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Higher Dietary Flavonol Intake Is Associated with Lower Incidence of Type 2 Diabetes[1,2]

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Abstract

Substantial experimental evidence suggests that several flavonoid classes are involved in glucose metabolism, but few clinical or epidemiologic studies exist that provide supporting human evidence for this relationship. The objective of this study was to determine if habitual intakes of specific flavonoid classes are related to incidence of type 2 diabetes (T2D). We followed 2915 members of the Framingham Offspring cohort who were free of T2D at baseline from 1991 to 2008. Diabetes was defined by either elevated fasting glucose (≥7.0 mmol/L) or initiation of hypoglycemic medication during follow-up. Dietary intakes of 6 flavonoid classes and total flavonoids were assessed using a validated, semiquantitative food frequency questionnaire. We observed 308 incident cases of T2D during a mean follow-up period of 11.9 y (range 2.5–16.8 y). After multivariable adjusted, time-dependent analyses, which accounted for long-term flavonoid intake during follow-up, each 2.5-fold increase in flavonol intake was associated with a 26% lower incidence of T2D [HR = 0.74 (95% CI: 0.61, 0.90); *P*-trend = 0.003] and each 2.5-fold increase in flavan-3-ol intake was marginally associated with an 11% lower incidence of T2D [HR = 0.89 (95% CI: 0.80, 1.00); *P*-trend = 0.06]. No other associations between flavonoid classes and risk of T2D were observed. Our observations support previous experimental evidence of a possible beneficial relationship between increased flavonol intake and risk of T2D. J. Nutr. 143: 1474–1480, 2013.

Introduction

Type 2 diabetes (T2D) is a largely preventable condition with serious health consequences, including a greater risk of heart disease, stroke, peripheral neuropathy, renal disease, and vision loss (1). Over the past 2 decades, the prevalence of T2D has increased dramatically worldwide due largely to an increase in obesity (2–7). Global estimates predict a continued growth in worldwide diabetes prevalence for the foreseeable future (8).

It is well established that diet, even independent of body weight, can influence the risk of T2D (9–11). Vegetables and fruits are notable components of diets associated with lower risk of T2D (9–14). Plant foods are not only good sources for nutrients associated with lower T2D risk, such as fiber (15), potassium (16), and magnesium (17), but they also provide a large array of other bioactive compounds, such as the polyphenols (18). These constitute the largest class of dietary phytochemicals, with intakes of >1 g/d reported (19,20).

There is growing evidence based on in vitro and animal research that polyphenols in general, and in particular the flavonoids, a class of polyphenols, can improve glucose homeostasis and enhance insulin secretion and sensitivity (21–25). Although there are relatively few clinical studies that examined the effect of flavonoid interventions in humans on glucose homeostasis and insulin resistance, a recent systematic review of cocoa trials showed that cocoa/chocolate interventions improved insulin resistance (HOMA-IR) due a significant reduction in insulin concentrations (26). To date, the limited epidemiologic studies relating flavonoid intake to T2D risk have been inconsistent (27–30). The lack of consistent findings may in part be based on the use of incomplete flavonoid databases in earlier epidemiologic studies (31) and the possibility that each flavonoid classes may exert specific biological effects, resulting in distinct impacts on health for the different classes (31,32).

The purpose of the present study was to examine in a well-characterized, clinically examined population the hypothesis that higher intakes of 3 flavonoid classes, specifically the flavonols, flavan-3-ols, and anthocyanins, are associated with a lower incidence of T2D whereas other flavonoid classes are not.

Subjects and Methods

Study design and population

The study participants were members of the Framingham Heart Study Offspring cohort. The original Framingham Heart Study began in 1948

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with 5209 adults aged 28–62 y residing in Framingham, a town west of Boston, Massachusetts (33) and has continued for more than 60 y, with the survivors returning every 2 y for a physical examination and to complete a series of questionnaires and laboratory and cardiovascular tests. By 1971, the original cohort included 1644 husband-wife pairs and 378 individuals who had developed cardiovascular disease (CVD). The offspring of these individuals and the offspring's spouses were invited to form the Offspring cohort, and 5135 of the 6838 eligible individuals participated in the first Framingham Offspring Study examination (34). The Offspring cohort undergoes repeat examination approximately every 3–4 y. For the present study, we used data derived from the 5th, 6th, 7th, and 8th study examinations, which spanned 17 y (1991–2008). The 5th examination served as the baseline for these analyses.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki. All procedures involving human participants were approved by the Boston University Medical Center Institutional Review Board and the present ancillary study was approved by the Tufts Medical Center Institutional Review Board.

Measurements

Assessment of flavonoid intakes. Dietary intakes were assessed using the Harvard semiquantitative FFQ (35) at the 5th, 6th, and 7th examinations. The FFQ consists of a list of foods with a standard serving size and a selection of 9 frequency categories ranging from never or <1 serving/mo to ≥6 servings/d. Participants were asked to report their frequency of consumption of each food item during the past year. Dietary information was judged as unreliable and excluded from further study if reported energy intakes were <600 kcal/d or >4000 kcal/d for women and >4200 kcal/d for men or if >12 food items were left blank.

The flavonoid database used for the FFQ was previously described (36) and was primarily derived from the USDA flavonoid content of foods and the proanthocyanidin databases (37,38). The same flavonoid database was used for all study examinations. We used the flavonoid classification of Cassidy et al. (36) (**Table 1**) to define 6 flavonoid classes. Total flavonoids were defined as the sum of all 6 classes. We did not evaluate isoflavone intakes, because habitual intakes are very low in the U.S. diet (39–42).

The validity of flavonoid intake from the Harvard FFQ has not been directly assessed, but the validity for the food intake based on a comparison of the FFQ and two 7-d diet records collected during the year time interval covered by the FFQ was previously published (43). This validation demonstrated relatively high correlation coefficients between intakes from the FFQ and diet records for the major dietary sources of flavonoids in the Framingham Offspring cohort, including apples/pears (0.70), bananas (0.95), oranges (0.76), orange juice (0.78), strawberries (0.38), muffins (0.66), tea (0.77), and red wine (0.83). The correlation for blueberries was not presented.

Assessment of incident diabetes. Presence of diabetes was based on elevated fasting glucose concentrations and/or a medical and medication use history obtained by a physician at each study examination. We defined diabetes at the baseline examination as a fasting plasma glucose concentration ≥7.0 mmol/L, a 2-h oral glucose tolerance test glucose concentration ≥11.1 mmol/L, or current use of hypoglycemic drug therapy. For T2D incidence, participants were followed from baseline through the 8th study examination (2005–2008). We used the examination visit date on which a new case of diabetes was identified as the date of diagnosis. We defined diabetes at follow-up as development of a fasting plasma glucose concentration ≥7.0 mmol/L or new use of hypoglycemic drug therapy during the study interval. More than 99% of diabetes cases among Framingham Offspring cohort are T2D (44). Diabetes incidence was determined without knowledge of flavonoid intake or any other dietary information.

Assessment of covariates. Covariates used in our analyses included age at the 5th study examination, BMI, waist circumference, physical activity, current smoking (y/n), prevalent CVD (y/n), and intakes of energy, dietary fiber, potassium, magnesium, meat and processed meat, and fruits and vegetables. The criteria for the diagnoses of cardiovascular events have been described elsewhere (45). BMI was calculated as body weight in kilograms divided by the square of height in meters using examiner-assessed weight and height. Waist circumference was measured to the nearest 0.25 inch (0.635 cm) at the level of the umbilicus. Physical activity level was assessed using a physical activity index based on time spent performing the activity in a typical day and the intensity of the activity (46). We considered not only fruit and vegetable intake but also some of the potentially bioactive compounds of fruit and vegetables, including dietary fiber, potassium, and magnesium, which are related to T2D incidence (15–17) as potential confounders. We also adjusted for meat and processed meat, which have been suggested in some studies as increasing T2D risk (47–50). Meat included chicken, turkey, hamburger, liver, and beef, pork, or lamb as a mixed or main dish. Processed meat included hot dogs, bacon, sausage, salami, and other processed meats.

Statistical methods

We used a time-dependent approach to the statistical analyses in which flavonoid intake data were updated at each exam as the mean of intakes from all previous exams. For example, events at the 6th examination were related to intake at the 5th examination, events at the 7th examination were related to the mean of the intakes from the 5th and 6th examinations, and events at the 8th examination were related to the mean of the intakes from the 5th, 6th, and 7th examinations. If participants were missing intake data at one of the follow-up examinations, the mean intake was based on the available intake data. Those who had data missing at baseline or 2 consecutive follow-up examinations prior to the development of T2D or the end of follow-up were excluded from analyses. The natural logarithms of the different flavonoid class intakes were used as the exposure variables. Our outcome was incident T2D. The time-dependent covariates (BMI, smoking, and prevalent CVD) were updated at each examination and all dietary covariates, like the flavonoid intakes, were updated as a cumulative mean.

HRs derived from Cox proportional hazards regression models (SAS PROC PHREG) were used to characterize the prospective associations between flavonoid intakes and incidence of T2D. Because flavonoid intakes were transformed using a natural logarithm, the HRs represent the risk for a relative difference in flavonoid intake. We presented HRs for a 2.5-fold difference in flavonoid intake, which approximated the smallest relative difference between the 75th and 25th percentile values for intake of the individual flavonoid classes across study examinations (**Table 2**).

We considered 3 different models based on inclusion of covariates, each adding covariates to the prior model: *1*) an age- and sex-adjusted

TABLE 1 Classification of flavonoids

Flavonoid class	Flavonoid compounds
Flavonols	Quercetin, kaempferol, myricetin, isohamnetin
Flavones	Luteolin, apigenin
Flavanones	Eriodictyol, hesperetin, naringenin
Flavan-3-ols	Catechin, gallocatechin, epicatechin, epigallocatechin, epicatechin 3-gallate, epigallocatchin 3-gallate
Anthocyanins	Cyanidin, delphinidin, malvidin, pelargonidin, petunidin, peonidin
Polymeric flavonoids	Proanthocyanidins (dimers, trimers, 4–6 mers, 7–10 mers, polymers, excluding monomers), theaflavins, thearubigins

TABLE 2 Flavonoid intake for members of the Framingham Heart Study Offspring cohort at 5th through 7th examinations[1]

Flavonoid class	Exam 5 (1991–1995)	Exam 6 (1995–1998)	Exam 7 (1998–2001)
	mg/d	*mg/d*	*mg/d*
Flavonols	10.6 (6.6,16.4)	10.9 (6.9, 16.5)	10.9 (7.1, 16.5)
Flavones	1.6 (0.8, 2.5)	1.8 (0.9, 2.7)	2.0 (0.9, 2.8)
Flavanones	33.8 (10.5, 61.0)	38.9 (11.8, 62.6)	38.3 (11.6, 62.2)
Flavan-3-ols	21.8 (11.8, 49.4)	22.5 (12.3, 49.3)	23.4 (12.6, 51.5)
Anthocyanins	9.0 (3.4, 17.2)	10.1 (3.6, 18.1)	12.4 (3.9, 20.0)
Polymeric flavonoids	114 (60, 222)	116 (62, 225)	123 (64, 238)
Total flavonoids[2]	210 (124, 368)	214 (132, 379)	225 (136, 386)

[1] Values are medians (25th, 75th percentiles), n = 2915.
[2] Total flavonoid intakes exclude isoflavones, which were not measured in this study.

model (model 1); 2) model 1 with additional adjustment for BMI and energy intake, prevalence of CVD, current smoking (model 2); and 3) model 2 with additional adjustment for fruit and vegetable intake (model 3). Secondary analyses included mutual adjustment of the intakes from the different flavonoid classes. Additional secondary analyses included adjustment for dietary factors previously demonstrated to be associated with T2D risk and potentially correlated with flavonoid intake, including potassium, magnesium, fiber, and meat and processed meat, and waist circumference and physical activity.

To examine the relation between the top food sources of the flavonoids and T2D risk, we identified all foods that contributed at least 10% of the intake of each flavonoid classes for one or more of the study examinations and related servings of these foods to T2D incidence. We classified food intake into 4 categories (<1 serving/wk, 1–4 servings/wk, 5–6 servings/wk, and ≥7 servings/wk) and applied the same time-dependent analysis approach using Cox proportional hazards regression that was described above for the flavonoids. A test for trend across food serving categories was based on assigning the median servings in each category to individuals in that category and treating that resulting variable as a continuous variable in the regression models.

All analyses were performed using SAS version 9.2 (SAS Institute). $P < 0.05$ was considered significant.

Results

Of the 3799 Offspring cohort members who attended the 5th examination, baseline for the present analysis, 346 individuals who had diabetes were excluded. In addition, participants who were missing data on diet (n = 333) or age, BMI, or smoking status (n = 16) at the 5th study examination and participants who were missing dietary data at baseline or 2 consecutive follow-up examinations prior to diagnosis of T2D or the end of follow-up (n = 189) were excluded. The time-dependent analysis using cumulative mean flavonoid intake was based on 2915 participants with 308 events during a mean follow-up period of 11.9 y (range 2.5–16.8 y).

Table 2 displays the median and 25th and 75th percentile values for intake of the different flavonoid classes (mg/d). Total flavonoid intakes increased modestly over time, driven largely by increased intakes of anthocyanins and polymeric flavonoids. There was a wide range of intakes for all flavonoid classes. This can be seen using the ratio of the 75th and 25th percentile values for the different flavonoid classes. This ratio ranged from 2.3-fold for flavonol intake at the 7th examination to 5.8-fold for flavanone intake at the 5th examination. These data indicate that the flavonoid intakes for the quarter of the population with the highest intakes exceeded the intake of those in the lowest quarter of the population by at least 2.3-fold for all flavonoid classes.

The mean age at baseline was 54 y old and participants were on average overweight (**Table 3**). Men constituted 46% of the sample, 19% of the sample were current smokers, and ~7% had existing CVD. There were strong associations between many of participants' characteristics and lifestyle behaviors and total flavonoid intakes. Men were much less likely to consume higher amounts of total flavonoid than were women (P-trend < 0.001). There was a modest increase in intakes with age (P-trend = 0.05) and a decrease in intakes with increasing BMI (P-trend < 0.001). Participants who were smokers and who had CVD were less likely to have higher flavonoid intakes (P-trend < 0.001 and 0.005, respectively). Energy, fruit, vegetable, fiber, potassium, and magnesium intakes were positively associated with flavonoid intakes (P-trend < 0.001), whereas meat and processed

TABLE 3 Participant characteristics of members of the Framingham Heart Study Offspring cohort across quartile categories of total flavonoid intake at baseline (5th examination)[1]

	All (n = 2915)	Q1 (n = 728)	Q2 (n = 729)	Q3 (n = 729)	Q4 (n = 729)	P-trend
Total flavonoid intake,[2] *mg/d*	210 (2, 1963)	85 (2, 124)	165 (125, 210)	272 (211, 368)	537 (369, 1963)	
Male,[3] *%*	45.5 (43.7, 47.3)	51.0 (47.4, 54.6)	49.8 (46.2, 53.4)	48.0 (44.4, 51.6)	33.3 (29.7, 36.9)	<0.001
Age, *y*	54.2 (53.8, 54.5)	53.4 (52.7, 54.1)	54.2 (53.5, 54.9)	54.6 (53.9, 55.3)	54.6 (53.9, 55.3)	0.05
BMI,[4] *kg/m²*	26.7 (26.5, 26.9)	27.2 (26.9, 27.5)	26.9 (26.6, 27.2)	26.6 (26.3, 26.9)	26.1 (25.8, 26.4)	<0.001
Current smoker, *%*	18.7 (17.3, 20.1)	30.0 (27.2, 32.8)	17.7 (14.9, 20.4)	14.7 (11.9, 17.4)	12.3 (9.5, 15.1)	<0.001
CVD, *%*	7.2 (6.3, 8.1)	9.1 (7.3, 10.9)	6.6 (4.8, 8.5)	8.0 (6.2, 9.9)	4.9 (3.1, 6.8)	0.005
Energy intake,[4] *MJ/d*	7.46 (7.38, 7.56)	6.12 (5.99, 6.26)	7.39 (7.23, 7.55)	8.05 (7.87, 8.23)	8.53 (8.34, 8.72)	<0.001
Fiber,[5] *g/d*	16.4 (16.2, 16.6)	13.5 (13.2, 13.8)	16.1 (15.8, 16.5)	18.0 (17.6, 18.4)	18.3 (17.9, 18.7)	<0.001
Potassium,[5] *g/d*	2.88 (2.85, 2.90)	2.59 (2.55, 2.63)	2.82 (2.78, 2.87)	3.05 (3.00, 3.10)	3.07 (3.03, 3.11)	<0.001
Magnesium,[5] *mg/d*	283 (281, 286)	258 (253, 263)	280 (275, 285)	298 (293, 303)	298 (293, 304)	<0.001
Vegetables,[5] *g/d*	237 (233, 241)	206 (198, 213)	233 (225, 241)	255 (246, 264)	258 (249, 268)	<0.001
Fruits,[5] *g/d*	201 (193, 209)	91 (84, 98)	220 (204, 237)	292 (271, 315)	278 (257, 300)	<0.001
Meat,[5] *g/d*	88.3 (86.1, 90.5)	92.9 (88.2, 97.8)	91.5 (87.1, 96.1)	85.3 (81.2, 89.6)	83.8 (79.7, 88.2)	0.004
Processed meat,[5] *g/d*	3.1 (2.9, 3.3)	4.5 (4.0, 5.1)	3.1 (2.7, 3.5)	2.9 (2.5, 3.3)	2.3 (2.0, 2.6)	<0.001
Cumulative diabetes incidence, *%*	10.7 (9.6–11.9)	13.1 (10.9–15.4)	10.7 (8.5–12.9)	9.6 (7.4–11.8)	9.4 (7.2–11.7)	0.08

[1] CVD, cardiovascular disease.
[2] Total flavonoid intakes exclude isoflavones, which were not measured in this study. Values are medians (min, max).
[3] Values are age- and sex-adjusted means or percents (95% CIs). Percent male was only adjusted for age and age was only adjusted for sex.
[4] Values are age- and sex-adjusted geometric means (95% CIs).
[5] Values are age-, sex-, and energy-adjusted geometric means (95% CIs).

meat intakes were inversely associated with flavonoid intakes (P-trend = 0.004 and < 0.001, respectively). Age- and sex-adjusted total flavonoid intake, based on only baseline values, was inversely associated with cumulative incidence of T2D (P-trend = 0.08).

In multivariable-adjusted analyses, we observed a significant inverse association between flavonol intakes and T2D incidence (**Table 4**). These time-dependent analyses, which accounted for long-term flavonoid intake during the follow-up period, demonstrated that a 2.5-fold higher intake of flavonols was association with a 26% lower incidence of T2D [HR = 0.74 (95% CI: 0.61, 0.90); P-trend = 0.003]. We also observed a marginally significant inverse association between flavan-3-ol intake and T2D risk after multivariable adjustment [HR = 0.89 (95% CI: 0.80, 1.00); P-trend = 0.06). No other associations between intakes of other flavonoid classes or total flavonoids and risk of T2D were observed after multivariable adjustment. Further adjustment for fruit and vegetable intakes resulted in a slightly stronger association between flavonols and T2D incidence [HR = 0.68 (95% CI: 0.54, 0.86); P-trend = 0.001] but did not materially alter any of the relationships between other flavonoids and T2D risk.

In secondary analyses, we adjusted the flavonol intakes for intakes of all the other flavonoid classes and total flavonoids. The relation between flavonol intake and T2D incidence was unchanged by this adjustment, but the associations with flavan-3-ols, polymeric flavonoids, and total flavonoids were all attenuated after they were adjusted for flavonol intake. We also adjusted for dietary fiber, potassium, magnesium, meat and processed meat intakes, which had no effect on the association between flavonol intake and T2D risk. Similarly, further adjustment for dietary fiber and potassium did not affect the observed association between flavan-3-ol intake and T2D, but adjustment for meat and processed meat [HR = 0.91 (95% CI: 0.81, 1.02); P-trend = 0.11] and magnesium [HR = 0.92 (95% CI: 0.82, 1.03); P-trend = 0.15] intakes did attenuate this association. Finally, additional adjustment for waist circumference and physical activity did not materially affect our findings.

We identified the foods that were the top contributors to each of the flavonoid classes (**Table 5**). Based on the observed associations between flavonols and flavan-3-ols, we examined the associations between the foods that were the major contributors of these flavonoid classes and T2D incidence. Tea and apples/pears, the only foods contributing ≥10% of the total flavonol intake, together contributed ~30% of the flavonol intake. Tea, apples/pears, and bananas, the 3 foods that contributed ≥10% of the total flavan-3-ol intake, combined accounted for just more than 50% of flavan-3-ol intake in this population. None of these foods was individually associated with T2D risk (**Table 6**).

Discussion

In our study of a well-characterized population based on clinical examinations, we observed that higher flavonol intakes were associated with a 26% lower incidence of T2D. We also observed a marginally significant inverse association between flavan-3-ol intakes and risk of T2D, but there was no association with anthocyanin intake. None of the individual foods that were major contributors of the flavonols and flavan-3-ols were individually associated with T2D incidence. This latter observation suggests that the observed associations between the flavonols and flavan-3-ols were not a consequence of confounding by higher consumption foods that happen to be high in these flavonoids.

Results from 2 previous observational studies also suggested an inverse association between habitual flavonol intake and T2D risk. Wedick et al. (29) observed a significant inverse association between flavonol intake and T2D incidence in the Nurses' Health Study cohort (16% reduction in risk) and the Health Professionals Follow-up Study cohort (12% reduction in risk), but not in a cohort of younger women (Nurses' Health Study II) or in a pooled analyses of their 3 cohorts. Knekt et al. (27) showed a marginally significant inverse association between intakes of the flavonols quercetin and myricetin, but not kaempferol, and incidence of T2D in Finnish men and women. Earlier epidemiological studies by Nettleton et al. (28) and Song et al. (30) reported no associations between any flavonoid class and T2D risk in U.S. women, but these studies were performed before a more complete version of the flavonoid database was available. Our observation that flavonol intake was associated with a lower risk of T2D is supported by animal studies, which showed that the flavonol quercetin decreased plasma glucose concentrations, improved insulin concentrations, preserved the integrity of pancreatic B-cells, alleviated diabetic symptoms, and reduced hepatic gene expression in streptozotocin-induced diabetic models (21,51–53).

There is limited epidemiologic evidence supporting a relationship between flavan-3-ol intake and T2D risk. Wedick et al.

TABLE 4 Relation between cumulative mean flavonoid intake and diabetes incidence in members of the Framingham Heart Study Offspring cohort: time-dependent analyses[1]

	Age and sex adjusted		Multivariable model[2]		Multivariable model plus vegetable and fruit intake	
Flavonoid class	HR (CI)	P value	HR (CI)	P value	HR (CI)	P value
Flavonols	0.72 (0.60–0.87)	<0.001	0.74 (0.61–0.90)	0.003	0.68 (0.54, 0.86)	0.001
Flavones	0.90 (0.75–1.09)	0.29	0.93 (0.77–1.14)	0.50	0.99 (0.77, 1.28)	0.97
Flavanones	0.97 (0.89–1.06)	0.52	0.97 (0.89–1.07)	0.58	1.01 (0.90, 1.13)	0.86
Flavan-3-ols	0.86 (0.77–0.96)	0.006	0.89 (0.80–1.00)	0.06	0.90 (0.80, 1.01)	0.07
Anthocyanins	0.98 (0.88–1.09)	0.65	0.98 (0.88–1.10)	0.78	1.00 (0.88, 1.13)	0.98
Polymeric flavonoids	0.88 (0.78–0.99)	0.03	0.90 (0.79–1.02)	0.11	0.90 (0.79, 1.04)	0.15
Total flavonoids[3]	0.85 (0.74–0.98)	0.03	0.88 (0.76–1.02)	0.10	0.89 (0.75, 1.05)	0.17

[1] Flavonoid intakes were transformed using natural logarithms. HRs represent the difference in risk associated with a 2.5-fold increase in flavonoid intake.

[2] Multivariable model is adjusted for sex and time dependent variables age, cardiovascular disease (y/n), current smoker (y/n), BMI, and cumulative mean energy intake.

[3] Total flavonoid intakes exclude isoflavones, which were not measured in this study.

TABLE 5 Mean contributions of flavonoids from foods providing at least 10% of the total intake for each flavonoid class at one or more examination cycles for members of the Framingham Heart Study Offspring cohort

	Flavonoid class contribution		
	Exam 5	Exam 6	Exam 7
		%	
Flavonols			
Tea	17.5	17.6	17.5
Apples/pears	13.1	12.3	12.0
Flavones			
Orange juice	39.0	38.9	39.7
Oranges	12.5	12.9	11.3
Red wine	8.0	9.8	10.8
Flavanones			
Orange juice	50.1	50.1	52.6
Oranges	22.4	23.2	21.4
Flavan-3-ols			
Tea	30.7	31.3	31.5
Apples/pears	12.6	11.5	11.1
Bananas	10.3	11.2	11.4
Anthocyanins			
Muffins	21.9	18.8	16.7
Blueberries	20.1	21.5	24.9
Strawberries	14.7	14.4	14.9
Apples/pears	13.7	12.2	11.0
Red wine	9.7	12.1	13.1
Polymeric flavonoids			
Tea	25.7	26.2	26.0
Apples/pears	25.1	23.5	22.7
Total flavonoids			
Tea	22.2	22.2	22.2
Apples/pears	16.3	15.2	14.5
Orange juice	12.5	12.8	13.2

(29) observed an inverse association between flavan-3-ol intake and T2D risk in older women (Nurses' Health Study) but not in their other 2 cohorts. Two early publications that did not have access to the more complete version of the flavonoid database reported no associations between habitual flavan-3-ol intakes and risk of T2D (28,30). Our observation that flavan-3-ol intake was associated with a lower risk of T2D is supported by consistent findings for both acute and chronic effects observed in dietary intervention trials of flavan-3-ol–rich products. To date, these trials have mainly focused on cocoa/chocolate and cardiovascular health biomarkers. In a systematic review of 42 acute and short-term chronic trials (duration ≤18 wk), insulin resistance as assessed by HOMA-IR was improved by chocolate/cocoa as a result of a significant reduction in serum insulin concentrations (26). A combined flavan-3-ol and isoflavone 1-y intervention trial in medicated T2D postmenopausal women also demonstrated a significant improvement in insulin resistance and sensitivity (54). The available data also suggest that dose of the flavan-3-ol epicatechin may be important for cardiovascular risk, with doses >50 mg being more efficacious; however, too few studies were available to assess the effect of dose on HOMA-IR and insulin (26). The mean intake in our study increased from 21.8 to 23.4 mg/d across follow-up, with ~25% or more of the study population achieving intakes of 50 mg/d.

In our study, we did not confirm the protective association for anthocyanin intake observed by Wedick et al. (29). This was surprising given the growing mechanistic data showing that anthocyanins and their degradation products/metabolites enhance insulin sensitivity and secretion, protect β-cell function, and improve glucose homeostasis (23,55,56). We considered the possibility that apparent differences in dietary sources and amounts of anthocyanins might explain the discrepancy between our findings and those of Wedick et al., but our analyses did not support either explanation.

The major strengths of our study were the large sample size, availability of meticulous clinical examinations, the use of multiple dietary assessment measures of flavonoid intake so that we could assess cumulative intakes, and the availability of a more complete flavonoid database to more accurately characterize the intake of the range of flavonoid classes present in the habitual diet. In addition to these strengths, there are some potential limitations. The importance of vegetables and fruits as sources of many flavonoid classes confound our ability to separate the independent contributions of overall vegetable and fruit intake and intakes of the flavonoids. However, adjustment for some of the potentially bioactive components of the fruits and vegetables associated with T2D risk, including fiber (15), potassium (16), and magnesium (17), had no impact on the flavonol intake association, suggesting that this association was independent of these and perhaps other phytochemical components of vegetables and fruits. However, the relation between flavan-3-ols and T2D risk was slightly attenuated by this adjustment. Our findings are based on observational data and we cannot rule out the potential for residual bias related to lifestyle differences between individuals consuming higher or lower amounts of flavonoids. Finally, our findings were based on a cohort that was largely Caucasian of western European heritage, so generalizability to other race and ethnic groups may be limited.

TABLE 6 Relation between cumulative mean food intake and diabetes incidence in members of the Framingham Heart Study Offspring cohort: time-dependent analyses

	Age and sex adjusted		Multivariable adjusted[2]	
Food[1]	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Tea, mL/wk				
<30	1.0	—[3]	1.0	—
30–132	0.89 (0.69–1.15)	0.38	0.95 (0.74–1.22)	0.68
133–191	0.99 (0.57–1.72)	0.97	0.99 (0.57–1.73)	0.98
≥192	0.86 (0.60–1.22)	0.39	0.97 (0.68–1.39)	0.88
P-trend		0.42		0.89
Apples and pears, g/wk				
<138	1.0	—	1.0	—
138–620	1.13 (0.76–1.66)	0.55	0.99 (0.67–1.46)	0.96
621–896	0.67 (0.34–1.35)	0.27	0.63 (0.31–1.26)	0.19
≥897	0.76 (0.36–1.61)	0.47	0.73 (0.35–1.56)	0.42
P-trend		0.20		0.18
Banana, g/wk				
<114	1.0	—	1.0	—
114–512	1.27 (0.85–1.89)	0.25	1.16 (0.78–1.73)	0.47
513–740	1.07 (0.60–1.89)	0.83	1.06 (0.59–1.89)	0.84
≥741	1.29 (0.72–2.29)	0.39	1.36 (0.76–2.43)	0.30
P-trend		0.72		0.43

[1] Foods contributing at least 10% of the total intake for flavonols and flavan-3-ols.
[2] Multivariable models are adjusted for sex and time-dependent variables age, cardiovascular disease (y/n), current smoker (y/n), BMI, and cumulative mean energy intake.
[3] Referent category.

In summary, the evidence relating flavonoid class intake to risk of T2D is promising although still very limited. To date, we are not aware of any human intervention studies relating flavonoid intake to T2D incidence, and there are few long-term clinical studies that have examined interventions with flavonoid-rich diets in humans with respect to intermediate risk factors for T2D such as glucose homeostasis and insulin resistance. Our knowledge of the effects of flavonoids on T2D risk would greatly benefit from additional human intervention studies and prospective observational studies examining relations with markers of T2D risk.

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