Dietary Intakes of Individual Flavanols and Flavonols Are Inversely Associated with Incident Type 2 Diabetes in European Populations\(^1\-^3\)

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Abstract

Dietary flavanols and flavonoids, flavonoid subclasses, have been recently associated with a lower risk of type 2 diabetes (T2D) in Europe. Even within the same subclass, flavonoids may differ considerably in bioavailability and bioactivity. We aimed to examine the association between individual flavanol and flavonol intakes and risk of developing T2D across European countries. The European Prospective Investigation into Cancer and Nutrition (EPIC)–InterAct case-cohort study was conducted in 8 European countries across 26 study centers with 340,234 participants contributing 3.99 million person-years of follow-up, among whom 12,403 incident T2D cases were ascertained and a center-stratified subcohort of 16,154 individuals was defined. We estimated flavonoid intake at baseline from validated dietary questionnaires using a database developed from Phenol-Explorer and USDA databases. We used country-specific Prentice-weighted Cox regression models and random-effects meta-analysis methods to estimate HRs. Among the flavanol subclass, we observed significant inverse trends between intakes of all individual flavan-3-ol monomers and risk of T2D across Europe. The European study showed inverse associations between all individual flavan-3-ol monomers, proanthocyanidins with a low polymerization degree and trimers (HR: 0.91; 95% CI: 0.80, 1.04; P-trend = 0.07) but not for proanthocyanidins with a greater polymerization degree. Among the flavonol subclass, myricetin (HR: 0.77; 95% CI: 0.64, 0.93; P-trend = 0.001) was associated with a lower incidence of T2D. This large and heterogeneous European study showed inverse associations between all individual flavan-3-ol monomers, proanthocyanidins with a low...
Introduction

Prospective studies have shown that the consumption of plant-based foods, such as fruit and vegetables (1), tea (2), and wine (3,4), is related to a lower risk of type 2 diabetes (T2D) (5). Flavonoids and other polyphenolic compounds may play a relevant role in the health effects of plant-based diets, but the evidence is limited. Flavonoids are a large group of secondary metabolites in plants that comprise 6 subclasses: flavanols, flavan-3-ols (flavan-3-ol monomers, proanthocyanidins, and theaflavins), anthocyanidins, flavonols, flavanones, and isoflavones.

We recently reported that diets rich in flavonoids are associated with a lower incidence of T2D in the European Prospective Investigation into Cancer and Nutrition (EPIC–InterAct study) (5). In particular, flavanols (including flavan-3-ol monomers and theaflavins, but not proanthocyanidins) and flavonols were the flavonoid subclasses that were significantly inversely associated with T2D (5). Similar results for flavonol intake were reported in a Finnish study (6), whereas no association for these flavonoids was observed in studies conducted in the United States (3,7,8). As a result of consider-
Flavanol and flavonol intake. Estimated flavanol and flavonol intakes were derived from foods included in the dietary questionnaires through a comprehensive food composition database on flavonoids as previously described (11,12,18). Our database on flavonols (flavan-3-ol monomers, proanthocyanidins, and theaflavins) and flavonols was based on USDA databases (19,20) and Phenol-Explorer (21). This online database compiles composition data on individual flavan-3-ol monomers (catechin, epigallocatechin, epicatechin, epicatechin 3-gallate, epigallocatechin 3-gallate, gallatechin, catechin 3-gallate), proanthocyanidin groups (dimers, trimers, 4–6 monomers, 7–10 monomers; polymers), and the individual flavonols (isorhamnetin, kaempferol, myricetin, quercetin). Data on flavonoids were expressed as aglycone equivalents, after conversion of the flavonoid glycosides into aglycone contents using their respective molecular weights. The final database contains 1877 food items, including raw foods, cooked foods, and recipes, and 10% of values for these food items are missing.

Statistical analysis. We assessed the distributions of intakes of total and individual flavan-3-ol monomers, proanthocyanidins, theaflavins, and flavonols by using means, SDs, medians, and 5th and 95th percentiles because the data were skewed to the right. We used Spearman correlations to assess whether individual flavonoid intakes were correlated to each other within the same flavonoid subclass. The contribution of each food group to individual flavonoid intake was also computed as a percentage. We examined baseline characteristics and dietary intakes in the subcohort by quintiles of the sum of flavanol and flavonol intake. Prentice-weighted Cox regression models (22), which account for the subcohort-wide quintiles. Tests for linear trend were performed by assigning the medians of each quintile as scores. Intakes were also analyzed continuously after a log2 transformation so that a 1-unit increase represents a doubling of flavonoid intake. We estimated HRs and their 95% CIs by using the following modeling strategy based on already known confounding variables. Age was used as the underlying time scale, with entry time defined as the participant’s age at baseline and exit time as age at diagnosis of diabetes, censoring, or death (whichever came first). All models were stratified by center to control for center effects such as follow-up procedures and questionnaire design. Model 1 was adjusted for sex and total energy intake (kcal/d). Model 2 was additionally adjusted for educational level (none, primary school, technical/professional, secondary school, longer education), physical activity index (inactive, moderately inactive, moderately active, and active) (17), smoking status (never, former, and current), BMI (kg/m2), and alcohol intake (g/d). Model 3 was additionally adjusted for intakes of red meat, processed meat, sugar-sweetened soft drinks, and coffee (g/d). Model 4 was additionally adjusted for intakes of fiber (g/d), vitamin C, magnesium, fruit, and vegetables; and a lower consumption of processed meat compared with those in the lowest quintile; however, participants in the top quintile reported greater alcohol and red meat intake, and a lower intake of coffee (Table 2). Participants across quintiles had similar frequencies of prevalent diseases.

The pooled HRs (95% CIs) for T2D comparing quintiles of individual flavan-3-ol monomer, proanthocyanidin, and flavonol intakes are shown in Tables 3–5, respectively. We observed statistically significant inverse associations in model 1 (stratified by center and adjusted for age (as underlying time scale), sex, and total energy) for all individual compounds, except for the flavonol isorhamnetin. After further adjustment for potential confounders (models 2 and 3), all associations were attenuated. When we additionally included fiber, vitamin C, and magnesium in the multivariable models (model 4), we observed significant inverse trends between incidence of T2D and all individual flavan-3-ol monomers, although the HR for the highest versus the lowest quintile was ony significant for epigallocatechin 3-gallate (HR: 0.64; 95% CI: 0.44, 0.92), catechin (HR: 0.86; 95% CI: 0.75, 0.99), catechin 3-gallate (HR comparing extreme quintiles: 0.80; 95% CI: 0.69, 0.93), and gallochelatin (HR: 0.71; 95% CI: 0.59, 0.85). For proanthocyanidins, we found a significant inverse association with dimers (HR: 0.81; 95% CI: 0.71, 0.92; P-trend = 0.003) and a borderline inverse trend with trimers (HR: 0.91; 95% CI: 0.80, 1.04; P-trend = 0.07). For flavonols, we found a significant inverse association with myricetin (HR: 0.77; 95% CI: 0.64, 0.93; P-trend = 0.001) and a
were strengthened. After further adjustment for waist circumference, family history of diabetes was added in model 4, associations of T2D when dietary flavan-3-ol monomer, proanthocyanidin, and flavonol exposures were assessed as a continuous variable after log, transformation (Tables 3–5). We detected no significant heterogeneity between countries for the associations of flavan-3-ol monomers (I² = 19.4%, P = 0.28), proanthocyanidins (I² = 0.0%, P = 0.77), and flavonols (I² = 26.8%, P = 0.21) with T2D. For intakes of flavan-3-ol monomers, proanthocyanidins, and flavonols, we found no interactions with sex (P-interaction = 0.44, 0.45, and 0.12, respectively), BMI (P-interaction = 0.75, 0.73, and 0.83, respectively), or smoking status (P-interaction = 0.18, 0.79, and 0.23, respectively).

In sensitivity analyses, we observed similar results after the exclusion of T2D cases diagnosed within the first 2 y of follow-up or participants with prevalent cardiovascular diseases. When family history of diabetes was added in model 4, associations were strengthened. After further adjustment for waist circumference (model 4), the findings were almost identical (data not shown).

### Discussion

In this large prospective study across 8 European countries, all flavan-3-ol monomers, proanthocyanidins with lower degree of polymerization, and the flavonol myricetin were inversely related to a lower risk of T2D. We found inverse trends between all individual flavan-3-ol monomer intakes and risk of T2D. Furthermore, among them, intakes of catechin, epigallocatechin 3-gallate, gallatechin, and catechin 3-gallate were significantly inversely associated with incident T2D comparing extreme quantiles. Indeed, the main food sources of flavan-3-ol monomers (tea and some fruit, particularly apples and pears) in the EPIC study (11) were also inversely associated with incidence of T2D in several prospective studies (1,2,7,26). In contrast to our findings, no associations between flavanols and T2D were reported in any of the previous cohorts conducted in the United States (3,7). Differences in the range of intakes between countries could partially explain these inconsistencies. In the present European study, the median of flavan-3-ol monomer intake was 41.4 mg/d (10th–90th percentiles: 12.9–428.9 mg/d), whereas in 1 of the U.S. studies the median was 27.0 mg/d (10th–90th percentiles: 8.4–135.1 mg/d) (7). Several in vitro and in vivo studies have evaluated the antidiabetic effects of individual flavan-3-ol monomers and flavan-3-ol-rich foods (e.g., cocoa and tea), showing a high range of activities related to improving glucose homeostasis, such as inhibition of glucosidase activity and glucose absorption from the intestine, protection of pancreatic β cells, increased insulin secretion, activation of insulin receptors and glucose uptake in the insulin-sensitive tissues, and modulation of intracellular signaling pathways and genes involved in glucogenogenesis and glycogenesis (27–29).

As reported earlier, in the EPIC-InterAct study (5) and in a U.S.-based study (3), total proanthocyanidin subclass intake was not significantly related to T2D. However, examining the relations of dietary proanthocyanidins according to polymerization degree in the current study, a significant inverse association was observed between proanthocyanidin dimer intakes and risk of T2D. Moreover, a potential trend with proanthocyanidin trimer intake was found, but not with PAs with higher polymerization degrees. These results might be interpreted in 3 different ways. First, proanthocyanidin dimers are more bioactive than proanthocyanidin polymers. In the gut, proanthocyanidins inhibit the glucosidase activity and the formation of advanced glycation endproducts in an inverse polymerization degree manner; however, proanthocyanidin polymers showed a stronger inhibitory activity against α-amylase than did proanthocyanidin oligomers (30). Second, proanthocyanidin dimers and trimers are more bioavailable than polymers, and, as such, they can be better absorbed in the gut than proanthocyanidin polymers (9). Several pharmacokinetic studies have shown that proanthocyanidin polymers may not be degraded to monomers in the stomach (31) and glycation significantly impairs intestinal absorption of dietary fibers.
addition, proanthocyanidins were able to regulate microRNA, and their degradation into phenolic acids decreases as the degree of polymerization increases (34). After proanthocyanidin hydrolyzation, phenolic acids can be absorbed in the colon, and then those may exert their antidiabetic effects, such as increasing insulin secretion, improving glucose uptake in muscle cells, and inducing hepatic glucokinase activity (28). These findings suggest a different effect of proanthocyanidins by polymerization degree in T2D, highlighting that a role in the prevention of T2D for proanthocyanidins may be confined to dimers and probably trimers but not to proanthocyanidins with a greater polymerization degree.

### TABLE 2 Baseline characteristics and dietary intakes of the EPIC-InterAct subcohort according to quintiles of sum of flavanol and flavonol intake

| Characteristic                          | All (n = 15,258) | 1 (n = 3052) | 2 (n = 3052) | 3 (n = 3051) | 4 (n = 3052) | 5 (n = 3051) |
|----------------------------------------|------------------|--------------|--------------|--------------|--------------|--------------|
| Cutoff, mg/d                           |                  | <139.8       | 139.8–217.5  | 217.6–321.7  | 321.8–526.0  | >526.0       |
| Median intake, mg/d                    | 97.6             | 176.6        | 265.2        | 397.1        | 713.6        |
| Sociodemographic characteristics      |                  |              |              |              |              |              |
| Age, y                                 | 52.4 ± 9.1       | 52.1 ± 9.4   | 52.1 ± 9.0   | 51.7 ± 9.1   | 51.8 ± 8.6   | 54.2 ± 9.1   |
| Men, %                                 | 37.8             | 40.3         | 35.8         | 34.6         | 38.7         | 39.8         |
| Educational level, %                   |                  |              |              |              |              |              |
| None                                   | 7.7              | 7.6          | 8.7          | 9.6          | 8.4          | 4.1          |
| Primary school                         | 33.3             | 40.3         | 33.9         | 33.4         | 31.7         | 27           |
| Technical/professional                 | 23.2             | 24.5         | 22.6         | 21.6         | 21.7         | 25.8         |
| Secondary school                       | 15.1             | 12.3         | 13.8         | 15.7         | 16.6         | 17.2         |
| Longer education                       | 20.7             | 15.3         | 21.1         | 19.6         | 21.7         | 25.9         |
| Anthropometric characteristics         |                  |              |              |              |              |              |
| BMI, kg/m²                             | 26.0 ± 4.2       | 26.2 ± 4.3   | 26.2 ± 4.3   | 26.0 ± 4.0   | 26.2 ± 4.2   | 25.5 ± 3.9   |
| Waist circumference, cm                | 86.4 ± 12.6      | 87.2 ± 12.9  | 86.5 ± 12.8  | 86.9 ± 12.5  | 86.9 ± 12.4  | 86.4 ± 12.6  |
| Lifestyle characteristics              |                  |              |              |              |              |              |
| Smoking status, %                      |                  |              |              |              |              |              |
| Never                                  | 46.8             | 39.3         | 45.3         | 51.2         | 50.1         | 48.3         |
| Former                                 | 27.2             | 23.4         | 26.0         | 25.0         | 28.9         | 32.5         |
| Current                                | 26.0             | 37.3         | 28.7         | 23.8         | 20.9         | 19.2         |
| Physical activity, %                   |                  |              |              |              |              |              |
| Inactive                               | 23.6             | 27.5         | 26.3         | 24.0         | 21.4         | 18.9         |
| Moderately inactive                    | 33.7             | 33.9         | 34.0         | 33.5         | 35.3         | 31.5         |
| Moderately active                      | 22.7             | 21.5         | 20.5         | 23.8         | 22.4         | 25.1         |
| Active                                 | 20.1             | 17.0         | 19.3         | 18.7         | 20.9         | 24.4         |
| Prevalent diseases, yes, %             |                  |              |              |              |              |              |
| Cancer                                 | 3.2              | 3.6          | 3.7          | 2.8          | 3.1          | 3.1          |
| Myocardial infarction²                 | 1.4              | 1.8          | 1.8          | 0.9          | 1.0          | 1.5          |
| Stroke²                                | 0.9              | 1.3          | 1.0          | 0.6          | 0.6          | 0.8          |
| Angina²                                | 2.1              | 2.0          | 2.4          | 1.8          | 1.6          | 2.4          |
| Hypertension²                          | 18.6             | 18.3         | 20.0         | 19.4         | 18.0         | 17.2         |
| Hyperlipidemia²                        | 17.3             | 15.5         | 18.1         | 19.9         | 19.2         | 13.7         |
| Family history of diabetes²           | 19.2             | 19.8         | 18.9         | 20.4         | 21.7         | 16.5         |
| Dietary intake                         |                  |              |              |              |              |              |
| Total energy, kcal/d                   | 2140 ± 635       | 1920 ± 575   | 2080 ± 594   | 2170 ± 624   | 2260 ± 650   | 2260 ± 661   |
| Alcohol, g/d                           | 13.2 ± 18.5      | 8.8 ± 13.0   | 12.0 ± 16.8  | 13.1 ± 17.9  | 15.7 ± 20.1  | 16.4 ± 22.4  |
| Fiber, g/d                             | 22.8 ± 7.8       | 18.1 ± 5.9   | 21.3 ± 6.4   | 23.0 ± 6.8   | 25.3 ± 7.5   | 26.3 ± 8.9   |
| Vitamin C, mg/d                        | 124 ± 68         | 88 ± 52      | 116 ± 58     | 128 ± 61     | 145 ± 68     | 142 ± 79     |
| Magnesium, mg/d                        | 351 ± 103        | 310 ± 91     | 340 ± 97     | 352 ± 103    | 368 ± 104    | 384 ± 105    |
| Red meat, g/d                          | 46 ± 36          | 45 ± 36      | 45 ± 35      | 44 ± 35      | 46 ± 34      | 50 ± 40      |
| Processed meat, g/d                    | 37 ± 32          | 38 ± 31      | 40 ± 34      | 38 ± 33      | 36 ± 33      | 32 ± 31      |
| Soft drinks, g/d                       | 69 ± 155         | 76 ± 175     | 71 ± 154     | 65 ± 157     | 57 ± 127     | 74 ± 158     |
| Coffee, g/d                            | 384 ± 385        | 406 ± 436    | 433 ± 405    | 350 ± 365    | 303 ± 327    | 337 ± 349    |
| Fruit, g/d                             | 234 ± 198        | 109 ± 91     | 190 ± 116    | 250 ± 151    | 319 ± 196    | 365 ± 253    |
| Vegetables, g/d                        | 183 ± 119        | 139 ± 103    | 173 ± 109    | 183 ± 115    | 200 ± 122    | 219 ± 128    |

1 Values are means ± SDs or percentages. EPIC, European Prospective Investigation into Cancer and Nutrition.

2 Missing data: waist circumference (n = 1013), myocardial infarction (n = 230), stroke (n = 1209), angina (n = 5139), hypertension (n = 45), hyperlipidemia (n = 2944), family history of diabetes (n = 7643). Prevalent diseases were self-reported.
Among flavonols, myricetin was significantly inversely associated with T2D, and kaempferol tended to be inversely related to T2D risk. Similar results were reported for kaempferol and quercetin in the Finnish study (6), but no significant associations were observed for flavonol intakes in the U.S. studies (3,7,8). Surprisingly, in our study, quercetin, which was the most abundant contributor (70%) to flavonol intake, was not the main contributor to myricetin and kaempferol, whereas vegetables and fruit were the main food sources of quercetin.

### TABLE 3

**Pooled HRs (95% CIs) for the association between flavan-3-ol monomer intakes and type 2 diabetes: the EPIC-InterAct study**

| Flavan-3-ol monomer | Quintile 1 | Quintile 2 | Quintile 3 | Quintile 4 | Quintile 5 | P-trend | Continuous (log) |
|---------------------|------------|------------|------------|------------|------------|---------|----------------|
| (+)-Epigallocatechin 3-gallate, mg/d | <0.87 | 0.87–2.40 | 2.41–11.64 | 11.65–108.77 | >108.77 | 0.001 | 0.96 (0.94, 0.98) |
| Median intake, mg/d | 0.4 | 1.46 | 4.9 | 40.8 | 219.62 | | |
| Model 1 | 1 (ref) | 0.83 (0.73, 0.95) | 0.78 (0.66, 0.94) | 0.73 (0.59, 0.90) | 0.57 (0.44, 0.73) | <0.001 | 0.96 (0.94, 0.98) |
| Model 2 | 1 (ref) | 0.85 (0.74, 0.98) | 0.89 (0.70, 1.13) | 0.82 (0.63, 1.07) | 0.69 (0.47, 1.01) | 0.24 | 0.99 (0.97, 1.01) |
| Model 3 | 1 (ref) | 0.86 (0.74, 1.00) | 0.88 (0.69, 1.12) | 0.80 (0.61, 1.04) | 0.64 (0.45, 0.92) | 0.008 | 0.98 (0.96, 1.00) |
| Model 4 | 1 (ref) | 0.85 (0.74, 0.99) | 0.87 (0.69, 1.11) | 0.79 (0.60, 1.03) | 0.64 (0.44, 0.92) | 0.012 | 0.98 (0.96, 1.00) |
| (+)-Epicatechin 3-gallate, mg/d | <0.31 | 0.31–1.34 | 1.35–6.17 | 6.18–32.21 | >32.21 | 0.014 | 0.47 (0.41, 0.55) |
| Median intake, mg/d | 0.11 | 0.6 | 2.98 | 15.08 | 64.48 | | |
| Model 1 | 1 (ref) | 0.88 (0.79, 0.98) | 0.86 (0.73, 1.02) | 0.77 (0.63, 0.94) | 0.64 (0.51, 0.81) | <0.001 | 0.95 (0.93, 0.97) |
| Model 2 | 1 (ref) | 1.00 (0.89, 1.11) | 1.01 (0.81, 1.25) | 0.96 (0.79, 1.17) | 0.88 (0.66, 1.18) | 0.54 | 1.00 (0.98, 1.01) |
| Model 3 | 1 (ref) | 0.99 (0.88, 1.13) | 0.99 (0.79, 1.23) | 0.92 (0.74, 1.14) | 0.80 (0.60, 1.06) | 0.024 | 0.99 (0.97, 1.00) |
| Model 4 | 1 (ref) | 1.00 (0.87, 1.15) | 0.98 (0.77, 1.24) | 0.90 (0.71, 1.15) | 0.80 (0.59, 1.08) | 0.031 | 0.98 (0.97, 1.00) |

**NOTES**

1 For model 1, the pooled HRs were based on random-effects meta-analysis by using Prentice-weighted Cox regression analysis, stratified by center and adjusted for sex and total energy intake. Model 2 was additionally adjusted for educational level, smoking status, physical activity levels, BMI, and alcohol intake. Model 3 was additionally adjusted for red meat, processed meat, sugar-sweetened soft drinks, and coffee intakes. Model 4 was additionally adjusted for fiber, vitamin C, and magnesium intakes. EPIC, European Prospective Investigation into Cancer and Nutrition; ref, reference.

2 Obtained by assigning the median of each quintile as a score.

3 A 1-unit increase represents a doubling of flavan-3-ol monomer intake.

4 Catechin 3-gallates were assessed in 4 groups because there was a large group of nonconsumers, which resulted in an unbalanced division of catechin 3-gallates in quintiles: group 1, n = 9499 (36.4%); group 2, n = 5930 (22.7%); group 3, n = 5621 (21.6%); group 4, n = 5038 (19.3%).
which are modestly associated with a lower incidence of T2D (1). To our knowledge, all individual flavonols are able to inhibit the activity of digestive enzymes for glucose production, particularly α-amylase, as well as of the transporters responsible for glucose absorption [sodium-glucose cotransporter 1 (SGLT1) and glucose transporter 2 (GLUT2)] (28,33), although some differences in dose-response effects between individual flavonols may occur. Furthermore, enhanced pancreatic β-cell function and antioxidant, anti-inflammatory, and antiangiogenic activities of flavonols, through the regulation of signal transduction and different enzyme systems, may also be involved in their potential role against T2D (36,37).

Limitations in our study included the use of a baseline assessment of diet and other lifestyle variables. Therefore, changes in lifestyle could not be taken into account in these analyses. In addition, measurement error in collecting self-reported dietary intake is inevitable. To minimize this, we used country-specific validated questionnaires for main food groups and nutrients (14,15), although these have not been specifically validated for the intake of flavonoids. Moreover, flavanol and flavonol intake may be underestimated, although our database was mostly complete for these flavonoid subclasses (11,12), and herb/plant supplement intakes were omitted in these analyses (up to 5% in Denmark, the highest consuming country) (38). Nutritional biomarkers offer an alternative method for estimating dietary intake that is objective rather than subjective, and they provide more accurate measures than self-reported questionnaires. To date, there are few validated biomarkers of flavanol and flavonol intakes, so further research in this field is warranted (39,40). The association of dietary flavanol and flavonol intakes with T2D risk is likely susceptible to confounding because high flavanol and flavonol intake reflects a healthier lifestyle. In our models, we have adjusted for other determinants of a healthy lifestyle; however, possible residual confounding cannot be excluded. Finally, we realize that our study is prone to the well-known drawback of multiple comparisons, although Bender and Lange (41) concluded that adjustments for multiple testing are not necessary in exploratory studies such as this.

Strengths of the current study include the multicenter design and the large sample size at recruitment, from whom a large number of verified incident cases of T2D accrued during 3.99 million person-years of follow-up. This study also included a wide variation in flavanol and flavonol intakes among participants in 8 European countries. Furthermore, we were able to explore potential effect modifications and control for a number of plausible confounders and factors that may hide the etiologic pathway of the association between the intake of individual flavonoids (42) and T2D risk.

Flavanols and flavonols and type 2 diabetes

### Table 4: Pooled HRs (95% CIs) for the association between proanthocyanidin intakes and type 2 diabetes: the EPIC-InterAct study

| Proanthocyanidin Quintile | Median Intake, mg/d | P-value<sup>2</sup> | Continuous (log)<sup>2</sup> |
|---------------------------|---------------------|----------------------|-----------------------------|
| Dimers, mg/d              |                     |                      |                             |
| <14.1                     | 9.33                | 0.001                | 0.92 (0.88, 0.97)           |
| 14.1–22.1                 | 17.92               | 0.001                | 0.92 (0.88, 0.97)           |
| 22.2–32.3                 | 26.82               | 0.001                | 0.92 (0.88, 0.97)           |
| 33.4–49.5                 | 39.65               | 0.001                | 0.92 (0.88, 0.97)           |
| >49.5                     | 66.52               | 0.001                | 0.92 (0.88, 0.97)           |
| Model 1                   |                     |                      |                             |
| 1 (ref)                   | 0.87 (0.80, 0.94)   | 0.82 (0.73, 0.92)    | 0.78 (0.69, 0.88)           |
| Model 2                   | 0.84 (0.81, 1.00)   | 0.90 (0.76, 1.01)    | 0.82 (0.71, 0.95)           |
| Model 3                   | 0.93 (0.84, 1.04)   | 0.90 (0.77, 1.05)    | 0.81 (0.70, 0.94)           |
| Model 4                   | 0.93 (0.84, 1.03)   | 0.90 (0.77, 1.05)    | 0.81 (0.70, 0.94)           |
| Trimmers, mg/d            | <6.6                | 6.6–10.2             | 10.3–14.2                   |
| Median Intake, mg/d       | 4.4                 | 8.36                 | 12.12                       |
| Model 1                   | 0.87 (0.80, 0.94)   | 0.82 (0.73, 0.92)    | 0.78 (0.69, 0.88)           |
| Model 2                   | 0.94 (0.84, 1.06)   | 0.92 (0.79, 1.07)    | 0.96 (0.86, 1.07)           |
| Model 3                   | 0.93 (0.84, 1.04)   | 0.90 (0.76, 1.01)    | 0.93 (0.80, 1.08)           |
| Model 4                   | 0.93 (0.84, 1.03)   | 0.90 (0.77, 1.05)    | 0.91 (0.80, 1.04)           |
| 4–6mers, mg/d             | <17.8               | 17.8–27.6            | 27.7–39.0                   |
| Model 1                   | 11.92               | 22.67                | 32.9                        |
| Model 2                   | 0.87 (0.80, 0.94)   | 0.81 (0.74, 0.88)    | 0.81 (0.73, 0.90)           |
| Model 3                   | 0.90 (0.82, 1.00)   | 0.89 (0.80, 1.01)    | 0.93 (0.83, 1.04)           |
| Model 4                   | 0.91 (0.82, 1.01)   | 0.89 (0.80, 1.01)    | 0.96 (0.85, 1.08)           |
| 7–10mers, mg/d            | <2.3                | 12.3–19.6            | 19.6–28.7                   |
| Model 1                   | 7.81                | 15.92                | 23.76                       |
| Model 2                   | 0.86 (0.78, 0.95)   | 0.85 (0.75, 0.92)    | 0.80 (0.72, 0.89)           |
| Model 3                   | 0.92 (0.87, 1.07)   | 0.93 (0.82, 1.06)    | 0.91 (0.86, 1.06)           |
| Model 4                   | 0.92 (0.86, 1.00)   | 0.92 (0.82, 1.08)    | 0.90 (0.80, 1.07)           |
| Polymers, mg/d            | >27.9               | 27.9–43.2            | 43.3–61.0                   |
| Model 1                   | 18.78               | 35.57                | 51.35                       |
| Model 2                   | 0.86 (0.78, 0.95)   | 0.87 (0.72, 0.87)    | 0.81 (0.74, 0.89)           |
| Model 3                   | 0.95 (0.97, 1.07)   | 0.96 (0.94, 1.03)    | 0.95 (0.81, 1.01)           |
| Model 4                   | 0.95 (0.97, 1.04)   | 0.95 (0.92, 1.07)    | 0.92 (0.80, 1.05)           |

<sup>1</sup> For model 1, the pooled HRs were based on random-effects meta-analysis by using Prentice-weighted Cox regression analysis, stratified by center and adjusted for sex and total energy intake. Model 2 was additionally adjusted for educational level, smoking status, physical activity levels, BMI, and alcohol intake. Model 3 was additionally adjusted for red meat, processed meat, sugar-sweetened soft drink, and coffee intakes. Model 4 was additionally adjusted for fiber, vitamin C, and magnesium intakes. EPIC, European Prospective Investigation into Cancer and Nutrition; ref, reference; 4–6mers, 4–6 monomers; 7–10mers, 7–10 monomers.

<sup>2</sup> Obtained by assigning the median of each quintile as scores.

<sup>3</sup> A 1-unit increase represents a doubling of proanthocyanidin intake.

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flavonoids and T2D. In all sensitivity analysis, the associations were almost identical, denoting the robustness of our results.

In conclusion, this large, prospective case-cohort study supports a protective role for all individual flavan-3-ol monomers, proanthocyanidins of low polymerization degree, and the flavonol myricetin against T2D in men and women across European countries. These results highlight the importance of the assessment of individual flavonoids in addition to that of the flavonoid subclasses. More studies in different populations are needed to confirm these potential inverse associations between the intake of individual flavanols and flavonols and the risk of developing T2D.

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TABLE 5 Pooled HRs (95% CIs) for the association between flavonol intakes and type 2 diabetes: the EPIC-InterAct study

| Flavonol | Quintile 1 | Quintile 2 | Quintile 3 | Quintile 4 | Quintile 5 | P-trend | Continuous (log2) |
|----------|------------|------------|------------|------------|------------|---------|------------------|
| Quercetin, mg/d | 0.98 (0.83, 1.16) | 0.94 (0.81, 1.10) | 0.92 (0.79, 1.05) | 0.86 (0.72, 1.04) | 0.86 (0.71, 1.03) | 0.95 (0.80, 1.13) | 0.95 (0.89, 1.02) |

1 For model 1, the pooled HRs were based on random-effects meta-analysis by using Prentice-weighted Cox regression analysis, stratified by center and adjusted for sex and total energy intake. Model 2 was additionally adjusted for educational level, smoking status, physical activity levels, BMI, and alcohol intake. Model 3 was additionally adjusted for red meat, processed meat, sugar-sweetened soft drink, and coffee intakes. Model 4 was additionally adjusted for fiber, vitamin C, and magnesium intakes. EPIC, European Prospective Investigation into Cancer and Nutrition; ref, reference.

2 Obtained by assigning the median of each quintile as scores.

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