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# Dietary antioxidant consumption and the risk of type 2 diabetes in South Korean adults: A prospective cohort study based on the Health Examinees study

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## ABSTRACT

**Objectives**: Antioxidants are common dietary compounds with multiple health benefits. This study aimed to identify the association between dietary antioxidant consumption and the incidence of type 2 diabetes mellitus (T2D, defined using the Korean Diabetes Association criteria) in South Korean adults.

**Design**: Baseline and follow-up data from the Health Examinees (HEXA) study, a large-scale community-based genomic cohort study conducted in South Korea

**Setting:** A South Korean community

**Participants:** A total of 20,594 participants, aged 40–79 years, who participated in the baseline and follow-up surveys of the HEXA study were included. After an average of 5 years of follow-up, there were 332 men and 360 women with T2D.

**Results*:*** Participants with the highest total flavonoid consumption (Q5) had a lower risk of T2D (men: hazard ratio [HR], 0.63; 95% confidence interval [CI], 0.42–0.93; *P* for trend = 0.0169]; and women: HR, 0.54; 95% CI, 0.438–0.78; *P* for trend = 0.0001) than those with the lowest consumption (Q1). Dietary total antioxidant capacity was significantly inversely associated with the development of T2D mellitus in women participants alone (HR, 0.58; 95% CI, 0.40–0.83; *P* for trend = 0.0004). Stratified analyses according to age and body mass index showed that dietary total flavonoid consumption and total antioxidant capacity had a protective effect against the development of T2D in women aged > 52 years and women with BMI > 25 kg/m$^2$.

**Conclusions**: Dietary flavonoid consumption and total antioxidant capacity were associated with a lower risk of T2D in South Korean adults, especially in women aged > 52 years and

overweight. The findings of this study may provide reference data for the modification of dietary guidelines for South Koreans.

## Strengths and limitations of the study

- This study used a large-scale community-based genomic cohort study conducted in South Korea with 5 years of follow-up.
- Stratified analyses were conducted to focus on one certain exposure.
- Although this study reported a longitudinal relationship between antioxidant consumption and diabetes incidence, we could not assess the causality.
- Dietary measurement errors were inevitable due to using self-reported FFQ.

**Keywords**: Cohort study, Diabetes, Dietary antioxidant, Flavonoid, Health Examinees study, South Korean adults, Total antioxidant capacity

## INTRODUCTION

Diabetes is a metabolic disease characterized by high blood glucose levels, impaired glucose tolerance, impaired insulin secretion, and insulin resistance.(1, 2) Currently, ≥ 400 million people are living with type 2 diabetes (T2D) mellitus worldwide.(3) The prevalence of T2D mellitus increases with age. The 2018 Korean Diabetes Association diabetes fact sheet reported that the prevalence of T2D in the total population aged ≥ 65 years was 29.8%.(4) It is projected that T2D will be the seventh leading cause of death by 2030.(3) Given that T2D is accompanied by various serious complications, including cardiovascular disease, peripheral vascular disease, retinopathy, nephropathy, neuropathy, and recently, sarcopenia, its prevention and treatment are extremely important.(3, 5) Both genetic and environmental factors contribute to the development and progression of T2D mellitus. However, its growing prevalence is the result of result of changing dietary habits and lifestyles observed in modern societies.(6)

Dietary flavonoids, abundant in fruits and vegetables, are a group of naturally occurring polyphenolic compounds.(7, 8) There are seven subgroups of flavonoids: flavonols, flavanones, isoflavones, flavones, flavan-3-ols, anthocyanins, and proanthocyanidins.(9-11) Flavonoids are associated with various health-promoting effects, including anti-inflammatory, antihypertensive, anti-obesity, and anti-diabetic.

Previous studies have reported that dietary antioxidants decreased oxidative stress, an important risk factor for T2D, played a key role as anti-inflammatory factors by blocking the nuclear factor kappa-light-chain-enhancer of the activated B (NF-κB) and mitogen-activated protein kinase (MAPK) cell signaling pathways. MAPK pathway was associated with the induction of proinflammatory genes and the promotion of Akt/protein kinase B, an insulin-signaling pathway.(12-15) As a result, antioxidants improve insulin resistance,

which is involved in the pathogenesis of T2D mellitus, by promoting the transportation of GLUT4 through the regulation of the insulin-signaling pathway.(16, 17)

Previous studies have investigated the correlation between dietary antioxidants and obesity, dyslipidemia, and metabolic syndrome.(18-21) Azad et al. (22) showed that a diet high in antioxidants had protective effects against the development of T2D in the Iranian population. However, few studies have been conducted to determine the association between dietary antioxidant intake and T2D in South Korean populations. In addition, whether there is a dose–response relationship between dietary antioxidants and T2D is unclear. It is pertinent to determine whether a relationship exists between dietary antioxidant intake and T2D in South Korean adults. Moreover, the effect of dietary antioxidants on T2D has not been investigated according to the flavonoid subclasses, antioxidant capacities of flavonoids, or total antioxidant capacity (TAC), which is an index to indicate whole dietary antioxidant content.(23) Therefore, we conducted this study to explore the association between dietary antioxidant and the incidence of T2D by analyzing data from the Health Examinees (HEXA) study.

## METHODS

### Patient and public involvement

Patients and public were not involved in the design of the study.

### Study population

This study was based on the baseline and follow-up data from the HEXA study, a large-scale community-based genomic cohort study conducted in South Korea. More specific details of the HEXA study design are described elsewhere.(24) A total of 173,357

participants aged ≥ 40 years were initially included in the baseline survey, which was conducted from 2003 to 2014; 65,642 of these participants were included in the follow-up survey, which was conducted from 2012 to 2016. At baseline, we excluded participants who had T2D mellitus or had no information on fasting plasma glucose or $HbA_{1C}$ levels (n = 41,311) and those with a history of diseases closely related to T2D mellitus (i.e., hyperlipidemia, stroke, transient ischemic attacks, angina pectoris, and myocardial infarction) (n = 3,082). At follow-up, we excluded those with missing information on biomarkers for T2D mellitus (fasting plasma glucose, $HbA_{1C}$) (n = 11), those who had an implausible energy intake (< 3,349 or ≥ 16,743 kJ/day for men and < 2,093 or ≥ 14,650 kJ/day for women; n = 630 (25)), and those who were missing values for covariables such as drinking (n = 9) and body mass index (BMI) (n = 5). Ultimately, a total of 20,594 participants (6,327 men and 14,267 women) were included in this study.

**Dietary assessment and estimation of antioxidant components**

Dietary intake was assessed using the self-administered, 106-item, food frequency questionnaire (FFQ) developed for the Korean Genome Epidemiologic Study.(24) Participants reported the frequencies and average portions of food or beverage items consumed during the last year before participating in the HEXA study. The reproducibility and validity of the FFQ have been assessed in a previous study using a reference method by collecting information on 12-day dietary records.(26) The median correlation coefficient for all nutrients was 0.39 between the FFQ and 12-day dietary record, and the researchers concluded that the FFQ could be an acceptable tool for dietary assessment.(26)

In this study, we estimated the participants' intake of antioxidant components using self-reported dietary data linked to the TAC database for common South Korean foods.(11, 27) Dietary TAC and intake of each flavonoid component were expressed as vitamin C

equivalent antioxidant capacity (mg VCE/100 g). The intake of individual antioxidant components from a food item was calculated by multiplying the antioxidant component per gram of food item by the total weight in grams of daily intake of this food item. The daily intake of individual total dietary antioxidant components was calculated as the sum of the intake of each antioxidant component from all the food sources reported in the HEXA FFQ data (mg VCE/day). After summing all individual total dietary antioxidant components, we obtained the dietary TAC per person per day.

Total flavonoid intake was classified into seven categories: anthocyanidins (cyanidin, delphinidin, pelargonidin, malvidin, peonidin, and petunidin), isoflavones (daidzein, genistein, and glycitein), proanthocyanidins (proanthocyanidin-dimer, proanthocyanidin-trimer, proanthocyanidin-4-6mers, proanthocyanidin-7-10mers, and proanthocyanidin-polymers), flavonols (quercetin, kaempferol, myricetin, and isorhamnetin), flavones (luteolin and apigenin), flavanones (eriodictyol, hesperetin, and naringenin), and flavan-3-ols (catechin, epicatechin, epigallocatechin, theaflavin, theaflavin-3-gallate, theaflavin-3′-gallate, and theaflavin-3-3-digallate).

**Definition of type 2 diabetes**

T2D was determined in accordance with the definition provided by the Korean Diabetes Association.(28) T2D was defined as a diagnosis by a physician, increased fasting plasma glucose level ≥ 6.99 mmol/L (126 mg/dL), or elevated $HbA_{1C}$ level ≥ 47.5 mmol/mol (6.5%).

**Covariables**

In the HEXA study, the sociodemographic information of each participant was collected using a questionnaire. Our covariables of interest included age, BMI, level of education (middle school or lower, high school, or college or higher), and health-related

behaviors, such as smoking (current smoker, past smoker, or non-smoker), alcohol consumption (never or current drinker), level of physical activity (inactive or active), and total energy intake (kJ/day). BMI was calculated as the quotient of the body weight (kg) and height (m) squared ($kg/m^2$).(29) Smoking status was categorized into three groups based on the participants' responses to the question, "Have you smoked ≥ 20 packs (400 cigarettes) so far?" Participants who answered "never" were classified as "non-smokers," those who answered "yes" and were still smoking at the time of the survey were classified as "current smokers," and those who answered "yes" but had quit smoking at the time of the survey were classified as "past smokers." Alcohol consumption was classified based on the responses to the following question, "Are you unable to drink or refuse to do so for religious or other reasons?" in the HEXA survey. In the present analysis, we classified participants who replied "yes" as "alcohol non-drinkers;" the rest were classified as "alcohol drinkers." Regarding physical activity levels, participants were classified as "active" if they reported that they engaged in exercises resulting in sweating for ≥ 30 min twice a week.(30)

**Statistical analyses**

All statistical analyses were sex-stratified and performed using Statistical Analysis Systems software version 9.4 (SAS Institute, Cary, NC, USA). Statistical significance was set at $P < 0.05$. Continuous variables were presented as means ± standard deviations (SD), and the difference between them in the outcome groups was tested using a generalized linear model (GLM). The categorical variables were presented as numbers (percentages), and the difference between them in the outcome groups was tested using the chi-square test. A multivariable Cox proportional-hazards regression model was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for T2D after adjusting for categorical (educational level, current drinking status, current smoking status, and physical activity) and

continuous (age, BMI, and energy intake) covariables. The lowest quintile (Q1) of TAC or flavonoid intake served as a reference group. The median value of each quintile group was modeled as a continuous variable in the Cox model to test the trend. We also estimated the HRs and 95% CIs for an SD increment in dietary TAC and flavonoid intake and conducted stratified analyses according to BMI, age, smoking status, and alcohol consumption.

## RESULTS

A total of 20,594 individuals (aged 40–79 years) were included in this study. After an average of 5 years of follow-up, the incidence of T2D mellitus was 5.25% in men and 2.52% in women. The baseline general characteristics of participants according to quintiles of total flavonoid intake are shown in Table 1. Among both men and women participants, the highest consumption group (Q5) included more non-smokers, more participants with higher education levels, and more participants who engaged in physical activity (all $p$ value < 0.05).

Table 1. Baseline general characteristics of participants by total flavonoid consumption

| | Antioxidant consumption | | | | | |
|---|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | Q5 | *P*-value |
| Men, **n=6327** | | | | | | |
| **Cases / person-years** | **80** / 5103.00 | **74 / 5060.60** | **60 / 4995.40** | **71 / 5110.50** | **47 / 5182.60** | |
| Age, years | 54.45 ± 8.64 | 54.97 ± 8.51 | 54.20 ± 8.37 | 54.55 ± 8.32 | 54.89 ± 7.97 | 0.0758 |
| BMI, kg/m$^2$ | 24.07 ± 2.74 | 24.19 ± 2.73 | 24.21 ± 2.71 | 24.31 ± 2.65 | 24.32 ± 2.58 | 0.1348 |
| Smoking status | | | | | | **<.0001** |
| Never | 357 (28.22%) | 404 (31.91%) | 395 (31.27%) | 373 (29.56%) | 426 (33.84%) | |
| Past | 451 (35.65%) | 516 (40.76%) | 549 (43.47%) | 586 (46.43%) | 575 (45.67%) | |
| Current | 457 (36.13%) | 346 (27.33%) | 319 (25.26%) | 303 (24.01%) | 258 (20.49%) | |
| Educational level | | | | | | **<.0001** |
| Under middle school | 382 (30.32%) | 297 (23.52%) | 244 (19.40%) | 186 (14.77%) | 135 (10.69%) | |
| High school | 503 (39.92%) | 521 (41.25%) | 492 (39.11%) | 504 (40.03%) | 422 (33.41%) | |
| College or above | 375 (29.76%) | 445 (35.23%) | 522 (41.49%) | 569 (45.19%) | 706 (55.90%) | |
| Physical activity | | | | | | **<.0001** |
| Inactive | 1070 (84.65%) | 1024 (80.95%) | 999 (79.03%) | 976 (77.28%) | 896 (70.94%) | |
| Active | 194 (15.35%) | 241 (19.05%) | 265 (20.97%) | 287 (22.72%) | 367 (29.06%) | |
| Current alcohol consumption | | | | | | 0.2578 |
| No | 313 (24.74%) | 337 (26.62%) | 342 (27.04%) | 340 (26.86%) | 364 (28.77%) | |
| Yes | 952 (75.26%) | 929 (73.38%) | 923 (72.96%) | 926 (73.14%) | 901 (71.23%) | |
| Total energy intake, kcal/day | 1624.56 ± 401.**00** | 1764.89 ± 417.55 | 1842.23 ± 431.57 | 1926.29 ± 442.88 | 2110.85 ± 499.16 | **<.0001** |
| Carbohydrate, E% | 72.51 ± 7.71 | 71.63 ± 7.1**0** | 71.**00** ± 7.33 | 70.49 ± 6.88 | 70.07 ± 7.09 | **<.0001** |
| Protein, E% | 12.99 ± 2.41 | 13.33 ± 2.12 | 13.52 ± 2.25 | 13.79 ± 2.26 | 13.97 ± 2.37 | **<.0001** |
| Fat, E% | 14.**50** ± 5.73 | 15.04 ± 5.33 | 15.47 ± 5.48 | 15.73 ± 5.07 | 15.96 ± 5.15 | **<.0001** |
| Dietary fiber intake, g/day | 3.84 ± 1.12 | 4.72 ± 1.24 | 5.28 ± 1.33 | 5.91 ± 1.5**0** | 7.42 ± 2.14 | **<.0001** |
| Total flavonoid, mg VCE/d | 58.16 ± 15.38 | 97.92 ± 10.58 | 135.76 ± 11.78 | 185.2**0** ± 18.17 | 299.44 ± 77.77 | **<.0001** |
| Anthocyanidins, mg VCE/d | 11.73 ± 5.14 | 20.53 ± 6.74 | 28.17 ± 9.84 | 37.83 ± 13.24 | 62.9**0** ± 28.55 | **<.0001** |
| Isoflavones, mg VCE/d | 8.63 ± 4.74 | 11.56 ± 6.3**0** | 12.24 ± 6.53 | 13.16 ± 6.86 | 15.96 ± 9.48 | **<.0001** |
| Proanthocyanidins, mg VCE/d | 23.59 ± 9.01 | 41.24 ± 10.74 | 59.17 ± 14.68 | 80.74 ± 21.27 | 135.1**0** ± 47.83 | **<.0001** |
| Flavonols, mg VCE/d | 7.**50** ± 4.38 | 10.58 ± 6.08 | 13.18 ± 6.82 | 16.78 ± 9.23 | 24.31 ± 16.28 | **<.0001** |
| Flavones, mg VCE/d | 0.29 ± 0.15 | 0.45 ± 0.18 | 0.**60** ± 0.22 | 0.79 ± 0.29 | 1.19 ± 0.49 | **<.0001** |
| Flavanones, mg VCE/d | 1.**80** ± 1.52 | 3.**20** ± 1.96 | 4.56 ± 2.74 | 6.01 ± 3.76 | 10.29 ± 6.33 | **<.0001** |
| Flavan-3-ols, mg VCE/d | 4.63 ± 4.4**0** | 10.35 ± 9.7**0** | 17.84 ± 15.94 | 29.88 ± 23.91 | 49.69 ± 37.8**0** | **<.0001** |
| TAC, mg VCE/d | 113.96 ± 32.02 | 185.25 ± 30.65 | 252.44 ± 37.18 | 343.26 ± 51.65 | 542.84 ± 149.1**0** | **<.0001** |
| **W**omen, **n=14267** | | | | | | |

| **Cases / person-years** | **89 / 11021.20** | **82 / 11303.30** | **76 / 11322.20** | **59 / 11526.80** | **54 / 11650.80** | |
|---|---|---|---|---|---|---|
| Age, years | 52.64 ± 8.04 | 52.31 ± 7.84 | 52.19 ± 7.68 | 52.01 ± 7.23 | 52.18 ± 7.02 | 0.0832 |
| BMI, kg/m² | 23.44 ± 3.05 | 23.40 ± 2.93 | 23.32 ± 2.85 | 23.27 ± 2.80 | 23.19 ± 2.72 | 0.8879 |
| Smoking status | | | | | | **<.0001** |
| Never | 2746 (96.32%) | 2784 (97.72%) | 2788 (97.82%) | 2806 (98.39%) | 2768 (97.23%) | |
| Past | 31 (1.09%) | 21 (0.74%) | 24 (0.84%) | 21 (0.74%) | 35 (1.23%) | |
| Current | 74 (2.60%) | 44 (1.54%) | 38 (1.33%) | 25 (0.88%) | 44 (1.55%) | |
| Educational level | | | | | | **<.0001** |
| Under middle school | 1150 (40.41%) | 977 (34.33%) | 901 (31.74%) | 760 (26.73%) | 625 (22.01%) | |
| High school | 1236 (43.43%) | 1305 (45.85%) | 1297 (45.69%) | 1368 (48.12%) | 1341 (47.23%) | |
| College or above | 460 (16.16%) | 564 (19.82%) | 641 (22.58%) | 715 (25.15%) | 873 (30.75%) | |
| Physical activity | | | | | | **<.0001** |
| Inactive | 2449 (85.96%) | 2355 (82.63%) | 2294 (80.46%) | 2239 (78.48%) | 2120 (74.49%) | |
| Active | 400 (14.04%) | 495 (17.37%) | 557 (19.54%) | 614 (21.52%) | 726 (25.51%) | |
| Current alcohol consumption | | | | | | 0.2756 |
| No | 1900 (66.60%) | 1967 (68.92%) | 1932 (67.72%) | 1928 (67.55%) | 1966 (68.91%) | |
| Yes | 953 (33.40%) | 887 (31.08%) | 921 (32.28%) | 926 (32.45%) | 887 (31.09%) | |
| Total energy intake, kcal/day | 1429.83 ± 392.78 | 1577.31 ± 420.56 | 1659.22 ± 437.45 | 1761.14 ± 460.69 | 1947.92 ± 497.29 | **<.0001** |
| Carbohydrate, E% | 71.87 ± 8.06 | 71.25 ± 7.93 | 70.67 ± 7.63 | 70.30 ± 7.36 | 69.97 ± 7.30 | **<.0001** |
| Protein, E% | 13.39 ± 2.47 | 13.59 ± 2.42 | 13.76 ± 2.38 | 13.89 ± 2.33 | 14.01 ± 2.43 | **<.0001** |
| Fat, E% | 14.74 ± 6.03 | 15.16 ± 5.91 | 15.57 ± 5.65 | 15.81 ± 5.45 | 16.02 ± 5.33 | **<.0001** |
| Dietary fiber intake, g/day | 3.80 ± 1.11 | 4.61 ± 1.21 | 5.13 ± 1.30 | 5.97 ± 1.52 | 7.38 ± 2.10 | **<.0001** |
| Total flavonoid, mg VCE/d | 71.44 ± 17.73 | 116.97 ± 11.49 | 159.39 ± 13.42 | 213.52 ± 19.24 | 333.98 ± 94.24 | **<.0001** |
| Anthocyanidins, mg VCE/d | 15.24 ± 6.21 | 25.89 ± 8.12 | 35.35 ± 11.02 | 46.82 ± 14.12 | 74.77 ± 32.62 | **<.0001** |
| Isoflavones, mg VCE/d | 8.63 ± 4.48 | 10.67 ± 5.74 | 11.70 ± 6.42 | 13.28 ± 7.25 | 15.09 ± 9.07 | **<.0001** |
| Proanthocyanidins, mg VCE/d | 31.11 ± 10.57 | 52.62 ± 11.64 | 73.61 ± 15.79 | 101.51 ± 21.34 | 161.00 ± 54.19 | **<.0001** |
| Flavonols, mg VCE/d | 8.09 ± 4.63 | 11.18 ± 5.92 | 13.54 ± 7.50 | 16.94 ± 9.30 | 24.05 ± 16.19 | **<.0001** |
| Flavones, mg VCE/d | 0.35 ± 0.18 | 0.55 ± 0.23 | 0.71 ± 0.28 | 0.89 ± 0.34 | 1.31 ± 0.62 | **<.0001** |
| Flavanones, mg VCE/d | 2.56 ± 1.91 | 4.37 ± 2.55 | 5.98 ± 3.19 | 7.70 ± 3.84 | 12.62 ± 8.04 | **<.0001** |
| Flavan-3-ols, mg VCE/d | 5.45 ± 4.85 | 11.68 ± 10 | 18.51 ± 14.74 | 26.38 ± 20.18 | 45.13 ± 36.98 | **<.0001** |
| TAC (mg VCE/d) | 135.61 ± 36.42 | 216.26 ± 31.08 | 289.3 ± 38.71 | 380.21 ± 51.07 | 587.77 ± 176.53 | **<.0001** |

Values are presented as means ± standard deviations or numbers (%). *P*-values were calculated using a generalized linear model for continuous variables and Chi-square test for categorical variables. $p<0.05$ are shown in bold.
Total flavonoid intake was the sum of anthocyanidins, isoflavones, proanthocyanidins, flavonols, flavones, flavanones, and flavan-3-ols.
Total antioxidant capacity (TAC) was obtained by combining the individual antioxidant capacity of each antioxidant derived from every food item. BMI: body mass index, VCE: vitamin C equivalents.

Table 2 shows the range of dietary antioxidant intake by quintiles. The associations between dietary antioxidant intake and the HRs of T2D mellitus are presented in Table 3. All participants with the highest total dietary flavonoid intake (Q5) had a lower risk of developing T2D mellitus (men: HR, 0.63; 95% CI, 0.42–0.93 and women: HR, 0.54; 95% CI, 0.38–0.78; both *P* for trend < 0.05) than those with the lowest flavonoid intake (Q1). Consumption of more flavonols and proanthocyanidins had a protective effect against the development of T2D mellitus in men participants, and consumption of anthocyanidins, proanthocyanidins, flavonols, flavones, and flavanones showed a protective effect against T2D mellitus in women participants (all *P* for trend < 0.05). After estimation of HRs according to quintiles of TAC, the Q5 group of women participants still showed a lower risk of T2D mellitus (HR, 0.58; 95% CI, 0.40–0.83; *P* for trend = 0.0004) than the Q1 group. However, although the TAC Q5 group of men participants did not show any significant

association with T2D mellitus, they had an approximately 15% reduced risk of developing T2D mellitus for an SD increment in TAC (HR, 0.85; 95% CI, 0.75–0.96). After further adjustment for energy percent from carbohydrate, fat, and protein and dietary fiber intake, the results remained largely unchanged (Supplementary Table S1 and Table S2).

Table 2. Range of each dietary antioxidant intake by quintile

| | Antioxidant consumption | | | | |
|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | Q5 |
| Men | | | | | |
| Total flavonoid (mg VCE/d) | 58.16 (13.07 – 80.30) | 97.92 (80.32 – 116.38) | 135.76 (116.38 – 156.75) | 185.20 (156.80 – 221.23) | 299.44 (221.46 – 1150.79) |
| Anthocyanidins (mg VCE/d) | 9.69 (0.75 – 14.14) | 17.94 (14.14 – 21.97) | 26.58 (21.97 – 31.57) | 38.62 (31.57 – 46.86) | 68.33 (46.89 – 378.83) |
| Isoflavones (mg VCE/d) | 5.07 (0.10 – 6.80) | 8.07 (6.80 – 9.35) | 10.78 (9.35 – 12.22) | 14.16 (12.22 – 16.57) | 23.48 (16.57 – 94.05) |
| Proanthocyanidins (mg VCE/d) | 21.28 (1.43 – 31.14) | 39.10 (31.15 – 47.5) | 56.93 (47.52 – 67.33) | 81.94 (67.35 – 99.38) | 140.58 (99.41 – 723.02) |
| Flavonols (mg VCE/d) | 5.25 (0.69 – 7.30) | 8.81 (7.30 – 10.32) | 11.89 (10.33 – 13.65) | 16.14 (13.65 – 19.27) | 30.25 (19.27 – 231.83) |
| Flavones (mg VCE/d) | 0.23 (0.02 – 0.33) | 0.40 (0.33 – 0.48) | 0.57 (0.48 – 0.67) | 0.79 (0.67 – 0.93) | 1.32 (0.93 – 4.37) |
| Flavanones (mg VCE/d) | 1.03 (0.00 – 1.77) | 2.43 (1.77 – 3.09) | 3.93 (3.09 – 4.89) | 6.16 (4.89 – 7.80) | 12.33 (7.80 – 62.77) |
| Flavan–3–ols (mg VCE/d) | 2.98 (0.10 – 4.91) | 6.82 (4.92 – 8.87) | 11.79 (8.87 – 15.54) | 23.54 (15.56 – 41.05) | 67.26 (41.06 – 252.89) |
| TAC (mg VCE/d) | 111.21 (21.57 – 150.38) | 182.54 (150.45 – 215.60) | 251.21 (215.61 – 289.93) | 343.27 (289.98 – 406.09) | 549.53 (406.14 – 1811.29) |
| Women | | | | | |
| Total flavonoid (mg VCE/d) | 71.44 (7.28 – 96.65) | 116.97 (96.66 – 136.81) | 159.39 (136.81 – 183.19) | 213.52 (183.20 – 250.56) | 333.98 (250.59 – 1263.46) |
| Anthocyanidins (mg VCE/d) | 12.85 (0.44 – 18.47) | 23.33 (18.48 – 28.19) | 34.01 (28.19 – 40.07) | 47.64 (40.07 – 56.64) | 80.24 (56.65 – 372.08) |
| Isoflavones (mg VCE/d) | 4.83 (0.43 – 6.50) | 7.73 (6.50 – 8.96) | 10.31 (8.96 – 11.72) | 13.67 (11.72 – 16.02) | 22.83 (16.02 – 85.19) |
| Proanthocyanidins (mg VCE/d) | 28.89 (2.21 – 41.00) | 50.74 (41.01 – 60.82) | 72.48 (60.83 – 84.94) | 101.70 (84.95 – 121.70) | 166.05 (121.73 – 633.15) |
| Flavonols (mg VCE/d) | 5.72 (1.00 – 7.65) | 9.09 (7.65 – 10.55) | 12.11 (10.55 – 13.81) | 16.26 (13.81 – 19.38) | 30.62 (19.38 – 195.47) |
| Flavones (mg VCE/d) | 0.28 (0.01 – 0.39) | 0.48 (0.39 – 0.57) | 0.67 (0.57 – 0.77) | 0.89 (0.77 – 1.05) | 1.50 (1.05 – 7.62) |
| Flavanones (mg VCE/d) | 1.58 (0.00 – 2.58) | 3.44 (2.58 – 4.35) | 5.38 (4.35 – 6.55) | 7.95 (6.55 – 9.73) | 14.88 (9.73 – 132.99) |
| Flavan–3–ols (mg VCE/d) | 3.82 (0.25 – 6.06) | 8.18 (6.06 – 10.41) | 13.17 (10.41 – 16.31) | 21.85 (16.31 – 30.72) | 60.14 (30.72 – 376.53) |
| TAC | 132.65 (13.04 – 178.98) | 214.39 (178.99 – 248.73) | 287.62 (248.74 – 328.90) | 380.46 (328.94 – 442.53) | 594.04 (442.54 – 2240.46) |

Values were presented as mean (min–max). TAC: Total antioxidant capacity, VCE: vitamin C equivalents.

Table 3. Hazard ratios of type 2 diabetes mellitus during follow-up according to antioxidant consumption divided into quintiles, where Q5 represents highest

| | Antioxidant consumption | | | | | | |
|---|---|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | Q5 | *P* for trend | HR for an SD increment |
| Men | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Total flavonoid | Ref | 0.98 (0.71, 1.34) | 0.90 (0.64, 1.26) | 0.91 (0.65, 1.27) | 0.63 (0.42, 0.93) | 0.0169 | 0.85 (0.75, 0.97) |
| Anthocyanidins | Ref | 0.79 (0.56, 1.11) | 0.99 (0.72, 1.36) | 0.86 (0.62, 1.20) | 0.71 (0.50, 1.03) | 0.1167 | 0.87 (0.77, 0.99) |
| Isoflavones | Ref | 1.45 (1.03, 2.06) | 1.12 (0.78, 1.60) | 1.19 (0.83, 1.71) | 1.36 (0.94, 1.97) | 0.3151 | 1.05 (0.94, 1.17) |
| Proanthocyanidins | Ref | 1.04 (0.76, 1.44) | 0.97 (0.70, 1.36) | 0.77 (0.54, 1.09) | 0.72 (0.50, 1.05) | 0.0247 | 0.88 (0.77, 0.99) |
| Flavonols | Ref | 1.49 (1.08, 2.05) | 0.90 (0.63, 1.30) | 0.97 (0.68, 1.38) | 0.82 (0.56, 1.19) | 0.0381 | 0.84 (0.73, 0.97) |
| Flavones | Ref | 1.01 (0.73, 1.41) | 1.01 (0.72, 1.41) | 0.84 (0.59, 1.20) | 0.85 (0.59, 1.22) | 0.2322 | 0.90 (0.80, 1.01) |
| Flavanones | Ref | 0.83 (0.59, 1.17) | 1.23 (0.89, 1.68) | 0.94 (0.67, 1.31) | 0.82 (0.57, 1.18) | 0.3313 | 0.94 (0.83, 1.06) |
| Flavan-3-ols | Ref | 0.89 (0.64, 1.24) | 1.12 (0.81, 1.55) | 0.79 (0.55, 1.12) | 0.75 (0.52, 1.08) | 0.0744 | 0.90 (0.79, 1.01) |
| TAC | Ref | 1.08 (0.78, 1.49) | 0.95 (0.68, 1.33) | 0.87 (0.62, 1.24) | 0.73 (0.50, 1.06) | 0.0448 | 0.85 (0.75, 0.96) |
| Women | | | | | | | |
| Total flavonoid | Ref | 0.90 (0.66, 1.22) | 0.82 (0.60, 1.12) | 0.61 (0.44, 0.87) | 0.54 (0.38, 0.78) | 0.0001 | 0.80 (0.70, 0.90) |
| Anthocyanidins | Ref | 0.91 (0.68, 1.23) | 0.63 (0.45, 0.87) | 0.71 (0.52, 0.99) | 0.56 (0.39, 0.79) | 0.0006 | 0.85 (0.75, 0.97) |
| Isoflavones | Ref | 0.98 (0.71, 1.34) | 0.71 (0.51, 0.99) | 0.81 (0.58, 1.13) | 0.78 (0.56, 1.10) | 0.1353 | 0.92 (0.82, 1.04) |
| Proanthocyanidins | Ref | 0.90 (0.66, 1.23) | 1.04 (0.77, 1.41) | 0.66 (0.47, 0.93) | 0.50 (0.34, 0.72) | <.0001 | 0.79 (0.70, 0.90) |
| Flavonols | Ref | 0.83 (0.61, 1.12) | 0.68 (0.49, 0.94) | 0.57 (0.41, 0.80) | 0.61 (0.43, 0.86) | 0.0040 | 0.88 (0.77, 1.00) |
| Flavones | Ref | 0.81 (0.60, 1.10) | 0.74 (0.54, 1.01) | 0.54 (0.38, 0.76) | 0.56 (0.39, 0.79) | 0.0003 | 0.81 (0.71, 0.93) |
| Flavanones | Ref | 0.73 (0.54, 0.98) | 0.56 (0.41, 0.77) | 0.57 (0.41, 0.78) | 0.54 (0.39, 0.76) | 0.0005 | 0.83 (0.73, 0.95) |
| Flavan-3-ols | Ref | 0.83 (0.60, 1.13) | 0.79 (0.57, 1.08) | 0.64 (0.45, 0.90) | 0.79 (0.57, 1.10) | 0.3681 | 0.93 (0.82, 1.05) |
| TAC | Ref | 0.82 (0.60, 1.11) | 0.86 (0.64, 1.17) | 0.51 (0.36, 0.73) | 0.58 (0.40, 0.83) | 0.0004 | 0.81 (0.71, 0.92) |

Results are presented as the hazard ratio (HR) for a standard deviation (SD) increment in dietary antioxidant capacity using a cox model.
The multivariable Cox proportional hazards regression model was adjusted for age, body mass index (BMI), educational level, physical activity, drinking status, smoking status, and total energy intake.
Total flavonoid intake was the sum of anthocyanidins, isoflavones, proanthocyanidins, flavonols, flavones, flavanones, and flavan-3-ols.
Total antioxidant capacity (TAC) was obtained by combining the individual antioxidant capacity of each antioxidant derived from every food item.

We also performed stratified analyses according to age, BMI, drinking status for both sexes, and smoking status for men participants. Figure 1 shows the HRs of T2D mellitus in the Q5 and Q1 groups according to baseline age, baseline BMI, and alcohol drinking status

in the HEXA study. There was almost no significant association between T2D mellitus and dietary intake of antioxidant components in men participants. However, total flavonoid intake and dietary TAC showed a protective effect against the development of T2D mellitus in women participants who were aged > 52 years, had a BMI ≥ 25 kg/m$^2$, and regardless of alcohol consumption.

## Discussion

In this study, we discovered that dietary total flavonoid consumption and TAC are both associated with a reduced risk of developing T2D mellitus. After further analysis stratified according to age, and BMI, we found that dietary total flavonoid consumption and TAC had a protective effect against the development of type 2 diabetes mellitus in women participants who were overweight or aged > 52 years.

Oxidative stress, which is an imbalance between the production of reactive oxygen species (free radicals) and antioxidant defense mechanism, is a risk factor for T2D.(17) Previous studies have shown that oxidative stress impairs the secretion of insulin by pancreatic beta cells and interferes with the insulin signaling pathway, thereby accelerating the development and progression of T2D by increasing insulin resistance.(2, 3, 6, 31, 32) Oxidative stress can be regulated by antioxidants, which react with reactive oxygen species.(33) The consumption of dietary flavonoids has been shown to be associated with lower incidences of T2D. Several previous studies have indicated that flavonoids decrease plasma glucose levels and improve lipid profile, insulin secretion, and insulin resistance, factors which are implicated in the development of T2D.(2, 3, 8, 34) In a previous study, higher flavonol intake was associated with a 26% lower incidence of T2D.(35)~~(35)~~ In addition, the authors observed a marginally significant inverse association between flavan-3-ol intake and the risk of T2D, but there was no association with anthocyanin intake.(35)~~(35)~~

Knekt et al.(36) reported a marginally significant inverse association between the intake of the flavonols quercetin, and myricetin, but not kaempferol, and the incidence of T2D in Finnish men and women. Quercetin, in particular, is known to decrease plasma glucose concentration, improve insulin concentration, preserve the integrity of pancreatic beta cells, alleviate T2D symptoms, and reduce hepatic gene expression in streptozotocin-induced diabetic models.(37)-Flavan-3-ol and isoflavone intake is associated with a reduced risk of T2D and improved insulin resistance and serum insulin concentrations.(38) Dietary flavone intake is negatively associated with systolic blood pressure, triglyceride level, triglyceride/high-density lipoprotein-cholesterol level, and homeostatic model assessment of insulin resistance. Flavone intake may have some beneficial effects in the reduction of the prevalence of T2D in South Korean women.(8) Consumption of foods rich in anthocyanins, particularly blueberries, apples, and pears, is also inversely associated with the risk of T2D in the United States.(39)

A key potential mechanism for the protective effect of flavonoids against T2D is the protection of tissues from free oxygen radicals and lipid peroxidation through their antioxidant activity.(40) In addition, anti-inflammatory functions, improvement of endothelial functions, reduction of blood cholesterol concentration, and nicotinamide adenine dinucleotide phosphate oxidase activity are also associated with a reduced risk of T2D mellitus.(40) Flavonoids are known to interact with molecular targets and affect NF-κB and MAPK signaling pathways.(34) Furthermore, flavonoids modulate postprandial glucose levels by reducing the activities of digestive enzymes (a-amylase and a-glucosidase), decreasing the active transport of glucose across the intestinal brush border membrane, and inhibiting glucose transporters.(31) Antioxidant-rich fruits and vegetables contain relatively high fiber content, which can influence the beneficial effects of antioxidants against T2D.(41)

Furthermore, it has been reported that flavonoids inhibit α-glucosidase activity to alleviate hyperglycemia.(42, 43)

The effect of each type of flavonoid intake on the risk of T2D varies by sex. In this study, there was a correlation between anthocyanidin and proanthocyanidin intake and the risk of developing T2D in men. However, there was a greater correlation between the risk of T2D and intake of flavonoids, such as anthocyanidins, proanthocyanidins, flavonols, flavones, and flavanones, in women than in men. These sex-specific results are often seen in other phytochemical-related studies. In a previous study conducted using 2008–2011 data from the Korea National Health and Nutrition Examination Survey, a high intake of flavonoids did not reduce the incidence of obesity and abdominal obesity in men but significantly reduced obesity (18%) in women. In addition, high flavonoid intake was reported to reduce the incidence of abdominal obesity (19%) in that study.(2, 44, 45) The variations in these results appear to be due to differences between the dietary intake patterns of South Korean men and women. Sex-specific dietary patterns have been reported in previous studies; namely, men consume the recommended amount of vegetables more than women, whereas women consume the recommended amount of fruit more than men.(46) In addition, women generally consume higher amounts of dietary antioxidants than men.(2, 47) Higher intake of dietary antioxidants can induce high plasma concentrations of antioxidants and more beneficial effects on preventing development of T2D. Furthermore, gonadal hormones (menopausal estrogen and testosterone) have been implicated in sex-specific differences in glucose homeostasis.(48) Healthy women have lower skeletal muscle mass, higher adipose tissue mass, more circulating free fatty acids, and higher intramyocellular lipid content than men of the same age. These are all factors that could promote increased insulin resistance in women compared with men.(48)

Various factors, such as age and lifestyle, are known to contribute to the development and progression of T2D.(17) The prevalence of T2D in South Koreans increases rapidly with age.(4) Unhealthy lifestyle habits, such as smoking, excessive alcohol consumption, and inactivity, are known to contribute to the development of diabetes.(3, 49) We found that men with T2D were older and more likely to be current drinkers and current smokers than those without diabetes. However, our stratified analysis showed that there was no correlation between these factors except for current alcohol consumption. On the other hand, women with T2D were significantly older and had significantly higher BMI than those without diabetes. Furthermore, the stratified analysis showed that antioxidant consumption was inversely related to the HR of T2D in older women (> 52 years), women with a BMI > 25 kg/m$^2$, regardless of alcohol consumption. Although it is difficult to fully explain these variations in South Korean adults, these findings suggest that high antioxidant intake may be related to a decreased risk of T2D, especially in women with specific lifestyle habits.

**Strengths and limitations**

The main strength of this study was that it was conducted using a large-scale community-based genomic cohort study with 5 years of follow-up on average. Stratified analyses were conducted in the current study to focus on one certain exposure. This study had some limitations. First, although this study reported a longitudinal relationship between dietary antioxidant consumption and T2D incidence, we did not assess the causality. Second, we obtained dietary information and information on the intake of antioxidant components using self-reported FFQ; thus, dietary measurement errors were inevitable. However, the 106-item FFQ has been previously verified.(26) In addition, further studies are needed to measure the flavonoid concentration to verify the data. Third, we did not quantify the amount of alcohol consumption and smoking. Nevertheless, we found no association

between smoking status and T2D after stratification analyses. Dietary antioxidants showed a protective effect against the development of T2D only in women who were non-drinkers.

## Conclusions

The findings of this large-scale prospective cohort study suggest that dietary antioxidant consumption is associated with a lower risk of T2D in South Korean adults. The findings of this study can serve as a reference or guide for the modification of food intake recommendations in dietary guideline policies in South Korea. However, further studies are needed to validate the results of this study.

## Declarations

### Ethics approval and consent to participate

All participants voluntarily signed an informed written consent form before enrollment. This study was performed in accordance with the guidelines specified in the Declaration of Helsinki, and the study protocol was approved by the local Institutional Review Board (IRB) of the Ethics Committee of the Korean Genome and Epidemiology Study of the Korea National Institute of Health (IRB no. 2014-08-02-3C-A).

### Consent for publication

Not applicable.

### Availability of data and materials

The data that support the findings of this study are available from the National Genome Research Institute, Korea Centers for Disease Control and Prevention. How ever, restrictions apply to the availability of these data, which were used under lice nse for this study, and as such are not publicly available. Data are however availa ble from the authors upon reasonable request and with permission of the National Genome Research Institute, Korea Centers for Disease Control and Prevention.

## Competing interests

The authors declare that they have no competing interests.

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## Authors' contributions

S.S. supervised the project. S.S. contributed to the conceptualization or design of this study. S.J. and H.J. were contributed to establish the antioxidants database. L.J.T conducted the formal analysis. S.S. verified and validated the outcomes. L.J.T and S.B.H. co-wrote the first draft of the manuscript. S.J. and H.J. reviewed and revised the article

critically. All authors approved the final version of the article for publication. S.S. and L.J.T had full access to all the data in the study and take full responsibility for the integrity of the data and accuracy of the data analysis.

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## Figure Legend

**Figure 1.** Hazard ratios (HR) with 95% confidence intervals (CIs) for type 2 diabetes mellitus after comparison of antioxidant consumption in the Q5 and Q1 groups according to baseline age, baseline body mass index (BMI), alcohol consumption, smoking status in the Health Examinees study. TAC: total antioxidant capacity

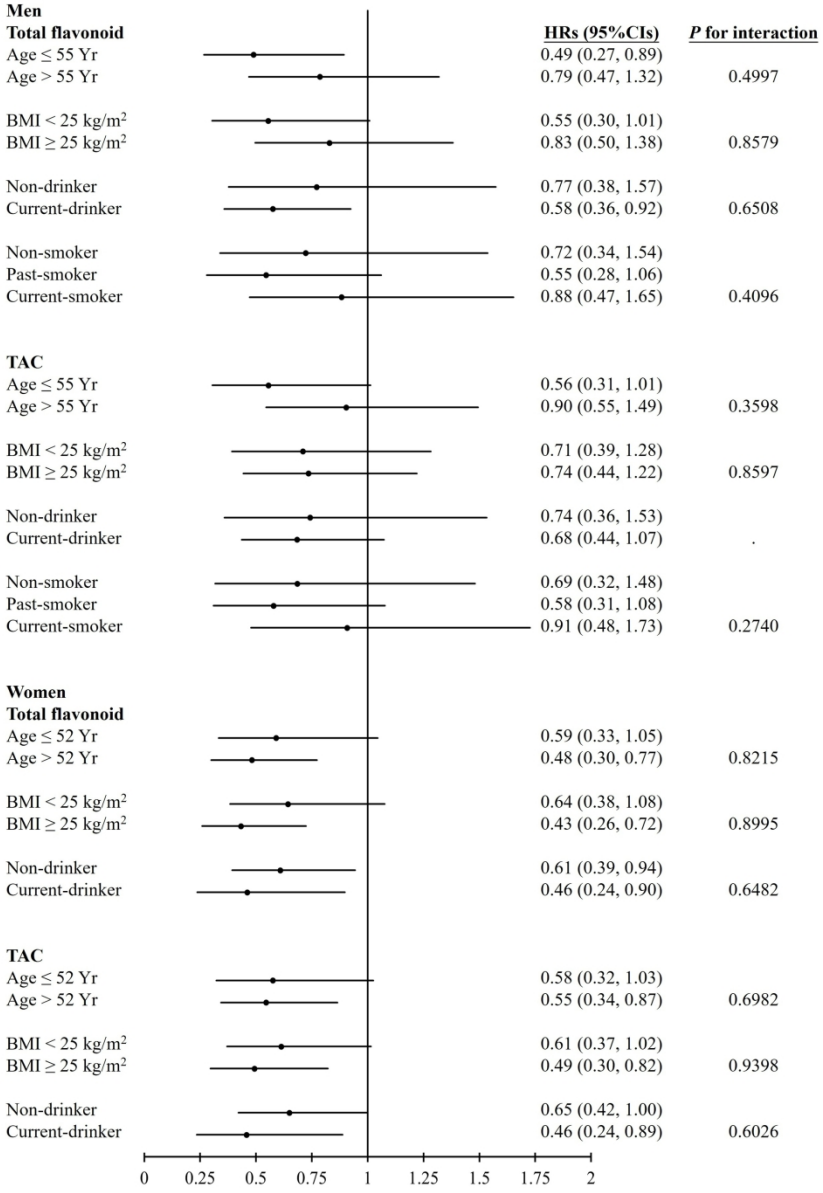


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**Table S1. Hazard ratios of type 2 diabetes during follow-up according to quintile of cumulative average antioxidant consumption in model 2**

| | Antioxidant consumption | | | | | | |
|---|---|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | Q5 | *P* for trend | HR for a SD increment |
| Men | | | | | | | |
| Total flavonoid | Ref | 0.97 (0.71, 1.34) | 0.89 (0.63, 1.25) | 0.89 (0.64, 1.24) | 0.62 (0.42, 0.92) | 0.0136 | 0.85 (0.75, 0.97) |
| Anthocyanidins | Ref | 0.78 (0.56, 1.10) | 0.98 (0.71, 1.35) | 0.85 (0.61, 1.19) | 0.70 (0.49, 1.01) | 0.0994 | 0.87 (0.76, 0.99) |
| Isoflavones | Ref | 1.44 (1.01, 2.04) | 1.10 (0.76, 1.59) | 1.18 (0.81, 1.70) | 1.32 (0.90, 1.95) | 0.4245 | 1.04 (0.92, 1.17) |
| Proanthocyanidins | Ref | 1.04 (0.76, 1.44) | 0.97 (0.70, 1.36) | 0.77 (0.54, 1.09) | 0.72 (0.50, 1.04) | 0.0226 | 0.87 (0.77, 0.99) |
| Flavonols | Ref | 1.46 (1.06, 2.00) | 0.88 (0.61, 1.27) | 0.93 (0.64, 1.33) | 0.77 (0.52, 1.14) | 0.0218 | 0.82 (0.71, 0.95) |
| Flavones | Ref | 1.00 (0.72, 1.38) | 1.00 (0.71, 1.40) | 0.82 (0.57, 1.17) | 0.83 (0.57, 1.21) | 0.1941 | 0.89 (0.79, 1.01) |
| Flavanones | Ref | 0.83 (0.59, 1.17) | 1.21 (0.88, 1.67) | 0.93 (0.66, 1.30) | 0.81 (0.56, 1.16) | 0.2998 | 0.93 (0.83, 1.05) |
| Flavan-3-ols | Ref | 0.88 (0.63, 1.23) | 1.11 (0.80, 1.54) | 0.78 (0.55, 1.11) | 0.74 (0.51, 1.08) | 0.0719 | 0.89 (0.79, 1.01) |
| TAC | Ref | 1.07 (0.77, 1.47) | 0.94 (0.67, 1.31) | 0.85 (0.59, 1.20) | 0.71 (0.48, 1.05) | 0.0347 | 0.84 (0.74, 0.96) |
| Women | | | | | | | |
| Total flavonoid | Ref | 0.92 (0.68, 1.24) | 0.84 (0.62, 1.15) | 0.63 (0.45, 0.89) | 0.55 (0.38, 0.80) | 0.0002 | 0.80 (0.71, 0.91) |
| Anthocyanidins | Ref | 0.92 (0.68, 1.24) | 0.64 (0.46, 0.89) | 0.72 (0.52, 1.00) | 0.56 (0.39, 0.80) | 0.0007 | 0.86 (0.75, 0.97) |
| Isoflavones | Ref | 0.99 (0.72, 1.35) | 0.72 (0.51, 1.02) | 0.84 (0.60, 1.17) | 0.83 (0.58, 1.18) | 0.2885 | 0.94 (0.84, 1.07) |
| Proanthocyanidins | Ref | 0.92 (0.67, 1.25) | 1.07 (0.79, 1.45) | 0.67 (0.48, 0.95) | 0.51 (0.35, 0.74) | <.0001 | 0.79 (0.70, 0.90) |
| Flavonols | Ref | 0.85 (0.62, 1.15) | 0.69 (0.50, 0.96) | 0.59 (0.42, 0.83) | 0.62 (0.44, 0.89) | 0.0066 | 0.89 (0.78, 1.02) |
| Flavones | Ref | 0.82 (0.60, 1.11) | 0.75 (0.55, 1.03) | 0.54 (0.38, 0.77) | 0.57 (0.40, 0.81) | 0.0004 | 0.82 (0.71, 0.93) |
| Flavanones | Ref | 0.74 (0.55, 1.00) | 0.57 (0.41, 0.79) | 0.58 (0.42, 0.80) | 0.55 (0.40, 0.77) | 0.0008 | 0.84 (0.73, 0.96) |
| Flavan-3-ols | Ref | 0.84 (0.62, 1.15) | 0.81 (0.59, 1.12) | 0.66 (0.47, 0.92) | 0.81 (0.58, 1.13) | 0.4157 | 0.93 (0.82, 1.06) |
| TAC | Ref | 0.84 (0.62, 1.14) | 0.89 (0.65, 1.21) | 0.53 (0.37, 0.75) | 0.60 (0.42, 0.86) | 0.0007 | 0.81 (0.71, 0.93) |

The multivariable Cox proportional-hazards regression model was adjusted for age, body mass index (BMI), educational level, physical activity, alcohol consumption, smoking status, total energy intake, energy percent from carbohydrate, energy percent from protein, and energy percent from fat.

Total flavonoid intake was the sum of anthocyanidins, isoflavones, proanthocyanidins, flavonols, flavones, flavanones, and flavan-3-ols.

Total antioxidant capacity (TAC) was obtained by combining the individual antioxidant capacity of each antioxidant derived from every food item.

**Table S2. Hazard ratios of type 2 diabetes during follow-up according to quintile of cumulative average antioxidant consumption in model 3**

| | Antioxidant consumption | | | | | | |
|---|---|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | Q5 | *P* for trend | HR for a SD increment |
| Men | | | | | | | |
| Total flavonoid | Ref | 1.00 (0.72, 1.39) | 0.94 (0.66, 1.34) | 0.98 (0.68, 1.40) | 0.71 (0.45, 1.13) | 0.1553 | 0.89 (0.76, 1.04) |
| Anthocyanidins | Ref | 0.82 (0.58, 1.15) | 1.06 (0.76, 1.47) | 0.96 (0.67, 1.37) | 0.85 (0.56, 1.30) | 0.6471 | 0.92 (0.79, 1.08) |
| Isoflavones | Ref | 1.53 (1.08, 2.18) | 1.22 (0.84, 1.76) | 1.31 (0.90, 1.89) | 1.61 (1.09, 2.38) | 0.0731 | 1.12 (0.99, 1.26) |
| Proanthocyanidins | Ref | 1.06 (0.77, 1.46) | 1.02 (0.72, 1.43) | 0.83 (0.58, 1.20) | 0.81 (0.54, 1.22) | 0.1640 | 0.92 (0.79, 1.06) |
| Flavonols | Ref | 1.54 (1.12, 2.13) | 0.96 (0.66, 1.39) | 1.05 (0.72, 1.54) | 0.97 (0.62, 1.52) | 0.3271 | 0.88 (0.74, 1.05) |
| Flavones | Ref | 1.06 (0.76, 1.48) | 1.09 (0.77, 1.54) | 0.95 (0.65, 1.38) | 1.07 (0.69, 1.65) | 0.9493 | 0.96 (0.83, 1.11) |
| Flavanones | Ref | 0.85 (0.61, 1.21) | 1.29 (0.94, 1.79) | 1.03 (0.73, 1.47) | 0.95 (0.64, 1.40) | 0.8985 | 0.98 (0.87, 1.11) |
| Flavan-3-ols | Ref | 0.93 (0.66, 1.29) | 1.19 (0.86, 1.66) | 0.85 (0.59, 1.23) | 0.84 (0.57, 1.23) | 0.2206 | 0.92 (0.81, 1.05) |
| TAC | Ref | 1.13 (0.81, 1.57) | 1.02 (0.71, 1.45) | 0.98 (0.67, 1.44) | 0.88 (0.55, 1.40) | 0.3967 | 0.88 (0.75, 1.04) |
| Women | | | | | | | |
| Total flavonoid | Ref | 0.90 (0.66, 1.23) | 0.82 (0.59, 1.13) | 0.62 (0.43, 0.89) | 0.54 (0.35, 0.83) | 0.0015 | 0.79 (0.68, 0.93) |
| Anthocyanidins | Ref | 0.93 (0.69, 1.25) | 0.64 (0.46, 0.90) | 0.73 (0.52, 1.04) | 0.58 (0.39, 0.86) | 0.0054 | 0.88 (0.77, 1.02) |
| Isoflavones | Ref | 1.01 (0.74, 1.39) | 0.75 (0.53, 1.06) | 0.88 (0.63, 1.23) | 0.89 (0.62, 1.27) | 0.4969 | 0.97 (0.86, 1.10) |
| Proanthocyanidins | Ref | 0.91 (0.67, 1.25) | 1.05 (0.78, 1.43) | 0.67 (0.47, 0.96) | 0.51 (0.34, 0.77) | 0.0003 | 0.80 (0.69, 0.92) |
| Flavonols | Ref | 0.83 (0.61, 1.14) | 0.69 (0.49, 0.97) | 0.58 (0.40, 0.85) | 0.62 (0.41, 0.96) | 0.0355 | 0.92 (0.78, 1.09) |
| Flavones | Ref | 0.81 (0.60, 1.11) | 0.75 (0.54, 1.03) | 0.55 (0.38, 0.79) | 0.57 (0.38, 0.85) | 0.0029 | 0.82 (0.70, 0.96) |
| Flavanones | Ref | 0.74 (0.55, 1.00) | 0.57 (0.42, 0.79) | 0.58 (0.42, 0.81) | 0.58 (0.40, 0.82) | 0.0038 | 0.86 (0.74, 0.99) |
| Flavan-3-ols | Ref | 0.85 (0.62, 1.17) | 0.83 (0.60, 1.15) | 0.69 (0.48, 0.98) | 0.87 (0.61, 1.23) | 0.7719 | 0.96 (0.84, 1.09) |
| TAC | Ref | 0.82 (0.60, 1.12) | 0.86 (0.62, 1.19) | 0.51 (0.34, 0.75) | 0.57 (0.36, 0.89) | 0.0039 | 0.80 (0.67, 0.95) |

The multivariable Cox proportional-hazards regression model was adjusted for age, body mass index (BMI), educational level, physical activity, drinking status, smoking status, and dietary fiber intake.
Total flavonoid intake was the sum of anthocyanidins, isoflavones, proanthocyanidins, flavonols, flavones, flavanones, and flavan-3-ols.
Total antioxidant capacity (TAC) was obtained by combining the individual antioxidant capacity of each antioxidant derived from every food item.

STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No | Recommendation | Page number |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | Page 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Pages 2–3 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | Pages 4–5 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | Pages 5–6 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Page 6 |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | Pages 6–7 |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | Pages 7–9 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | Pages 7–9 |
| Bias | 9 | Describe any efforts to address potential sources of bias | Pages 17–18 |
| Study size | 10 | Explain how the study size was arrived at | Pages 6–7 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | Page 9 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | |
| | | (*b*) Describe any methods used to examine subgroups and interactions | |
| | | (*c*) Explain how missing data were addressed | |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed | Page 9 |

| | | | |
|---|---|---|---|
| | | *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | |
| | | (*e*) Describe any sensitivity analyses | |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Pages 10–14 |
| | | (b) Give reasons for non-participation at each stage | |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Pages 10–12 |
| | | (b) Indicate number of participants with missing data for each variable of interest | |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | Page 11 |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Pages 12–13 |
| | | (*b*) Report category boundaries when continuous variables were categorized | |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | Page 14 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | Page 14 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | Pages 17–18 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | Pages 14–17 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | Page 18 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Page 19 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

# Dietary antioxidant consumption and the risk of type 2 diabetes in South Korean adults: A prospective cohort study based on the Health Examinees study



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| | |

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# Dietary antioxidant consumption and the risk of type 2 diabetes in South Korean adults: A prospective cohort study based on the Health Examinees study

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**Word count:** 3,342 words


## ABSTRACT

**Objectives**: Antioxidants are common dietary compounds with multiple health benefits. This study aimed to identify the association between dietary antioxidant consumption and the incidence of type 2 diabetes mellitus (T2D, defined using the Korean Diabetes Association criteria) in South Korean adults.

**Design**: Baseline and follow-up data from the Health Examinees (HEXA) study, a large-scale community-based genomic cohort study conducted in South Korea

**Setting:** A South Korean community

**Participants:** A total of 20,594 participants, aged 40–79 years, who participated in the baseline and follow-up surveys of the HEXA study were included. After an average of 5 years of follow-up, there were 332 men and 360 women with T2D.

**Results*:*** Participants with the highest total flavonoid consumption (Q5) had a lower risk of T2D (men: hazard ratio [HR], 0.63; 95% confidence interval [CI], 0.42–0.93; *P* for trend = 0.0169]; and women: HR, 0.54; 95% CI, 0.438–0.78; *P* for trend = 0.0001) than those with the lowest consumption (Q1). Dietary total antioxidant capacity was significantly inversely associated with the development of T2D mellitus in women participants alone (HR, 0.58; 95% CI, 0.40–0.83; *P* for trend = 0.0004). Stratified analyses according to age and body mass index showed that dietary total flavonoid consumption and total antioxidant capacity had a negative association with the development of T2D in women aged > 52 years and women with BMI > 25 kg/m$^2$.

**Conclusions**: Dietary flavonoid consumption and total antioxidant capacity were associated with a lower risk of T2D in South Korean adults, especially in women aged > 52 years and

overweight. The findings of this study may provide reference data for the modification of dietary guidelines for South Koreans.

## Strengths and limitations of the study

- This study used a large-scale community-based genomic cohort study conducted in South Korea with 5 years of follow-up.
- Stratified analyses were conducted to focus on one certain exposure.
- Although this study reported a longitudinal relationship between antioxidant consumption and diabetes incidence, we could not assess the causality.
- Dietary measurement errors were inevitable due to using self-reported FFQ.

**Keywords**: Cohort study, Diabetes, Dietary antioxidant, Flavonoid, Health Examinees study, South Korean adults, Total antioxidant capacity

## INTRODUCTION

Diabetes is a metabolic disease characterized by high blood glucose levels, impaired glucose tolerance, impaired insulin secretion, and insulin resistance.(1, 2) Currently, ≥ 400 million people are living with type 2 diabetes (T2D) mellitus worldwide.(3) The prevalence of T2D mellitus increases with age. The 2018 Korean Diabetes Association diabetes fact sheet reported that the prevalence of T2D in the total population aged ≥ 65 years was 29.8%.(4) It is projected that T2D will be the seventh leading cause of death by 2030.(3) Given that T2D is accompanied by various serious complications, including cardiovascular disease, peripheral vascular disease, retinopathy, nephropathy, neuropathy, and recently, sarcopenia, its prevention and treatment are extremely important.(3, 5) Both genetic and environmental factors contribute to the development and progression of T2D mellitus. However, its growing prevalence is the result of result of changing dietary habits and lifestyles observed in modern societies.(6)

Dietary flavonoids, abundant in fruits and vegetables, are a group of naturally occurring polyphenolic compounds.(7, 8) There are seven subgroups of flavonoids: flavonols, flavanones, isoflavones, flavones, flavan-3-ols, anthocyanins, and proanthocyanidins.(9-11) Flavonoids are associated with various health-promoting effects, including anti-inflammatory, antihypertensive, anti-obesity, and anti-diabetic.

Previous studies have reported that dietary antioxidants decreased oxidative stress, an important risk factor for T2D, played a key role as anti-inflammatory factors by blocking the nuclear factor kappa-light-chain-enhancer of the activated B (NF-κB) and mitogen-activated protein kinase (MAPK) cell signaling pathways. MAPK pathway was associated with the induction of proinflammatory genes and the promotion of Akt/protein kinase B, an insulin-signaling pathway.(12-15) As a result, antioxidants improve insulin resistance,

which is involved in the pathogenesis of T2D mellitus, by promoting the transportation of GLUT4 through the regulation of the insulin-signaling pathway.(16, 17)

Previous studies have investigated the correlation between dietary antioxidants and obesity, dyslipidemia, and metabolic syndrome.(18-21) Azad et al. (22) showed that a diet high in antioxidants had protective effects against the development of T2D in the Iranian population. However, few studies have been conducted to determine the association between dietary antioxidant intake and T2D in South Korean populations. In addition, whether there is a dose–response relationship between dietary antioxidants and T2D is unclear. It is pertinent to determine whether a relationship exists between dietary antioxidant intake and T2D in South Korean adults. Moreover, the effect of dietary antioxidants on T2D has not been investigated according to the flavonoid subclasses, antioxidant capacities of flavonoids, or total antioxidant capacity (TAC), which is an index to indicate whole dietary antioxidant content.(23) Therefore, we conducted this study to explore the association between dietary antioxidant and the incidence of T2D by analyzing data from the Health Examinees (HEXA) study.

## METHODS

### Patient and public involvement

Patients and public were not involved in the design of the study.

### Study population

This study was based on the baseline and follow-up data from the HEXA study, a large-scale community-based genomic cohort study conducted in South Korea. More specific details of the HEXA study design are described elsewhere.(24) A total of 173,357

participants aged ≥ 40 years were initially included in the baseline survey, which was conducted from 2003 to 2014; 65,642 of these participants were included in the follow-up survey, which was conducted from 2012 to 2016. At baseline, we excluded participants who had T2D mellitus or had no information on fasting plasma glucose or $HbA_{1C}$ levels (n = 41,311) and those with a history of diseases closely related to T2D mellitus (i.e., hyperlipidemia, stroke, transient ischemic attacks, angina pectoris, and myocardial infarction) (n = 3,082). At follow-up, we excluded those with missing information on biomarkers for T2D mellitus (fasting plasma glucose, $HbA_{1C}$) (n = 11), those who had an implausible energy intake (< 3,349 or ≥ 16,743 kJ/day for men and < 2,093 or ≥ 14,650 kJ/day for women; n = 630 (25)), and those who were missing values for covariables such as drinking (n = 9) and body mass index (BMI) (n = 5). Ultimately, a total of 20,594 participants (6,327 men and 14,267 women) were included in this study.

**Dietary assessment and estimation of antioxidant components**

Dietary intake was assessed using the self-administered, 106-item, food frequency questionnaire (FFQ) developed for the Korean Genome Epidemiologic Study.(24) Participants reported the frequencies and average portions of food or beverage items consumed during the last year before participating in the HEXA study. The reproducibility and validity of the FFQ have been assessed in a previous study using a reference method by collecting information on 12-day dietary records.(26) The median correlation coefficient for all nutrients was 0.39 between the FFQ and 12-day dietary record, and the researchers concluded that the FFQ could be an acceptable tool for dietary assessment.(26)

In this study, we estimated the participants' intake of antioxidant components using self-reported dietary data linked to the TAC database for common South Korean foods.(11, 27) Dietary TAC and intake of each flavonoid component were expressed as vitamin C

equivalent antioxidant capacity (mg VCE/100 g). The intake of individual antioxidant components from a food item was calculated by multiplying the antioxidant component per gram of food item by the total weight in grams of daily intake of this food item. The daily intake of individual total dietary antioxidant components was calculated as the sum of the intake of each antioxidant component from all the food sources reported in the HEXA FFQ data (mg VCE/day). After summing all individual total dietary antioxidant components, we obtained the dietary TAC per person per day.

Total flavonoid intake was classified into seven categories: anthocyanidins (cyanidin, delphinidin, pelargonidin, malvidin, peonidin, and petunidin), isoflavones (daidzein, genistein, and glycitein), proanthocyanidins (proanthocyanidin-dimer, proanthocyanidin-trimer, proanthocyanidin-4-6mers, proanthocyanidin-7-10mers, and proanthocyanidin-polymers), flavonols (quercetin, kaempferol, myricetin, and isorhamnetin), flavones (luteolin and apigenin), flavanones (eriodictyol, hesperetin, and naringenin), and flavan-3-ols (catechin, epicatechin, epigallocatechin, theaflavin, theaflavin-3-gallate, theaflavin-3′-gallate, and theaflavin-3-3-digallate).

**Definition of type 2 diabetes**

T2D was determined in accordance with the definition provided by the Korean Diabetes Association.(28) T2D was defined as a diagnosis by a physician, increased fasting plasma glucose level ≥ 6.99 mmol/L (126 mg/dL), or elevated $HbA_{1C}$ level ≥ 47.5 mmol/mol (6.5%).

**Covariables**

In the HEXA study, the sociodemographic information of each participant was collected using a questionnaire. Our covariables of interest included age, BMI, level of education (middle school or lower, high school, or college or higher), and health-related

behaviors, such as smoking (current smoker, past smoker, or non-smoker), alcohol consumption (never or current drinker), level of physical activity (inactive or active), and total energy intake (kJ/day). BMI was calculated as the quotient of the body weight (kg) and height (m) squared ($kg/m^2$).(29) Smoking status was categorized into three groups based on the participants' responses to the question, "Have you smoked ≥ 20 packs (400 cigarettes) so far?" Participants who answered "never" were classified as "non-smokers," those who answered "yes" and were still smoking at the time of the survey were classified as "current smokers," and those who answered "yes" but had quit smoking at the time of the survey were classified as "past smokers." Alcohol consumption was classified based on the responses to the following question, "Are you unable to drink or refuse to do so for religious or other reasons?" in the HEXA survey. In the present analysis, we classified participants who replied "yes" as "alcohol non-drinkers;" the rest were classified as "alcohol drinkers." Regarding physical activity levels, participants were classified as "active" if they reported that they engaged in exercises resulting in sweating for ≥ 30 min twice a week.(30)

**Statistical analyses**

All statistical analyses were sex-stratified and performed using Statistical Analysis Systems software version 9.4 (SAS Institute, Cary, NC, USA). Statistical significance was set at $P < 0.05$. Continuous variables were presented as means ± standard deviations (SD), and the difference between them in the outcome groups was tested using a generalized linear model (GLM). The categorical variables were presented as numbers (percentages), and the difference between them in the outcome groups was tested using the chi-square test. A multivariable Cox proportional-hazards regression model was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for T2D after adjusting for categorical (educational level, current drinking status, current smoking status, and physical activity) and

continuous (age, BMI, and energy intake) covariables. The lowest quintile (Q1) of TAC or flavonoid intake served as a reference group. The median value of each quintile group was modeled as a continuous variable in the Cox model to test the trend. We also estimated the HRs and 95% CIs for an SD increment in dietary TAC and flavonoid intake and conducted stratified analyses according to BMI, age, smoking status, and alcohol consumption. The strata indices for continuous variables (BMI and age) were median value referred to a previous study.(31)

## RESULTS

A total of 20,594 individuals (aged 40–79 years) were included in this study. After an average of 5 years of follow-up, the incidence of T2D mellitus was 5.25% in men and 2.52% in women. The baseline general characteristics of participants according to quintiles of total flavonoid intake are shown in Table 1. Among both men and women participants, the highest consumption group (Q5) included more non-smokers, more participants with higher education levels, and more participants who engaged in physical activity (all $p$ value < 0.05).

Table 1. Baseline general characteristics of participants by total flavonoid consumption

| | Antioxidant consumption | | | | | |
|---|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | Q5 | *P*-value |
| Men, **n=6327** | | | | | | |
| **Cases / person-years** | **80** / 5103.00 | **74 / 5060.60** | **60 / 4995.40** | **71 / 5110.50** | **47 / 5182.60** | |
| Age, years | 54.45 ± 8.64 | 54.97 ± 8.51 | 54.2**0** ± 8.37 | 54.55 ± 8.32 | 54.89 ± 7.97 | 0.0758 |
| BMI, kg/m² | 24.07 ± 2.74 | 24.19 ± 2.73 | 24.21 ± 2.71 | 24.31 ± 2.65 | 24.32 ± 2.58 | 0.1348 |
| Smoking status | | | | | | **<.0001** |
| Never | 357 (28.22%) | 404 (31.91%) | 395 (31.27%) | 373 (29.56%) | 426 (33.84%) | |
| Past | 451 (35.65%) | 516 (40.76%) | 549 (43.47%) | 586 (46.43%) | 575 (45.67%) | |
| Current | 457 (36.13%) | 346 (27.33%) | 319 (25.26%) | 303 (24.01%) | 258 (20.49%) | |
| Educational level | | | | | | **<.0001** |
| Under middle school | 382 (30.32%) | 297 (23.52%) | 244 (19.4**0**%) | 186 (14.77%) | 135 (10.69%) | |
| High school | 503 (39.92%) | 521 (41.25%) | 492 (39.11%) | 504 (40.03%) | 422 (33.41%) | |
| College or above | 375 (29.76%) | 445 (35.23%) | 522 (41.49%) | 569 (45.19%) | 706 (55.9**0**%) | |
| Physical activity | | | | | | **<.0001** |
| Inactive | 1070 (84.65%) | 1024 (80.95%) | 999 (79.03%) | 976 (77.28%) | 896 (70.94%) | |
| Active | 194 (15.35%) | 241 (19.05%) | 265 (20.97%) | 287 (22.72%) | 367 (29.06%) | |
| Current alcohol consumption | | | | | | 0.2578 |
| No | 313 (24.74%) | 337 (26.62%) | 342 (27.04%) | 340 (26.86%) | 364 (28.77%) | |
| Yes | 952 (75.26%) | 929 (73.38%) | 923 (72.96%) | 926 (73.14%) | 901 (71.23%) | |
| Total energy intake, kcal/day | 1624.56 ± 401.**00** | 1764.89 ± 417.55 | 1842.23 ± 431.57 | 1926.29 ± 442.88 | 2110.85 ± 499.16 | **<.0001** |
| Carbohydrate, E% | 72.51 ± 7.71 | 71.63 ± 7.1**0** | 71.**00** ± 7.33 | 70.49 ± 6.88 | 70.07 ± 7.09 | **<.0001** |
| Protein, E% | 12.99 ± 2.41 | 13.33 ± 2.12 | 13.52 ± 2.25 | 13.79 ± 2.26 | 13.97 ± 2.37 | **<.0001** |
| Fat, E% | 14.5**0** ± 5.73 | 15.04 ± 5.33 | 15.47 ± 5.48 | 15.73 ± 5.07 | 15.96 ± 5.15 | **<.0001** |
| Dietary fiber intake, g/day | 3.84 ± 1.12 | 4.72 ± 1.24 | 5.28 ± 1.33 | 5.91 ± 1.5**0** | 7.42 ± 2.14 | **<.0001** |
| Total flavonoid, mg VCE/d | 58.16 ± 15.38 | 97.92 ± 10.58 | 135.76 ± 11.78 | 185.2**0** ± 18.17 | 299.44 ± 77.77 | **<.0001** |
| Anthocyanidins, mg VCE/d | 11.73 ± 5.14 | 20.53 ± 6.74 | 28.17 ± 9.84 | 37.83 ± 13.24 | 62.9**0** ± 28.55 | **<.0001** |
| Isoflavones, mg VCE/d | 8.63 ± 4.74 | 11.56 ± 6.3**0** | 12.24 ± 6.53 | 13.16 ± 6.86 | 15.96 ± 9.48 | **<.0001** |
| Proanthocyanidins, mg VCE/d | 23.59 ± 9.01 | 41.24 ± 10.74 | 59.17 ± 14.68 | 80.74 ± 21.27 | 135.1**0** ± 47.83 | **<.0001** |
| Flavonols, mg VCE/d | 7.5**0** ± 4.38 | 10.58 ± 6.08 | 13.18 ± 6.82 | 16.78 ± 9.23 | 24.31 ± 16.28 | **<.0001** |

| | | | | | | |
|---|---|---|---|---|---|---|
| Flavones, mg VCE/d | 0.29 ± 0.15 | 0.45 ± 0.18 | 0.60 ± 0.22 | 0.79 ± 0.29 | 1.19 ± 0.49 | **<.0001** |
| Flavanones, mg VCE/d | 1.80 ± 1.52 | 3.20 ± 1.96 | 4.56 ± 2.74 | 6.01 ± 3.76 | 10.29 ± 6.33 | **<.0001** |
| Flavan-3-ols, mg VCE/d | 4.63 ± 4.40 | 10.35 ± 9.70 | 17.84 ± 15.94 | 29.88 ± 23.91 | 49.69 ± 37.80 | **<.0001** |
| TAC, mg VCE/d | 113.96 ± 32.02 | 185.25 ± 30.65 | 252.44 ± 37.18 | 343.26 ± 51.65 | 542.84 ± 149.10 | **<.0001** |
| **Women, n=14267** | | | | | | |
| **Cases / person-years** | **89 / 11021.20** | **82 / 11303.30** | **76 / 11322.20** | **59 / 11526.80** | **54 / 11650.80** | |
| Age, years | 52.64 ± 8.04 | 52.31 ± 7.84 | 52.19 ± 7.68 | 52.01 ± 7.23 | 52.18 ± 7.02 | 0.0832 |
| BMI, kg/m$^2$ | 23.44 ± 3.05 | 23.40 ± 2.93 | 23.32 ± 2.85 | 23.27 ± 2.80 | 23.19 ± 2.72 | 0.8879 |
| Smoking status | | | | | | **<.0001** |
| Never | 2746 (96.32%) | 2784 (97.72%) | 2788 (97.82%) | 2806 (98.39%) | 2768 (97.23%) | |
| Past | 31 (1.09%) | 21 (0.74%) | 24 (0.84%) | 21 (0.74%) | 35 (1.23%) | |
| Current | 74 (2.60%) | 44 (1.54%) | 38 (1.33%) | 25 (0.88%) | 44 (1.55%) | |
| Educational level | | | | | | **<.0001** |
| Under middle school | 1150 (40.41%) | 977 (34.33%) | 901 (31.74%) | 760 (26.73%) | 625 (22.01%) | |
| High school | 1236 (43.43%) | 1305 (45.85%) | 1297 (45.69%) | 1368 (48.12%) | 1341 (47.23%) | |
| College or above | 460 (16.16%) | 564 (19.82%) | 641 (22.58%) | 715 (25.15%) | 873 (30.75%) | |
| Physical activity | | | | | | **<.0001** |
| Inactive | 2449 (85.96%) | 2355 (82.63%) | 2294 (80.46%) | 2239 (78.48%) | 2120 (74.49%) | |
| Active | 400 (14.04%) | 495 (17.37%) | 557 (19.54%) | 614 (21.52%) | 726 (25.51%) | |
| Current alcohol consumption | | | | | | 0.2756 |
| No | 1900 (66.60%) | 1967 (68.92%) | 1932 (67.72%) | 1928 (67.55%) | 1966 (68.91%) | |
| Yes | 953 (33.40%) | 887 (31.08%) | 921 (32.28%) | 926 (32.45%) | 887 (31.09%) | |
| Total energy intake, kcal/day | 1429.83 ± 392.78 | 1577.31 ± 420.56 | 1659.22 ± 437.45 | 1761.14 ± 460.69 | 1947.92 ± 497.29 | **<.0001** |
| Carbohydrate, E% | 71.87 ± 8.06 | 71.25 ± 7.93 | 70.67 ± 7.63 | 70.30 ± 7.36 | 69.97 ± 7.30 | **<.0001** |
| Protein, E% | 13.39 ± 2.47 | 13.59 ± 2.42 | 13.76 ± 2.38 | 13.89 ± 2.33 | 14.01 ± 2.43 | **<.0001** |
| Fat, E% | 14.74 ± 6.03 | 15.16 ± 5.91 | 15.57 ± 5.65 | 15.81 ± 5.45 | 16.02 ± 5.33 | **<.0001** |
| Dietary fiber intake, g/day | 3.80 ± 1.11 | 4.61 ± 1.21 | 5.13 ± 1.30 | 5.97 ± 1.52 | 7.38 ± 2.10 | **<.0001** |
| Total flavonoid, mg VCE/d | 71.44 ± 17.73 | 116.97 ± 11.49 | 159.39 ± 13.42 | 213.52 ± 19.24 | 333.98 ± 94.24 | **<.0001** |
| Anthocyanidins, mg VCE/d | 15.24 ± 6.21 | 25.89 ± 8.12 | 35.35 ± 11.02 | 46.82 ± 14.12 | 74.77 ± 32.62 | **<.0001** |
| Isoflavones, mg VCE/d | 8.63 ± 4.48 | 10.67 ± 5.74 | 11.70 ± 6.42 | 13.28 ± 7.25 | 15.09 ± 9.07 | **<.0001** |
| Proanthocyanidins, mg VCE/d | 31.11 ± 10.57 | 52.62 ± 11.64 | 73.61 ± 15.79 | 101.51 ± 21.34 | 161.00 ± 54.19 | **<.0001** |
| Flavonols, mg VCE/d | 8.09 ± 4.63 | 11.18 ± 5.92 | 13.54 ± 7.50 | 16.94 ± 9.30 | 24.05 ± 16.19 | **<.0001** |
| Flavones, mg VCE/d | 0.35 ± 0.18 | 0.55 ± 0.23 | 0.71 ± 0.28 | 0.89 ± 0.34 | 1.31 ± 0.62 | **<.0001** |
| Flavanones, mg VCE/d | 2.56 ± 1.91 | 4.37 ± 2.55 | 5.98 ± 3.19 | 7.70 ± 3.84 | 12.62 ± 8.04 | **<.0001** |
| Flavan-3-ols, mg VCE/d | 5.45 ± 4.85 | 11.68 ± 10 | 18.51 ± 14.74 | 26.38 ± 20.18 | 45.13 ± 36.98 | **<.0001** |
| TAC (mg VCE/d) | 135.61 ± 36.42 | 216.26 ± 31.08 | 289.3 ± 38.71 | 380.21 ± 51.07 | 587.77 ± 176.53 | **<.0001** |

Values are presented as means ± standard deviations or numbers (%). *P*-values were calculated using a generalized linear model for continuous variables and Chi-square test for categorical variables. $p<0.05$ are shown in bold.

Total flavonoid intake was the sum of anthocyanidins, isoflavones, proanthocyanidins, flavonols, flavones, flavanones, and flavan-3-ols.

Total antioxidant capacity (TAC) was obtained by combining the individual antioxidant capacity of each antioxidant derived from every food item. BMI: body mass index, VCE: vitamin C equivalents.

Table 2 shows the range of dietary antioxidant intake by quintiles. The associations between dietary antioxidant intake and the HRs of T2D mellitus are presented in Table 3. All participants with the highest total dietary flavonoid intake (Q5) had a lower risk of developing T2D mellitus (men: HR, 0.63; 95% CI, 0.42–0.93 and women: HR, 0.54; 95% CI, 0.38–0.78; both *P* for trend < 0.05) than those with the lowest flavonoid intake (Q1). Consumption of more flavonols and proanthocyanidins had a protective effect against the development of T2D mellitus in men participants, and consumption of anthocyanidins, proanthocyanidins, flavonols, flavones, and flavanones showed a protective effect against T2D mellitus in women participants (all *P* for trend < 0.05). After estimation of HRs

according to quintiles of TAC, the Q5 group of women participants still showed a lower risk of T2D mellitus (HR, 0.58; 95% CI, 0.40–0.83; *P* for trend = 0.0004) than the Q1 group. However, although the TAC Q5 group of men participants did not show any significant association with T2D mellitus, they had an approximately 15% reduced risk of developing T2D mellitus for an SD increment in TAC (HR, 0.85; 95% CI, 0.75–0.96). After further adjustment for energy percent from carbohydrate, fat, and protein and dietary fiber intake, the results remained largely unchanged (Supplementary Table S1 and Table S2).

Table 2. Range of each dietary antioxidant intake by quintile

| | Antioxidant consumption | | | | |
|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | Q5 |
| Men | | | | | |
| Total flavonoid (mg VCE/d) | 58.16 (13.07 – 80.30) | 97.92 (80.32 – 116.38) | 135.76 (116.38 – 156.75) | 185.20 (156.80 – 221.23) | 299.44 (221.46 – 1150.79) |
| Anthocyanidins (mg VCE/d) | 9.69 (0.75 – 14.14) | 17.94 (14.14 – 21.97) | 26.58 (21.97 – 31.57) | 38.62 (31.57 – 46.86) | 68.33 (46.89 – 378.83) |
| Isoflavones (mg VCE/d) | 5.07 (0.10 – 6.80) | 8.07 (6.80 – 9.35) | 10.78 (9.35 – 12.22) | 14.16 (12.22 – 16.57) | 23.48 (16.57 – 94.05) |
| Proanthocyanidins (mg VCE/d) | 21.28 (1.43 – 31.14) | 39.10 (31.15 – 47.5) | 56.93 (47.52 – 67.33) | 81.94 (67.35 – 99.38) | 140.58 (99.41 – 723.02) |
| Flavonols (mg VCE/d) | 5.25 (0.69 – 7.30) | 8.81 (7.30 – 10.32) | 11.89 (10.33 – 13.65) | 16.14 (13.65 – 19.27) | 30.25 (19.27 – 231.83) |
| Flavones (mg VCE/d) | 0.23 (0.02 – 0.33) | 0.40 (0.33 – 0.48) | 0.57 (0.48 – 0.67) | 0.79 (0.67 – 0.93) | 1.32 (0.93 – 4.37) |
| Flavanones (mg VCE/d) | 1.03 (0.00 – 1.77) | 2.43 (1.77 – 3.09) | 3.93 (3.09 – 4.89) | 6.16 (4.89 – 7.80) | 12.33 (7.80 – 62.77) |
| Flavan–3–ols (mg VCE/d) | 2.98 (0.10 – 4.91) | 6.82 (4.92 – 8.87) | 11.79 (8.87 – 15.54) | 23.54 (15.56 – 41.05) | 67.26 (41.06 – 252.89) |
| TAC (mg VCE/d) | 111.21 (21.57 – 150.38) | 182.54 (150.45 – 215.60) | 251.21 (215.61 – 289.93) | 343.27 (289.98 – 406.09) | 549.53 (406.14 – 1811.29) |
| Women | | | | | |
| Total flavonoid (mg VCE/d) | 71.44 (7.28 – 96.65) | 116.97 (96.66 – 136.81) | 159.39 (136.81 – 183.19) | 213.52 (183.20 – 250.56) | 333.98 (250.59 – 1263.46) |
| Anthocyanidins (mg VCE/d) | 12.85 (0.44 – 18.47) | 23.33 (18.48 – 28.19) | 34.01 (28.19 – 40.07) | 47.64 (40.07 – 56.64) | 80.24 (56.65 – 372.08) |
| Isoflavones (mg VCE/d) | 4.83 (0.43 – 6.50) | 7.73 (6.50 – 8.96) | 10.31 (8.96 – 11.72) | 13.67 (11.72 – 16.02) | 22.83 (16.02 – 85.19) |
| Proanthocyanidins (mg VCE/d) | 28.89 (2.21 – 41.00) | 50.74 (41.01 – 60.82) | 72.48 (60.83 – 84.94) | 101.70 (84.95 – 121.70) | 166.05 (121.73 – 633.15) |
| Flavonols (mg VCE/d) | 5.72 (1.00 – 7.65) | 9.09 (7.65 – 10.55) | 12.11 (10.55 – 13.81) | 16.26 (13.81 – 19.38) | 30.62 (19.38 – 195.47) |
| Flavones (mg VCE/d) | 0.28 (0.01 – 0.39) | 0.48 (0.39 – 0.57) | 0.67 (0.57 – 0.77) | 0.89 (0.77 – 1.05) | 1.50 (1.05 – 7.62) |
| Flavanones (mg VCE/d) | 1.58 (0.00 – 2.58) | 3.44 (2.58 – 4.35) | 5.38 (4.35 – 6.55) | 7.95 (6.55 – 9.73) | 14.88 (9.73 – 132.99) |
| Flavan–3–ols (mg VCE/d) | 3.82 (0.25 – 6.06) | 8.18 (6.06 – 10.41) | 13.17 (10.41 – 16.31) | 21.85 (16.31 – 30.72) | 60.14 (30.72 – 376.53) |
| TAC | 132.65 (13.04 – 178.98) | 214.39 (178.99 – 248.73) | 287.62 (248.74 – 328.90) | 380.46 (328.94 – 442.53) | 594.04 (442.54 – 2240.46) |

Values were presented as mean (min–max). TAC: Total antioxidant capacity, VCE: vitamin C equivalents.

Table 3. Hazard ratios of type 2 diabetes mellitus during follow-up according to antioxidant consumption divided into quintiles, where Q5 represents highest

| | Antioxidant consumption | | | | | | |
|---|---|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | Q5 | *P* for trend | HR for an SD increment |
| Men | | | | | | | |
| Total flavonoid | Ref | 0.98 (0.71, 1.34) | 0.90 (0.64, 1.26) | 0.91 (0.65, 1.27) | 0.63 (0.42, 0.93) | 0.0169 | 0.85 (0.75, 0.97) |
| Anthocyanidins | Ref | 0.79 (0.56, 1.11) | 0.99 (0.72, 1.36) | 0.86 (0.62, 1.20) | 0.71 (0.50, 1.03) | 0.1167 | 0.87 (0.77, 0.99) |
| Isoflavones | Ref | 1.45 (1.03, 2.06) | 1.12 (0.78, 1.60) | 1.19 (0.83, 1.71) | 1.36 (0.94, 1.97) | 0.3151 | 1.05 (0.94, 1.17) |
| Proanthocyanidins | Ref | 1.04 (0.76, 1.44) | 0.97 (0.70, 1.36) | 0.77 (0.54, 1.09) | 0.72 (0.50, 1.05) | 0.0247 | 0.88 (0.77, 0.99) |
| Flavonols | Ref | 1.49 (1.08, 2.05) | 0.90 (0.63, 1.30) | 0.97 (0.68, 1.38) | 0.82 (0.56, 1.19) | 0.0381 | 0.84 (0.73, 0.97) |
| Flavones | Ref | 1.01 (0.73, 1.41) | 1.01 (0.72, 1.41) | 0.84 (0.59, 1.20) | 0.85 (0.59, 1.22) | 0.2322 | 0.90 (0.80, 1.01) |
| Flavanones | Ref | 0.83 (0.59, 1.17) | 1.23 (0.89, 1.68) | 0.94 (0.67, 1.31) | 0.82 (0.57, 1.18) | 0.3313 | 0.94 (0.83, 1.06) |
| Flavan-3-ols | Ref | 0.89 (0.64, 1.24) | 1.12 (0.81, 1.55) | 0.79 (0.55, 1.12) | 0.75 (0.52, 1.08) | 0.0744 | 0.90 (0.79, 1.01) |
| TAC | Ref | 1.08 (0.78, 1.49) | 0.95 (0.68, 1.33) | 0.87 (0.62, 1.24) | 0.73 (0.50, 1.06) | 0.0448 | 0.85 (0.75, 0.96) |
| Women | | | | | | | |
| Total flavonoid | Ref | 0.90 (0.66, 1.22) | 0.82 (0.60, 1.12) | 0.61 (0.44, 0.87) | 0.54 (0.38, 0.78) | 0.0001 | 0.80 (0.70, 0.90) |
| Anthocyanidins | Ref | 0.91 (0.68, 1.23) | 0.63 (0.45, 0.87) | 0.71 (0.52, 0.99) | 0.56 (0.39, 0.79) | 0.0006 | 0.85 (0.75, 0.97) |
| Isoflavones | Ref | 0.98 (0.71, 1.34) | 0.71 (0.51, 0.99) | 0.81 (0.58, 1.13) | 0.78 (0.56, 1.10) | 0.1353 | 0.92 (0.82, 1.04) |
| Proanthocyanidins | Ref | 0.90 (0.66, 1.23) | 1.04 (0.77, 1.41) | 0.66 (0.47, 0.93) | 0.50 (0.34, 0.72) | <.0001 | 0.79 (0.70, 0.90) |
| Flavonols | Ref | 0.83 (0.61, 1.12) | 0.68 (0.49, 0.94) | 0.57 (0.41, 0.80) | 0.61 (0.43, 0.86) | 0.0040 | 0.88 (0.77, 1.00) |
| Flavones | Ref | 0.81 (0.60, 1.10) | 0.74 (0.54, 1.01) | 0.54 (0.38, 0.76) | 0.56 (0.39, 0.79) | 0.0003 | 0.81 (0.71, 0.93) |
| Flavanones | Ref | 0.73 (0.54, 0.98) | 0.56 (0.41, 0.77) | 0.57 (0.41, 0.78) | 0.54 (0.39, 0.76) | 0.0005 | 0.83 (0.73, 0.95) |
| Flavan-3-ols | Ref | 0.83 (0.60, 1.13) | 0.79 (0.57, 1.08) | 0.64 (0.45, 0.90) | 0.79 (0.57, 1.10) | 0.3681 | 0.93 (0.82, 1.05) |
| TAC | Ref | 0.82 (0.60, 1.11) | 0.86 (0.64, 1.17) | 0.51 (0.36, 0.73) | 0.58 (0.40, 0.83) | 0.0004 | 0.81 (0.71, 0.92) |

Results are presented as the hazard ratio (HR) for a standard deviation (SD) increment in dietary antioxidant capacity using a cox model.
The multivariable Cox proportional hazards regression model was adjusted for age, body mass index (BMI), educational level, physical activity, drinking status, smoking status, and total energy intake.
Total flavonoid intake was the sum of anthocyanidins, isoflavones, proanthocyanidins, flavonols, flavones, flavanones, and flavan-3-ols.
Total antioxidant capacity (TAC) was obtained by combining the individual antioxidant capacity of each antioxidant derived from every food item.

We also performed stratified analyses according to age, BMI, drinking status for both sexes, and smoking status for men participants. Figure 1 shows the HRs of T2D mellitus in the Q5 and Q1 groups according to baseline age, baseline BMI, and alcohol drinking status in the HEXA study. There was almost no significant association between T2D mellitus and dietary intake of antioxidant components in men participants. However, total flavonoid intake and dietary TAC showed a protective effect against the development of T2D mellitus in women participants who were aged > 52 years, had a BMI ≥ 25 kg/m$^2$, and regardless of alcohol consumption.

## Discussion

In this study, we discovered that dietary total flavonoid consumption and TAC are both associated with a reduced risk of developing T2D mellitus. After further analysis stratified according to age, and BMI, we found that dietary total flavonoid consumption and TAC had a protective effect against the development of type 2 diabetes mellitus in women participants who were overweight or aged > 52 years.

Oxidative stress, which is an imbalance between the production of reactive oxygen species (free radicals) and antioxidant defense mechanism, is a risk factor for T2D.(17) Previous studies have shown that oxidative stress impairs the secretion of insulin by pancreatic beta cells and interferes with the insulin signaling pathway, thereby accelerating the development and progression of T2D by increasing insulin resistance.(2, 3, 6, 32, 33)

Oxidative stress can be regulated by antioxidants, which react with reactive oxygen species.(34) The consumption of dietary flavonoids has been shown to be associated with lower incidences of T2D. Several previous studies have indicated that flavonoids decrease plasma glucose levels and improve lipid profile, insulin secretion, and insulin resistance, factors which are implicated in the development of T2D.(2, 3, 8, 35) In a previous study, higher flavonol intake was associated with a 26% lower incidence of T2D.(36)~~(35)~~ In addition, the authors observed a marginally significant inverse association between flavan-3-ol intake and the risk of T2D, but there was no association with anthocyanin intake.(36)~~(35)~~ Knekt et al.(37) reported a marginally significant inverse association between the intake of the flavonols quercetin, and myricetin, but not kaempferol, and the incidence of T2D in Finnish men and women. Quercetin, in particular, is known to decrease plasma glucose concentration, improve insulin concentration, preserve the integrity of pancreatic beta cells, alleviate T2D symptoms, and reduce hepatic gene expression in streptozotocin-induced diabetic models.(38)-Flavan-3-ol and isoflavone intake is associated with a reduced risk of T2D and improved insulin resistance and serum insulin concentrations.(39) Dietary flavone intake is negatively associated with systolic blood pressure, triglyceride level, triglyceride/high-density lipoprotein-cholesterol level, and homeostatic model assessment of insulin resistance. Flavone intake may have some beneficial effects in the reduction of the prevalence of T2D in South Korean women.(8) Consumption of foods rich in anthocyanins, particularly blueberries, apples, and pears, is also inversely associated with the risk of T2D in the United States.(40)

A key potential mechanism for the protective effect of flavonoids against T2D is the protection of tissues from free oxygen radicals and lipid peroxidation through their antioxidant activity.(41) In addition, anti-inflammatory functions, improvement of

endothelial functions, reduction of blood cholesterol concentration, and nicotinamide adenine dinucleotide phosphate oxidase activity are also associated with a reduced risk of T2D mellitus.(41) Flavonoids are known to interact with molecular targets and affect NF-κB and MAPK signaling pathways.(42) Furthermore, flavonoids modulate postprandial glucose levels by reducing the activities of digestive enzymes (a-amylase and a-glucosidase), decreasing the active transport of glucose across the intestinal brush border membrane, and inhibiting glucose transporters.(32) Antioxidant-rich fruits and vegetables contain relatively high fiber content, which can influence the beneficial effects of antioxidants against T2D.(43) Furthermore, it has been reported that flavonoids inhibit α-glucosidase activity to alleviate hyperglycemia.(44, 45)

The effect of each type of flavonoid intake on the risk of T2D varies by sex. In this study, there was a correlation between anthocyanidin and proanthocyanidin intake and the risk of developing T2D in men. However, there was a greater correlation between the risk of T2D and intake of flavonoids, such as anthocyanidins, proanthocyanidins, flavonols, flavones, and flavanones, in women than in men. These sex-specific results are often seen in other phytochemical-related studies. In a previous study conducted using 2008–2011 data from the Korea National Health and Nutrition Examination Survey, a high intake of flavonoids did not reduce the incidence of obesity and abdominal obesity in men but significantly reduced obesity (18%) in women. In addition, high flavonoid intake was reported to reduce the incidence of abdominal obesity (19%) in that study.(2, 46, 47) The variations in these results appear to be due to differences between the dietary intake patterns of South Korean men and women. Sex-specific dietary patterns have been reported in previous studies; namely, men consume the recommended amount of vegetables more than women, whereas women consume the recommended amount of fruit more than men.(48) In

addition, women generally consume higher amounts of dietary antioxidants than men.(2, 49) Higher intake of dietary antioxidants can induce high plasma concentrations of antioxidants and more beneficial effects on preventing development of T2D. Furthermore, gonadal hormones (menopausal estrogen and testosterone) have been implicated in sex-specific differences in glucose homeostasis.(50) Healthy women have lower skeletal muscle mass, higher adipose tissue mass, more circulating free fatty acids, and higher intramyocellular lipid content than men of the same age. These are all factors that could promote increased insulin resistance in women compared with men.(50)

Various factors, such as age and lifestyle, are known to contribute to the development and progression of T2D.(17) The prevalence of T2D in South Koreans increases rapidly with age.(4) Unhealthy lifestyle habits, such as smoking, excessive alcohol consumption, and inactivity, are known to contribute to the development of diabetes.(3, 51) We found that men with T2D were older and more likely to be current drinkers and current smokers than those without diabetes. However, our stratified analysis showed that there was no correlation between these factors except for current alcohol consumption. On the other hand, women with T2D were significantly older and had significantly higher BMI than those without diabetes. Furthermore, the stratified analysis showed that antioxidant consumption was inversely related to the HR of T2D in older women (> 52 years), women with a BMI > 25 $kg/m^2$, regardless of alcohol consumption. Although it is difficult to fully explain these variations in South Korean adults, these findings suggest that high antioxidant intake may be related to a decreased risk of T2D, especially in women with specific lifestyle habits.

**Strengths and limitations**

The main strength of this study was that it was conducted using a large-scale community-based genomic cohort study with 5 years of follow-up on average. Stratified

analyses were conducted in the current study to focus on one certain exposure. This study had some limitations. First, although this study reported a longitudinal relationship between dietary antioxidant consumption and T2D incidence, we did not assess the causality. Second, we obtained dietary information and information on the intake of antioxidant components using self-reported FFQ; thus, dietary measurement errors were inevitable. However, the 106-item FFQ has been previously verified.(26) In addition, further studies are needed to measure the flavonoid concentration to verify the data. Third, we did not quantify the amount of alcohol consumption and smoking. Nevertheless, we found no association between smoking status and T2D after stratification analyses. Dietary antioxidants showed a protective effect against the development of T2D only in women who were non-drinkers.

## Conclusions

The findings of this large-scale prospective cohort study suggest that dietary antioxidant consumption is associated with a lower risk of T2D in South Korean adults. The findings of this study can serve as a reference or guide for the modification of food intake recommendations in dietary guideline policies in South Korea. However, further studies are needed to validate the results of this study.

## Declarations

### Ethics approval and consent to participate

All participants voluntarily signed an informed written consent form before enrollment. This study was performed in accordance with the guidelines specified in the Declaration of Helsinki, and the study protocol was approved by the local Institutional Review Board (IRB)

of the Ethics Committee of the Korean Genome and Epidemiology Study of the Korea National Institute of Health (IRB no. 2014-08-02-3C-A).

## Consent for publication

Not applicable.

## Availability of data and materials

The data that support the findings of this study are available from the National Genome Research Institute, Korea Centers for Disease Control and Prevention. How ever, restrictions apply to the availability of these data, which were used under lice nse for this study, and as such are not publicly available. Data are however availa ble from the authors upon reasonable request and with permission of the National Genome Research Institute, Korea Centers for Disease Control and Prevention.

## Competing interests

The authors declare that they have no competing interests.

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collection, analysis, and interpretation of data; writing the report; and did not impose any restrictions regarding the publication of the report. This research was supported by the Chung-Ang University Young Scientist Scholarship (CAYSS) in 2021.

## Authors' contributions

S.S. supervised the project. S.S. contributed to the conceptualization or design of this study. S.J. and H.J. were contributed to establish the antioxidants database. L.J.T conducted the formal analysis. S.S. verified and validated the outcomes. L.J.T and S.B.H. co-wrote the first draft of the manuscript. S.J. and H.J. reviewed and revised the article critically. All authors approved the final version of the article for publication. S.S. and L.J.T had full access to all the data in the study and take full responsibility for the integrity of the data and accuracy of the data analysis.

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## Figure Legend

**Figure 1.** Hazard ratios (HR) with 95% confidence intervals (CIs) for type 2 diabetes mellitus after comparison of antioxidant consumption in the Q5 and Q1 groups according to baseline age, baseline body mass index (BMI), alcohol consumption, smoking status in the Health Examinees study. TAC: total antioxidant capacity

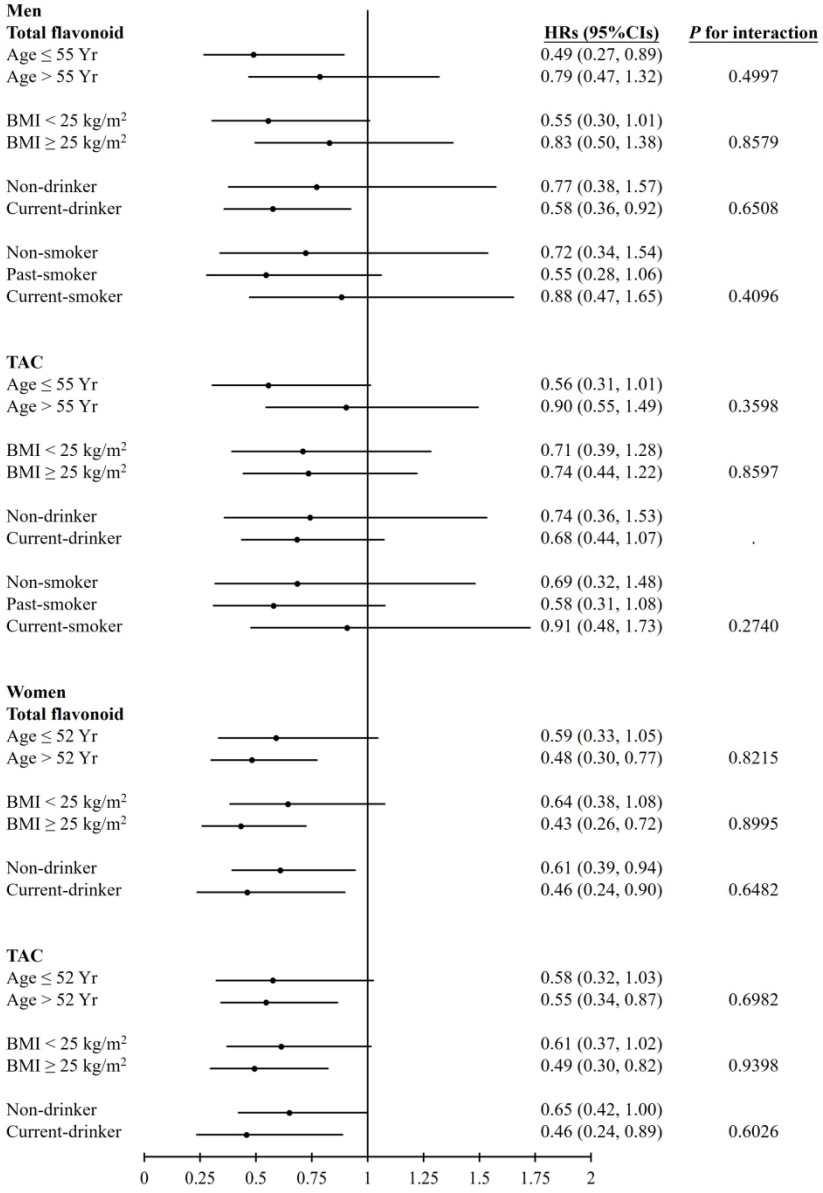


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**Table S1. Hazard ratios of type 2 diabetes during follow-up according to quintile of cumulative average antioxidant consumption in model 2**

| | Antioxidant consumption | | | | | | |
|---|---|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | Q5 | *P* for trend | HR for a SD increment |
| Men | | | | | | | |
| Total flavonoid | Ref | 0.97 (0.71, 1.34) | 0.89 (0.63, 1.25) | 0.89 (0.64, 1.24) | 0.62 (0.42, 0.92) | 0.0136 | 0.85 (0.75, 0.97) |
| Anthocyanidins | Ref | 0.78 (0.56, 1.10) | 0.98 (0.71, 1.35) | 0.85 (0.61, 1.19) | 0.70 (0.49, 1.01) | 0.0994 | 0.87 (0.76, 0.99) |
| Isoflavones | Ref | 1.44 (1.01, 2.04) | 1.10 (0.76, 1.59) | 1.18 (0.81, 1.70) | 1.32 (0.90, 1.95) | 0.4245 | 1.04 (0.92, 1.17) |
| Proanthocyanidins | Ref | 1.04 (0.76, 1.44) | 0.97 (0.70, 1.36) | 0.77 (0.54, 1.09) | 0.72 (0.50, 1.04) | 0.0226 | 0.87 (0.77, 0.99) |
| Flavonols | Ref | 1.46 (1.06, 2.00) | 0.88 (0.61, 1.27) | 0.93 (0.64, 1.33) | 0.77 (0.52, 1.14) | 0.0218 | 0.82 (0.71, 0.95) |
| Flavones | Ref | 1.00 (0.72, 1.38) | 1.00 (0.71, 1.40) | 0.82 (0.57, 1.17) | 0.83 (0.57, 1.21) | 0.1941 | 0.89 (0.79, 1.01) |
| Flavanones | Ref | 0.83 (0.59, 1.17) | 1.21 (0.88, 1.67) | 0.93 (0.66, 1.30) | 0.81 (0.56, 1.16) | 0.2998 | 0.93 (0.83, 1.05) |
| Flavan-3-ols | Ref | 0.88 (0.63, 1.23) | 1.11 (0.80, 1.54) | 0.78 (0.55, 1.11) | 0.74 (0.51, 1.08) | 0.0719 | 0.89 (0.79, 1.01) |
| TAC | Ref | 1.07 (0.77, 1.47) | 0.94 (0.67, 1.31) | 0.85 (0.59, 1.20) | 0.71 (0.48, 1.05) | 0.0347 | 0.84 (0.74, 0.96) |
| Women | | | | | | | |
| Total flavonoid | Ref | 0.92 (0.68, 1.24) | 0.84 (0.62, 1.15) | 0.63 (0.45, 0.89) | 0.55 (0.38, 0.80) | 0.0002 | 0.80 (0.71, 0.91) |
| Anthocyanidins | Ref | 0.92 (0.68, 1.24) | 0.64 (0.46, 0.89) | 0.72 (0.52, 1.00) | 0.56 (0.39, 0.80) | 0.0007 | 0.86 (0.75, 0.97) |
| Isoflavones | Ref | 0.99 (0.72, 1.35) | 0.72 (0.51, 1.02) | 0.84 (0.60, 1.17) | 0.83 (0.58, 1.18) | 0.2885 | 0.94 (0.84, 1.07) |
| Proanthocyanidins | Ref | 0.92 (0.67, 1.25) | 1.07 (0.79, 1.45) | 0.67 (0.48, 0.95) | 0.51 (0.35, 0.74) | <.0001 | 0.79 (0.70, 0.90) |
| Flavonols | Ref | 0.85 (0.62, 1.15) | 0.69 (0.50, 0.96) | 0.59 (0.42, 0.83) | 0.62 (0.44, 0.89) | 0.0066 | 0.89 (0.78, 1.02) |
| Flavones | Ref | 0.82 (0.60, 1.11) | 0.75 (0.55, 1.03) | 0.54 (0.38, 0.77) | 0.57 (0.40, 0.81) | 0.0004 | 0.82 (0.71, 0.93) |
| Flavanones | Ref | 0.74 (0.55, 1.00) | 0.57 (0.41, 0.79) | 0.58 (0.42, 0.80) | 0.55 (0.40, 0.77) | 0.0008 | 0.84 (0.73, 0.96) |
| Flavan-3-ols | Ref | 0.84 (0.62, 1.15) | 0.81 (0.59, 1.12) | 0.66 (0.47, 0.92) | 0.81 (0.58, 1.13) | 0.4157 | 0.93 (0.82, 1.06) |
| TAC | Ref | 0.84 (0.62, 1.14) | 0.89 (0.65, 1.21) | 0.53 (0.37, 0.75) | 0.60 (0.42, 0.86) | 0.0007 | 0.81 (0.71, 0.93) |

The multivariable Cox proportional-hazards regression model was adjusted for age, body mass index (BMI), educational level, physical activity, alcohol consumption, smoking status, total energy intake, energy percent from carbohydrate, energy percent from protein, and energy percent from fat.

Total flavonoid intake was the sum of anthocyanidins, isoflavones, proanthocyanidins, flavonols, flavones, flavanones, and flavan-3-ols.

Total antioxidant capacity (TAC) was obtained by combining the individual antioxidant capacity of each antioxidant derived from every food item.

**Table S2. Hazard ratios of type 2 diabetes during follow-up according to quintile of cumulative average antioxidant consumption in model 3**

| | Antioxidant consumption | | | | | | |
|---|---|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | Q5 | *P* for trend | HR for a SD increment |
| Men | | | | | | | |
| Total flavonoid | Ref | 1.00 (0.72, 1.39) | 0.94 (0.66, 1.34) | 0.98 (0.68, 1.40) | 0.71 (0.45, 1.13) | 0.1553 | 0.89 (0.76, 1.04) |
| Anthocyanidins | Ref | 0.82 (0.58, 1.15) | 1.06 (0.76, 1.47) | 0.96 (0.67, 1.37) | 0.85 (0.56, 1.30) | 0.6471 | 0.92 (0.79, 1.08) |
| Isoflavones | Ref | 1.53 (1.08, 2.18) | 1.22 (0.84, 1.76) | 1.31 (0.90, 1.89) | 1.61 (1.09, 2.38) | 0.0731 | 1.12 (0.99, 1.26) |
| Proanthocyanidins | Ref | 1.06 (0.77, 1.46) | 1.02 (0.72, 1.43) | 0.83 (0.58, 1.20) | 0.81 (0.54, 1.22) | 0.1640 | 0.92 (0.79, 1.06) |
| Flavonols | Ref | 1.54 (1.12, 2.13) | 0.96 (0.66, 1.39) | 1.05 (0.72, 1.54) | 0.97 (0.62, 1.52) | 0.3271 | 0.88 (0.74, 1.05) |
| Flavones | Ref | 1.06 (0.76, 1.48) | 1.09 (0.77, 1.54) | 0.95 (0.65, 1.38) | 1.07 (0.69, 1.65) | 0.9493 | 0.96 (0.83, 1.11) |
| Flavanones | Ref | 0.85 (0.61, 1.21) | 1.29 (0.94, 1.79) | 1.03 (0.73, 1.47) | 0.95 (0.64, 1.40) | 0.8985 | 0.98 (0.87, 1.11) |
| Flavan-3-ols | Ref | 0.93 (0.66, 1.29) | 1.19 (0.86, 1.66) | 0.85 (0.59, 1.23) | 0.84 (0.57, 1.23) | 0.2206 | 0.92 (0.81, 1.05) |
| TAC | Ref | 1.13 (0.81, 1.57) | 1.02 (0.71, 1.45) | 0.98 (0.67, 1.44) | 0.88 (0.55, 1.40) | 0.3967 | 0.88 (0.75, 1.04) |
| Women | | | | | | | |
| Total flavonoid | Ref | 0.90 (0.66, 1.23) | 0.82 (0.59, 1.13) | 0.62 (0.43, 0.89) | 0.54 (0.35, 0.83) | 0.0015 | 0.79 (0.68, 0.93) |
| Anthocyanidins | Ref | 0.93 (0.69, 1.25) | 0.64 (0.46, 0.90) | 0.73 (0.52, 1.04) | 0.58 (0.39, 0.86) | 0.0054 | 0.88 (0.77, 1.02) |
| Isoflavones | Ref | 1.01 (0.74, 1.39) | 0.75 (0.53, 1.06) | 0.88 (0.63, 1.23) | 0.89 (0.62, 1.27) | 0.4969 | 0.97 (0.86, 1.10) |
| Proanthocyanidins | Ref | 0.91 (0.67, 1.25) | 1.05 (0.78, 1.43) | 0.67 (0.47, 0.96) | 0.51 (0.34, 0.77) | 0.0003 | 0.80 (0.69, 0.92) |
| Flavonols | Ref | 0.83 (0.61, 1.14) | 0.69 (0.49, 0.97) | 0.58 (0.40, 0.85) | 0.62 (0.41, 0.96) | 0.0355 | 0.92 (0.78, 1.09) |
| Flavones | Ref | 0.81 (0.60, 1.11) | 0.75 (0.54, 1.03) | 0.55 (0.38, 0.79) | 0.57 (0.38, 0.85) | 0.0029 | 0.82 (0.70, 0.96) |
| Flavanones | Ref | 0.74 (0.55, 1.00) | 0.57 (0.42, 0.79) | 0.58 (0.42, 0.81) | 0.58 (0.40, 0.82) | 0.0038 | 0.86 (0.74, 0.99) |
| Flavan-3-ols | Ref | 0.85 (0.62, 1.17) | 0.83 (0.60, 1.15) | 0.69 (0.48, 0.98) | 0.87 (0.61, 1.23) | 0.7719 | 0.96 (0.84, 1.09) |
| TAC | Ref | 0.82 (0.60, 1.12) | 0.86 (0.62, 1.19) | 0.51 (0.34, 0.75) | 0.57 (0.36, 0.89) | 0.0039 | 0.80 (0.67, 0.95) |

The multivariable Cox proportional-hazards regression model was adjusted for age, body mass index (BMI), educational level, physical activity, drinking status, smoking status, and dietary fiber intake.
Total flavonoid intake was the sum of anthocyanidins, isoflavones, proanthocyanidins, flavonols, flavones, flavanones, and flavan-3-ols.
Total antioxidant capacity (TAC) was obtained by combining the individual antioxidant capacity of each antioxidant derived from every food item.

STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No | Recommendation | Page number |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | Page 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Pages 2–3 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | Pages 4–5 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | Pages 5–6 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Page 6 |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | Pages 6–7 |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | Pages 7–9 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | Pages 7–9 |
| Bias | 9 | Describe any efforts to address potential sources of bias | Pages 17–18 |
| Study size | 10 | Explain how the study size was arrived at | Pages 6–7 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | Page 9 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | |
| | | (*b*) Describe any methods used to examine subgroups and interactions | |
| | | (*c*) Explain how missing data were addressed | |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed | Page 9 |

| | | | |
|---|---|---|---|
| | | *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | |
| | | (*e*) Describe any sensitivity analyses | |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Pages 10–14 |
| | | (b) Give reasons for non-participation at each stage | |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Pages 10–12 |
| | | (b) Indicate number of participants with missing data for each variable of interest | |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | Page 11 |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Pages 12–13 |
| | | (*b*) Report category boundaries when continuous variables were categorized | |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | Page 14 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | Page 14 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | Pages 17–18 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | Pages 14–17 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | Page 18 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Page 19 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.