzed by using SPSS version 10.0.5 for WINDOWS (SPSS Inc, Chicago). Age- and sex-adjusted partial correlations of tea and flavonoid intakes with lifestyle factors and nutrient intakes were computed to identify potential confounders.

The risk of myocardial infarction with tea intake was estimated by Cox regression analysis with adjustment for age and sex. Associations were obtained separately for total, nonfatal, and fatal myocardial infarction. Survival time was calculated as the number of days from entry into the study until the time of the first myocardial infarction, the time until death, or until 31 December 1997, whichever came first. Tea intake was first entered continuously into the survival model, forcing a linear relation. Subsequently, tea intake was classified on the basis of the frequency distribution of the variable, yielding categories of 0 mL (reference), 1–375 mL (median: 250 mL), and >375 mL (median: 500 mL). The relative risks (RRs) and 95% CIs were obtained by category of tea intake. The same procedure was followed to calculate RRs in tertiles of flavonoid intake (total of quercetin, kaempferol, and myricetin intakes); the RR of a first myocardial infarction was calculated according to 3 categories of flavonoid intake: <22.8, 22.8–32.9, and >32.9 mg/d.

The analyses of tea and flavonoid intakes were repeated in a multivariate model adjusted for age, sex, body mass index, smoking status (current, former, never), pack-years of cigarette smoking (ie, the average number of packs of cigarettes smoked per day × the number of years smoked) for current and former smokers, education level [low (primary education), intermediate (secondary general or vocational education), or high (higher vocational education, university)], and daily intakes of alcohol (0, >0–5, >5–10, >10–20, and >20 g/d), coffee (mL), polyunsaturated fat (g), saturated fat (g), fiber (g), vitamin E (mg), and total energy (kJ). Stratified analyses were performed according to sex. Data were also analyzed separately for current, former, and never smokers to examine in more detail the role of confounding by smoking. In addition, the interaction of tea or flavonoid intake with smoking in determining the risk of myocardial infarction was examined by adding interaction terms to the model.

The possibility that preexisting illness, which could be related to dietary changes, influenced the risk estimates was examined in an analysis in which data from the first year of follow-up were discarded for all subjects. A total of 52 subjects with an early myocardial infarction were not included in this analysis. Finally, we investigated whether serum HDL or total cholesterol could be intermediary factors in the relation of tea intake with cardiac events by adding these variables to the survival model and examining the changes in risk estimates. Similarly, potential intermediary roles of blood pressure and diabetes mellitus were examined.

RESULTS

The study population comprised 1836 men and 2971 women with a mean (±SD) age of 67.4 ± 7.8 y; 84% of the men and 90% of the women were tea drinkers. The mean daily intake of tea in

TABLE 1
General characteristics of 4807 Dutch participants in the Rotterdam Study, by categories of tea intake

	Tea intake			
	0 mL/d (n = 583)	1–375 mL/d (n = 2340)	>375 mL/d (n = 1884)	Unadjusted P[1]
Men (%)	50.4	42.7	29.0	<0.001
Age (y)	64.2 ± 6.7[2]	66.7 ± 7.1	69.2 ± 7.7	<0.001
BMI (kg/m^2)	26.5 ± 3.9	26.3 ± 3.4	26.2 ± 3.7	0.15
Smoking status (%)				<0.001
Current	46.6	23.9	15.4	
Former	35.8	43.2	40.7	
Never	17.6	32.9	44.0	
Educational level (%)[3]				0.024
Low	32.7	34.7	34.2	
Intermediate	51.1	54.0	54.9	
High	16.2	11.3	10.9	
Blood pressure (mm Hg)				
Systolic	135.1 ± 20.2	138.3 ± 22.5	140.0 ± 21.9	<0.001
Diastolic	74.5 ± 10.9	74.1 ± 11.2	73.1 ± 11.3	0.005
Serum cholesterol (mmol/L)				
Total	6.7 ± 1.2	6.7 ± 1.2	6.6 ± 1.2	0.082
HDL	1.4 ± 0.3	1.4 ± 0.4	1.4 ± 0.4	0.045
Diabetes mellitus	8.7	8.3	9.0	0.71

[1] Unadjusted P value for linear trend test (continuous variables) or P value from chi-square test (discrete variables). After adjustment for age and sex, tea intake was significantly inversely associated with BMI, smoking status, and serum total cholesterol, and significantly positively associated with education level.
[2] $\bar{x}$ ± SD.
[3] Low, primary education; intermediate, secondary general or vocational education; high, higher vocational education, university.

the total population was 371 ± 257 mL, or ≈3 cups. The mean intake of flavonoids was 28.6 ± 12.3 mg/d. The general characteristics of the study population by categories of tea intake are presented in **Table 1**. After adjustment for age and sex, tea intake was significantly inversely associated with body mass index, smoking status, and serum total cholesterol and significantly positively associated with education level.

The dietary intakes of the participants are shown in **Table 2** by categories of tea intake. A significant association of tea with all dietary intakes was observed after adjustment for age, sex, and total energy. Intakes of flavonoids and tea were strongly correlated (r = 0.81, P < 0.001). The proportions of tea drinkers in consecutive tertiles of flavonoid intake (<22.8, 22.8–32.9, and >32.9 mg/d) were 69%, 95%, and 99%, respectively.

The study had a mean follow-up of 5.6 ± 1.3 y and consisted of 26733 person-years. The incidence of myocardial infarction was 8.3/1000 person-years in men (n = 1836 persons and 84 events) and 3.7/1000 person-years in women (n = 2971 persons and 62 events) free of myocardial infarction at baseline. Thirty subjects experienced a fatal myocardial infarction and 475 subjects died from other causes during follow-up. In the study of the age- and sex-adjusted linear association of tea drinking with incidence of myocardial infarction, a 8.2% risk reduction was observed per 100-mL increase in tea intake (P = 0.02; data not shown). After adjustment for body mass index, smoking status, alcohol intake, education level, and dietary factors, the association was attenuated to a 6.2% risk reduction per 100-mL increase in tea intake (P = 0.09).

The RRs of a first myocardial infarction by categories of tea intake are shown in **Table 3**. The incidence of myocardial infarction was inversely associated with tea intake after adjustment for age and sex; the RR was 0.51 (95% CI: 0.30, 0.84) for intakes >375 mL/d (≈3 cups/d) compared with an intake of 0 mL/d. After additional adjustment for body mass index, smoking status, pack-years of cigarette smoking, education level, and daily intakes of alcohol, coffee, polyunsaturated fat, saturated fat, fiber, vitamin E, and total energy, the association of tea intake with all incident myocardial infarctions was attenuated in the upper category of tea intake (RR: 0.57; 95% CI: 0.33, 0.98). Further adjustment for dietary intakes of riboflavin (mg/d), vitamin B-6 (mg/d), vitamin C (mg/d), β-carotene (mg/d), bread (g/d), vegetables (g/d), and fruit (g/d) did not change the results. Tea drinking was related both to nonfatal and to fatal myocardial infarctions, but only the association with fatal events in the upper category of tea intake was significant (RR: 0.30; 95% CI: 0.09, 0.94).

The RRs of a myocardial infarction (fatal or nonfatal) by tea intake were no longer significant when the analysis was stratified by sex. In women, the RR was 0.71 (95% CI: 0.32, 1.60) for intakes ≤375 mL/d and was 0.46 (95% CI: 0.19, 1.10) for intakes >375 mL/d. In men, the RR was 0.76 (95% CI: 0.41, 1.40) for intakes ≤375 mL/d and was 0.61 (95% CI: 0.30, 1.26) for intakes >375 mL/d, but the interaction term of tea and sex was not significant. The inverse association of tea drinking with myocardial infarction was more pronounced in current smokers [n = 1114 and 38 events; RR of 0.58 (95% CI: 0.27, 1.24) and 0.47 (0.17, 1.47)] than in former smokers [n = 2000 and 72 events; RR of 0.74 (0.35, 1.56) and 0.50 (0.22, 1.14)] or never smokers [n = 1693 and 36 events; RR of 1.22 (0.28, 5.33) and 0.87 (0.19, 3.95)] in the mid and upper categories of tea intake, respectively. The interaction term for tea intake and smoking status was not significant in the multivariate model. The reduction in risk of myocardial infarction with increasing tea intake remained essentially unchanged after the exclusion of data for 52 subjects who had a myocardial infarction or who died within 1 y of follow-up [multivariate RR: 0.77 (0.45, 1.30) and 0.59 (0.33, 1.06) in the mid and upper categories of tea intake, respectively].

TABLE 2
Daily dietary intakes of 4807 Dutch participants in the Rotterdam Study, by categories of tea intake

	Tea intake			
	0 mL/d (n = 583)	1–375 mL/d (n = 2340)	>375 mL/d (n = 1884)	Unadjusted P[1]
Median tea intake (mL)	0.0	250.0	500.0	
Alcohol intake				
(%)	82.8	80.3	77.9	<0.001
(g)[2]	19.3 ± 22.3[3]	13.2 ± 15.7	10.2 ± 12.8	<0.001
Coffee intake				
(%)	98.5	98.2	95.4	<0.001
(mL)[4]	655.9 ± 309.0	497.4 ± 208.2	439.9 ± 188.2	<0.001
Dietary intake				
Total energy (kJ/d)	8335 ± 2435	8281 ± 2125	8171 ± 1955	0.047
Riboflavin (mg/d)	1.64 ± 0.61	1.56 ± 0.54	1.52 ± 0.47	<0.001
Vitamin B-6 (mg/d)	1.56 ± 0.46	1.56 ± 0.41	1.61 ± 0.37	<0.001
Vitamin C (mg/d)	115.3 ± 53.8	119.2 ± 54.2	124.1 ± 53.6	<0.001
Vitamin E (mg/d)	13.1 ± 5.8	13.8 ± 6.3	13.9 ± 6.0	0.033
Flavonoids (mg/d)[5]	14.8 ± 8.1	24.1 ± 7.9	38.5 ± 10.2	<0.001
β-Carotene (mg/d)	1.56 ± 1.01	1.50 ± 0.65	1.56 ± 0.76	0.30
Fiber (g/d)	16.5 ± 5.8	16.6 ± 5.0	17.0 ± 5.0	0.006
Polyunsaturated fat (g/d)	15.0 ± 7.7	15.3 ± 7.8	15.0 ± 11.3	0.38
Saturated fat (g/d)	32.4 ± 12.9	32.1 ± 11.8	31.5 ± 7.6	0.12
Total fat (g/d)	81.8 ± 30.1	81.1 ± 27.5	79.3 ± 26.0	0.019

[1] Unadjusted P value for linear trend (continuous variables) or P value from chi-square test (discrete variables). After adjustment for age, sex, and total energy intake, tea intake was significantly positively associated with intakes of vitamin B-6, vitamin C, vitamin E, flavonoids, β-carotene, fiber, polyunsaturated fat and significantly inversely associated with intakes of riboflavin, alcohol, coffee, saturated fat, and total fat.
[2] Computation includes data only from subjects who drank alcohol.
[3] $\bar{x}$ ± SD.
[4] Computation includes data only from subjects who drank coffee.
[5] Total of quercetin, kaempferol, and myricetin.

Dietary flavonoids were nearly significantly related to the risk of myocardial infarction, with a 12.7% reduction in risk per 10-mg increase in daily flavonoid intake after adjustment for age and sex (P = 0.07; data not shown). Further adjustment for confounders attenuated the risk reduction to 9.0% per 10-mg increase in flavonoid intake, which was no longer significant. The RRs of myocardial infarction by tertiles of flavonoid intake are shown in **Table 4**. For all incident cases of myocardial infarction, a nonsignificant inverse association was observed in the middle (RR: 0.74; 95% CI: 0.49, 1.11) and upper (RR: 0.76; 95% CI: 0.49, 1.18) tertiles of flavonoid intake. In a separate analysis of the risk of nonfatal and fatal myocardial infarctions in relation to flavonoid intake, a nearly significant association, was observed only for fatal events in a comparison of the middle (RR: 0.42; 95% CI: 0.17, 1.06) and upper (RR: 0.35; 95% CI: 0.13, 0.98) tertiles with the lower tertile.

TABLE 3
Relative risk (RR) of a first myocardial infarction in 4807 Dutch participants in the Rotterdam Study, by categories of tea intake

	Tea intake		
	0 mL/d	1–375 mL/d	>375 mL/d
Median tea intake (mL/d)	0.0	250.0	500.0
Number of subjects	583	2340	1884
Follow-up time (person-years)	3277	12990	10588
All incident myocardial infarctions			
Number of events	24	77	45
RR, age- and sex-adjusted model	1	0.72 (0.49, 1.13)[1]	0.51 (0.30, 0.84)
RR, multivariate model[2]	1	0.77 (0.48, 1.25)	0.57 (0.33, 0.98)
Nonfatal myocardial infarctions			
Number of events	18	61	57
RR, age- and sex-adjusted model	1	0.80 (0.47, 1.36)	0.62 (0.35, 1.11)
RR, multivariate model[2]	1	0.84 (0.49, 1.47)	0.68 (0.37, 1.26)
Fatal myocardial infarction			
Number of events	6	16	8
RR, age- and sex-adjusted model	1	0.47 (0.18, 1.23)	0.24 (0.08, 0.72)
RR, multivariate model[2]	1	0.58 (0.22, 1.57)	0.30 (0.09, 0.94)

[1] 95% CI in parentheses. Values obtained with a Cox proportional hazards analysis.
[2] Model adjusted for age, sex, BMI, smoking status, pack-years of cigarette smoking, education level, and daily intakes of alcohol, coffee, polyunsaturated fat, saturated fat, fiber, vitamin E, and total energy.

TABLE 4
Relative risk (RR) of a first myocardial infarction in 4807 Dutch participants in the Rotterdam Study, by tertiles of flavonoid intake

	Tertile of flavonoid intake		
	Lower (<22.8 mg/d)	Middle (22.8–32.9 mg/d)	Upper (>32.9 mg/d)
Median flavonoid intake (mg/d)	16.8	27.5	40.0
Number of subjects	1602	1603	1602
Follow-up time (person-years)	8851	8909	8973
All incident myocardial infarctions			
Number of events	62	43	41
RR, age- and sex-adjusted model	1	0.69 (0.47, 1.02)[1]	0.68 (0.46, 1.02)
RR, multivariate model[2]	1	0.74 (0.49, 1.11)	0.76 (0.49, 1.18)
Nonfatal myocardial infarctions			
Number of events	45	36	35
RR, age- and sex-adjusted model	1	0.81 (0.52, 1.26)	0.83 (0.53, 1.30)
RR, multivariate model[2]	1	0.85 (0.54, 1.34)	0.93 (0.57, 1.52)
Fatal myocardial infarction			
Number of events	17	7	6
RR, age- and sex-adjusted model	1	0.38 (0.16, 0.93)	0.33 (0.13, 0.83)
RR, multivariate model[2]	1	0.42 (0.17, 1.06)	0.35 (0.13, 0.98)

[1] 95% CI in parentheses. Values obtained with a Cox proportional hazards analysis.
[2] Model adjusted for age, sex, BMI, smoking status, pack-years of cigarette smoking, education level, and daily intakes of alcohol, coffee, polyunsaturated fat, saturated fat, fiber, vitamin E, and total energy.

An inverse relation of dietary flavonoid intake with incident myocardial infarction was observed in women in the middle (RR: 0.53; 95% CI: 0.28, 1.00) and upper (RR: 0.59; 95% CI: 0.31, 1.14) tertiles of intake, which was nearly significant. In men, however, dietary flavonoid intake was not associated with incident myocardial infarction in the middle (RR: 0.92; 95% CI: 0.54, 1.56) and upper (0.95; 95% CI: 0.52, 1.76) tertiles. The interaction term for flavonoid intake and sex was not significant in the multivariate model. A subgroup analysis according to smoking status yielded nonsignificantly different RRs of myocardial infarction by flavonoid intake (data not shown).

A repeat of the analyses of tea and flavonoid intakes after adjustment for serum HDL and total cholesterol, systolic and diastolic blood pressures, or diabetes mellitus did not change the results significantly, indicating no strong intermediary roles for these indexes.

DISCUSSION

We observed significant inverse associations of tea and flavonoid intakes with incident myocardial infarction in the general Dutch population. The reductions in risk were strongest for fatal events.

Tea drinking in Western populations is generally associated with a healthy lifestyle and diet. In the present study, tea intake was higher in lean, educated people who smoked less and consumed a relatively healthy diet. The risk reductions for myocardial infarction were attenuated after adjustment for lifestyle and dietary confounders, which indicates that diet and lifestyle explain part of the protective effect of tea. Although the observed associations were strong, residual confounding could not be excluded. Smoking was associated with tea and flavonoid intakes and is a strong risk factor for myocardial infarction. The association of tea intake, but not of flavonoid intake, with myocardial infarction was weaker in nonsmokers than in smokers. This finding suggests that smoking, despite adjustment for smoking status and pack-years of cigarette smoking, caused some residual confounding of the risk estimates. An alternative explanation for the differences in RRs between smokers and nonsmokers is that smokers have a greater need for flavonoids (and other antioxidants) because of the vascular damage caused by smoking. The study lacked the power to examine separately the risk of fatal myocardial infarction with tea intake in categories of smoking.

Unfortunately, data on physical activity were not collected during the baseline survey of the Rotterdam Study; therefore, we could not adjust for it. However, we adjusted for total energy intake, which is closely related to energy expenditure, and lifestyle factors such as smoking and alcohol intake. Adjustment for these correlates of physical activity removed some of the confounding, but it is possible that residual confounding remained. Serum HDL-cholesterol, which is favorably affected by physical activity (31), did not differ significantly by categories of tea intake after adjustment for age and sex. Therefore, we believe that physical activity was not a strong confounder in our cohort. Prevalent illness should be taken into account when studying the effect of diet on incident disease or mortality because dietary changes resulting from clinical or subclinical disease could lead to biased risk estimates. For this reason, we excluded subjects with a history of myocardial infarction at baseline. Additional exclusion of subjects with a nonfatal myocardial infarction or fatal event within 1 y of follow-up yielded nonsignificantly different risk estimates.

Flavonoids have been shown to protect against the oxidation of LDL in vitro, to inhibit platelet aggregation, to reduce inflammatory processes, and to improve vascular function (6–17). Black tea contains substantial concentrations of the flavonols quercetin (10–25 mg/L), kaempferol (7–17 mg/L), and myricetin (2–5 mg/L) (26). Regrettably, we could not examine the potential cardioprotective effect of catechins and polyphenols, which are also abundant in tea (28, 29). In men in the Zutphen Elderly Study, tea drinkers had a risk of 5-y mortality from ischemic heart disease that was >50% lower than that of nontea drinkers (1), which is comparable with our findings. No association between tea intake and ischemic heart disease was observed in the Health Professionals Follow-up Study of men, who were on average 10 y younger than our study participants (4). Tea accounted for 25%

of the flavonoid intake in the Health Professionals Study, whereas tea intake accounted for >50% of the flavonoid intake in our study. In the Caerphilly Study of Welsh men aged 45–79 y, no protective effect of tea against ischemic heart disease was observed (5). It was later suggested that residual confounding by socioeconomic status blurred the association of tea with ischemic heart disease in the Caerphilly Study (32).

Tea and flavonoid intakes were predominantly related to fatal myocardial infarctions; the relation with nonfatal events was weak or absent in our study. Also, in the Zutphen Elderly Study the RR of mortality from ischemic heart disease was stronger than that of incident myocardial infarction, which included nonfatal events (1). The Finnish study by Knekt et al (2) showed strongly reduced risks of mortality from ischemic heart disease in subjects with a high flavonoid intake. However, no such relation was observed in the Health Professionals Study, in which nonfatal myocardial infarction was the outcome of interest (4). Possibly, subjects with a fatal event had more severe atherosclerosis than did those with no fatal event. In the cohort of the Rotterdam Study, we showed a strong inverse association of tea intake with severe aortic calcification, whereas no association with mild atherosclerosis was observed (20). Our findings suggest that the severity of underlying cardiovascular disease may modify the relation of flavonoids with coronary events. It is also possible that flavonoids (together with other antioxidants) reduce oxidative stress and prevent excess damage after ischemia, thereby increasing the chance of recovery from a myocardial infarction. Furthermore, flavonoids could be involved in thrombotic processes that may influence the severity of a coronary event (13, 14). Unfortunately, we cannot conclude from our observational data which of the above mechanisms, if any, accounted for the discrepant findings on fatal and nonfatal myocardial infarctions.

In our previous study of the relation between tea intake and aortic atherosclerosis in the Rotterdam Study, we observed a strong inverse relation in women (20). In the present study we observed a strong inverse relation between tea intake and incident myocardial infarction, and the relation was stronger in women than in men. For flavonoid intake, a strong relation with incident myocardial infarction was observed only in women, which raises the hypothesis that flavonoids act not only as antioxidants or antithrombogenic factors but possibly also as phytoestrogens. An estrogenic effect of kaempferol, present in tea, was shown previously in vitro (33). In the female participants of the Rotterdam Study, we found a positive association of tea drinking with prolactin secretion, which was used as a bioassay of estrogenic activity (34). Another study in women showed a positive association of tea intake with bone mineral density, which is known to be strongly influenced by estrogenic activity (35). The structure of flavonoids shows similarities to that of isoflavones in soy (33, 36), for which beneficial cardiovascular actions have been reported (37). However, the flavonoids in tea are less potent estrogenic compounds than are isoflavones in vitro. More research is needed to assess whether the estrogenic activity of tea is biologically important to the human body.

In conclusion, our findings suggest a protective effect of tea and flavonoid intakes against myocardial infarction. The underlying biological mechanisms for this effect and the potential role of tea flavonoids in cardiovascular disease prevention deserve further study.

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