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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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1 **Dietary antioxidant consumption and the risk of type 2 diabetes in South Korean adults:**  
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5 **A prospective cohort study based on the Health Examinees study**  
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3 20 **Word count:** 3,342 words  
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6 21 **ABSTRACT**  
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10 22 **Objectives:** Antioxidants are common dietary compounds with multiple health benefits.  
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12 23 This study aimed to identify the association between dietary antioxidant consumption and  
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14 24 the incidence of type 2 diabetes mellitus (T2D, defined using the Korean Diabetes  
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16 25 Association criteria) in South Korean adults.

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19 26 **Design:** Baseline and follow-up data from the Health Examinees (HEXA) study, a large-  
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21 27 scale community-based genomic cohort study conducted in South Korea  
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23 28 **Setting:** A South Korean community  
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26 29 **Participants:** A total of 20,594 participants, aged 40–79 years, who participated in the  
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28 30 baseline and follow-up surveys of the HEXA study were included. After an average of 5  
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30 31 years of follow-up, there were 332 men and 360 women with T2D.  
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32 32 **Results:** Participants with the highest total flavonoid consumption (Q5) had a lower risk of  
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34 33 T2D (men: hazard ratio [HR], 0.63; 95% confidence interval [CI], 0.42–0.93; *P* for trend =  
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36 34 0.0169]; and women: HR, 0.54; 95% CI, 0.438–0.78; *P* for trend = 0.0001) than those with  
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38 35 the lowest consumption (Q1). Dietary total antioxidant capacity was significantly inversely  
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40 36 associated with the development of T2D mellitus in women participants alone (HR, 0.58;  
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42 37 95% CI, 0.40–0.83; *P* for trend = 0.0004). Stratified analyses according to age and body  
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44 38 mass index showed that dietary total flavonoid consumption and total antioxidant capacity  
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46 39 had a protective effect against the development of T2D in women aged > 52 years and  
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48 40 women with BMI > 25 kg/m<sup>2</sup>.  
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53 41 **Conclusions:** Dietary flavonoid consumption and total antioxidant capacity were associated  
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55 42 with a lower risk of T2D in South Korean adults, especially in women aged > 52 years and  
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3 43 overweight. The findings of this study may provide reference data for the modification of  
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5 44 dietary guidelines for South Koreans.  
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9 **45 Strengths and limitations of the study**

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12 46 • This study used a large-scale community-based genomic cohort study conducted in  
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14 South Korea with 5 years of follow-up.  
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17 48 • Stratified analyses were conducted to focus on one certain exposure.  
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19 49 • Although this study reported a longitudinal relationship between antioxidant  
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21 consumption and diabetes incidence, we could not assess the causality.  
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24 51 • Dietary measurement errors were inevitable due to using self-reported FFQ.  
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27 **52 Keywords:** Cohort study, Diabetes, Dietary antioxidant, Flavonoid, Health Examinees  
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29 53 study, South Korean adults, Total antioxidant capacity  
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## 54 INTRODUCTION

55 Diabetes is a metabolic disease characterized by high blood glucose levels, impaired  
56 glucose tolerance, impaired insulin secretion, and insulin resistance.(1, 2) Currently,  $\geq 400$   
57 million people are living with type 2 diabetes (T2D) mellitus worldwide.(3) The prevalence  
58 of T2D mellitus increases with age. The 2018 Korean Diabetes Association diabetes fact  
59 sheet reported that the prevalence of T2D in the total population aged  $\geq 65$  years was  
60 29.8%.(4) It is projected that T2D will be the seventh leading cause of death by 2030.(3)  
61 Given that T2D is accompanied by various serious complications, including cardiovascular  
62 disease, peripheral vascular disease, retinopathy, nephropathy, neuropathy, and recently,  
63 sarcopenia, its prevention and treatment are extremely important.(3, 5) Both genetic and  
64 environmental factors contribute to the development and progression of T2D mellitus.  
65 However, its growing prevalence is the result of result of changing dietary habits and  
66 lifestyles observed in modern societies.(6)

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

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

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3 78 which is involved in the pathogenesis of T2D mellitus, by promoting the transportation of  
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5 79 GLUT4 through the regulation of the insulin-signaling pathway.(16, 17)  
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8 80 Previous studies have investigated the correlation between dietary antioxidants and  
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10 81 obesity, dyslipidemia, and metabolic syndrome.(18-21) Azad et al. (22) showed that a diet  
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12 82 high in antioxidants had protective effects against the development of T2D in the Iranian  
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14 83 population. However, few studies have been conducted to determine the association between  
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16 84 dietary antioxidant intake and T2D in South Korean populations. In addition, whether there  
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18 85 is a dose-response relationship between dietary antioxidants and T2D is unclear. It is  
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20 86 pertinent to determine whether a relationship exists between dietary antioxidant intake and  
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22 87 T2D in South Korean adults. Moreover, the effect of dietary antioxidants on T2D has not  
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24 88 been investigated according to the flavonoid subclasses, antioxidant capacities of flavonoids,  
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26 89 or total antioxidant capacity (TAC), which is an index to indicate whole dietary antioxidant  
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28 90 content.(23) Therefore, we conducted this study to explore the association between dietary  
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30 91 antioxidant and the incidence of T2D by analyzing data from the Health Examinees (HEXA)  
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32 92 study.  
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## 42 94 **METHODS**

### 43 44 45 95 **Patient and public involvement**

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48 96 Patients and public were not involved in the design of the study.  
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### 51 97 **Study population**

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54 98 This study was based on the baseline and follow-up data from the HEXA study, a large-  
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56 99 scale community-based genomic cohort study conducted in South Korea. More specific  
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58 100 details of the HEXA study design are described elsewhere.(24) A total of 173,357  
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3 101 participants aged  $\geq 40$  years were initially included in the baseline survey, which was  
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5 102 conducted from 2003 to 2014; 65,642 of these participants were included in the follow-up  
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7 103 survey, which was conducted from 2012 to 2016. At baseline, we excluded participants who  
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9 104 had T2D mellitus or had no information on fasting plasma glucose or HbA<sub>1C</sub> levels (n =  
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11 105 41,311) and those with a history of diseases closely related to T2D mellitus (i.e.,  
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13 106 hyperlipidemia, stroke, transient ischemic attacks, angina pectoris, and myocardial  
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15 107 infarction) (n = 3,082). At follow-up, we excluded those with missing information on  
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17 108 biomarkers for T2D mellitus (fasting plasma glucose, HbA<sub>1C</sub>) (n = 11), those who had an  
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19 109 implausible energy intake ( $< 3,349$  or  $\geq 16,743$  kJ/day for men and  $< 2,093$  or  $\geq 14,650$   
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21 110 kJ/day for women; n = 630 (25)), and those who were missing values for covariables such  
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23 111 as drinking (n = 9) and body mass index (BMI) (n = 5). Ultimately, a total of 20,594  
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25 112 participants (6,327 men and 14,267 women) were included in this study.  
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### 31 **Dietary assessment and estimation of antioxidant components**

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34 114 Dietary intake was assessed using the self-administered, 106-item, food frequency  
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36 115 questionnaire (FFQ) developed for the Korean Genome Epidemiologic Study.(24)  
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38 116 Participants reported the frequencies and average portions of food or beverage items  
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40 117 consumed during the last year before participating in the HEXA study. The reproducibility  
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42 118 and validity of the FFQ have been assessed in a previous study using a reference method by  
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44 119 collecting information on 12-day dietary records.(26) The median correlation coefficient for  
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46 120 all nutrients was 0.39 between the FFQ and 12-day dietary record, and the researchers  
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48 121 concluded that the FFQ could be an acceptable tool for dietary assessment.(26)  
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53 122 In this study, we estimated the participants' intake of antioxidant components using  
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55 123 self-reported dietary data linked to the TAC database for common South Korean foods.(11,  
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57 124 27) Dietary TAC and intake of each flavonoid component were expressed as vitamin C  
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3 125 equivalent antioxidant capacity (mg VCE/100 g). The intake of individual antioxidant  
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5 126 components from a food item was calculated by multiplying the antioxidant component per  
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7 127 gram of food item by the total weight in grams of daily intake of this food item. The daily  
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9 128 intake of individual total dietary antioxidant components was calculated as the sum of the  
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11 129 intake of each antioxidant component from all the food sources reported in the HEXA FFQ  
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13 130 data (mg VCE/day). After summing all individual total dietary antioxidant components, we  
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15 131 obtained the dietary TAC per person per day.

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20 132 Total flavonoid intake was classified into seven categories: anthocyanidins (cyanidin,  
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22 133 delphinidin, pelargonidin, malvidin, peonidin, and petunidin), isoflavones (daidzein,  
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24 134 genistein, and glycitein), proanthocyanidins (proanthocyanidin-dimer, proanthocyanidin-  
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26 135 trimer, proanthocyanidin-4-6mers, proanthocyanidin-7-10mers, and proanthocyanidin-  
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28 136 polymers), flavonols (quercetin, kaempferol, myricetin, and isorhamnetin), flavones  
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30 137 (luteolin and apigenin), flavanones (eriodictyol, hesperetin, and naringenin), and flavan-3-  
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32 138 ols (catechin, epicatechin, epigallocatechin, theaflavin, theaflavin-3-gallate, theaflavin-3'-  
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34 139 gallate, and theaflavin-3-3-digallate).

## 35 36 37 38 39 140 **Definition of type 2 diabetes**

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42 141 T2D was determined in accordance with the definition provided by the Korean Diabetes  
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44 142 Association.(28) T2D was defined as a diagnosis by a physician, increased fasting plasma  
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46 143 glucose level  $\geq 6.99$  mmol/L (126 mg/dL), or elevated HbA<sub>1C</sub> level  $\geq 47.5$  mmol/mol (6.5%).  
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## 49 144 **Covariables**

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52 145 In the HEXA study, the sociodemographic information of each participant was  
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54 146 collected using a questionnaire. Our covariables of interest included age, BMI, level of  
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56 147 education (middle school or lower, high school, or college or higher), and health-related  
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3 148 behaviors, such as smoking (current smoker, past smoker, or non-smoker), alcohol  
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5 149 consumption (never or current drinker), level of physical activity (inactive or active), and  
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8 150 total energy intake (kJ/day). BMI was calculated as the quotient of the body weight (kg) and  
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10 151 height (m) squared (kg/m<sup>2</sup>).<sup>(29)</sup> Smoking status was categorized into three groups based on  
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12 152 the participants' responses to the question, "Have you smoked  $\geq$  20 packs (400 cigarettes)  
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14 153 so far?" Participants who answered "never" were classified as "non-smokers," those who  
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16 154 answered "yes" and were still smoking at the time of the survey were classified as "current  
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18 155 smokers," and those who answered "yes" but had quit smoking at the time of the survey  
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20 156 were classified as "past smokers." Alcohol consumption was classified based on the  
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22 157 responses to the following question, "Are you unable to drink or refuse to do so for religious  
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24 158 or other reasons?" in the HEXA survey. In the present analysis, we classified participants  
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26 159 who replied "yes" as "alcohol non-drinkers;" the rest were classified as "alcohol drinkers."  
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28 160 Regarding physical activity levels, participants were classified as "active" if they reported  
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30 161 that they engaged in exercises resulting in sweating for  $\geq$  30 min twice a week.<sup>(30)</sup>  
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### 36 162 **Statistical analyses**

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39 163 All statistical analyses were sex-stratified and performed using Statistical Analysis  
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41 164 Systems software version 9.4 (SAS Institute, Cary, NC, USA). Statistical significance was  
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43 165 set at  $P < 0.05$ . Continuous variables were presented as means  $\pm$  standard deviations (SD),  
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45 166 and the difference between them in the outcome groups was tested using a generalized linear  
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47 167 model (GLM). The categorical variables were presented as numbers (percentages), and the  
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49 168 difference between them in the outcome groups was tested using the chi-square test. A  
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51 169 multivariable Cox proportional-hazards regression model was used to estimate the hazard  
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53 170 ratios (HRs) and 95% confidence intervals (CIs) for T2D after adjusting for categorical  
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55 171 (educational level, current drinking status, current smoking status, and physical activity) and  
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172 continuous (age, BMI, and energy intake) covariables. The lowest quintile (Q1) of TAC or  
 173 flavonoid intake served as a reference group. The median value of each quintile group was  
 174 modeled as a continuous variable in the Cox model to test the trend. We also estimated the  
 175 HRs and 95% CIs for an SD increment in dietary TAC and flavonoid intake and conducted  
 176 stratified analyses according to BMI, age, smoking status, and alcohol consumption.

177 **RESULTS**

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

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

	Antioxidant consumption					<i>P</i> -value
	Q1	Q2	Q3	Q4	Q5	
<b>Men, n=6327</b>						
<b>Cases / person-years</b>	<b>80 / 5103.00</b>	<b>74 / 5060.60</b>	<b>60 / 4995.40</b>	<b>71 / 5110.50</b>	<b>47 / 5182.60</b>	
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 <sup>2</sup>	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 ± 7.10	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 ± 1.50	7.42 ± 2.14	<.0001
Total flavonoid, mg VCE/d	58.16 ± 15.38	97.92 ± 10.58	135.76 ± 11.78	185.20 ± 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	62.90 ± 28.55	<.0001
Isoflavones, mg VCE/d	8.63 ± 4.74	11.56 ± 6.30	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	135.10 ± 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 ± 4.40	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
<b>Women, n=14267</b>						

<b>Cases / person-years</b>	<b>89 / 11021.20</b>	<b>82 / 11303.30</b>	<b>76 / 11322.20</b>	<b>59 / 11526.80</b>	<b>54 / 11650.80</b>	
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 <sup>2</sup>	23.44 ± 3.05	23.40 ± 2.93	23.32 ± 2.85	23.27 ± 2.80	23.19 ± 2.72	0.8879
Smoking status						<b>&lt;.0001</b>
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						<b>&lt;.0001</b>
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						<b>&lt;.0001</b>
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	<b>&lt;.0001</b>
Carbohydrate, E%	71.87 ± 8.06	71.25 ± 7.93	70.67 ± 7.63	70.30 ± 7.36	69.97 ± 7.30	<b>&lt;.0001</b>
Protein, E%	13.39 ± 2.47	13.59 ± 2.42	13.76 ± 2.38	13.89 ± 2.33	14.01 ± 2.43	<b>&lt;.0001</b>
Fat, E%	14.74 ± 6.03	15.16 ± 5.91	15.57 ± 5.65	15.81 ± 5.45	16.02 ± 5.33	<b>&lt;.0001</b>
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	<b>&lt;.0001</b>
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	<b>&lt;.0001</b>
Anthocyanidins, mg VCE/d	15.24 ± 6.21	25.89 ± 8.12	35.35 ± 11.02	46.82 ± 14.12	74.77 ± 32.62	<b>&lt;.0001</b>
Isoflavones, mg VCE/d	8.63 ± 4.48	10.67 ± 5.74	11.70 ± 6.42	13.28 ± 7.25	15.09 ± 9.07	<b>&lt;.0001</b>
Proanthocyanidins, mg VCE/d	31.11 ± 10.57	52.62 ± 11.64	73.61 ± 15.79	101.51 ± 21.34	161.00 ± 54.19	<b>&lt;.0001</b>
Flavonols, mg VCE/d	8.09 ± 4.63	11.18 ± 5.92	13.54 ± 7.50	16.94 ± 9.30	24.05 ± 16.19	<b>&lt;.0001</b>
Flavones, mg VCE/d	0.35 ± 0.18	0.55 ± 0.23	0.71 ± 0.28	0.89 ± 0.34	1.31 ± 0.62	<b>&lt;.0001</b>
Flavanones, mg VCE/d	2.56 ± 1.91	4.37 ± 2.55	5.98 ± 3.19	7.70 ± 3.84	12.62 ± 8.04	<b>&lt;.0001</b>
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	<b>&lt;.0001</b>
TAC (mg VCE/d)	135.61 ± 36.42	216.26 ± 31.08	289.3 ± 38.71	380.21 ± 51.07	587.77 ± 176.53	<b>&lt;.0001</b>

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

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

209 **Table 2. Range of each dietary antioxidant intake by quintile**

	Antioxidant consumption				
	Q1	Q2	Q3	Q4	Q5
<b>Men</b>					
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 – 378.83)
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 – 94.05)
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 – 31.57)
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 – 221.23)
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 – 46.86)
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 – 1.81)
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 – 17.81)
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 – 116.38)
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 – 811.29)
<b>Women</b>					
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 – 416.37)
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 – 116.38)
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 – 31.57)
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 – 221.23)
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 – 46.86)
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 – 2.04)
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 – 21.78)
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 – 90.85)
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 – 811.29)

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					P for trend	HR for an SD increment
	Q1	Q2	Q3	Q4	Q5		
<b>Men</b>							

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)

215 Results are presented as the hazard ratio (HR) for a standard deviation (SD) increment in dietary antioxidant  
216 capacity using a cox model.

217 The multivariable Cox proportional hazards regression model was adjusted for age, body mass index (BMI),  
218 educational level, physical activity, drinking status, smoking status, and total energy intake.

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

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

223

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

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3 227 in the HEXA study. There was almost no significant association between T2D mellitus and  
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5 228 dietary intake of antioxidant components in men participants. However, total flavonoid  
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7 229 intake and dietary TAC showed a protective effect against the development of T2D mellitus  
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9 230 in women participants who were aged > 52 years, had a BMI  $\geq$  25 kg/m<sup>2</sup>, and regardless of  
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11 231 alcohol consumption.  
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## 14 15 232 **Discussion**

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18 233 In this study, we discovered that dietary total flavonoid consumption and TAC are both  
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20 234 associated with a reduced risk of developing T2D mellitus. After further analysis stratified  
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22 235 according to age, and BMI, we found that dietary total flavonoid consumption and TAC had  
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24 236 a protective effect against the development of type 2 diabetes mellitus in women participants  
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26 237 who were overweight or aged > 52 years.  
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30 238 Oxidative stress, which is an imbalance between the production of reactive oxygen  
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32 239 species (free radicals) and antioxidant defense mechanism, is a risk factor for T2D.(17)  
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34 240 Previous studies have shown that oxidative stress impairs the secretion of insulin by  
35  
36 241 pancreatic beta cells and interferes with the insulin signaling pathway, thereby accelerating  
37  
38 242 the development and progression of T2D by increasing insulin resistance.(2, 3, 6, 31, 32)  
39  
40 243 Oxidative stress can be regulated by antioxidants, which react with reactive oxygen  
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42 244 species.(33) The consumption of dietary flavonoids has been shown to be associated with  
43  
44 245 lower incidences of T2D. Several previous studies have indicated that flavonoids decrease  
45  
46 246 plasma glucose levels and improve lipid profile, insulin secretion, and insulin resistance,  
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48 247 factors which are implicated in the development of T2D.(2, 3, 8, 34) In a previous study,  
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50 248 higher flavonol intake was associated with a 26% lower incidence of T2D.(35)(35) In  
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52 249 addition, the authors observed a marginally significant inverse association between flavan-  
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54 250 3-ol intake and the risk of T2D, but there was no association with anthocyanin intake.(35)(35)  
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3 251 Knekt et al.(36) reported a marginally significant inverse association between the intake of  
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5 252 the flavonols quercetin, and myricetin, but not kaempferol, and the incidence of T2D in  
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8 253 Finnish men and women. Quercetin, in particular, is known to decrease plasma glucose  
9  
10 254 concentration, improve insulin concentration, preserve the integrity of pancreatic beta cells,  
11  
12 255 alleviate T2D symptoms, and reduce hepatic gene expression in streptozotocin-induced  
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14 256 diabetic models.(37)-Flavan-3-ol and isoflavone intake is associated with a reduced risk of  
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17 257 T2D and improved insulin resistance and serum insulin concentrations.(38) Dietary flavone  
18  
19 258 intake is negatively associated with systolic blood pressure, triglyceride level,  
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22 259 triglyceride/high-density lipoprotein-cholesterol level, and homeostatic model assessment  
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24 260 of insulin resistance. Flavone intake may have some beneficial effects in the reduction of  
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26 261 the prevalence of T2D in South Korean women.(8) Consumption of foods rich in  
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28 262 anthocyanins, particularly blueberries, apples, and pears, is also inversely associated with  
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31 263 the risk of T2D in the United States.(39)

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33  
34 264 A key potential mechanism for the protective effect of flavonoids against T2D is the  
35  
36 265 protection of tissues from free oxygen radicals and lipid peroxidation through their  
37  
38 266 antioxidant activity.(40) In addition, anti-inflammatory functions, improvement of  
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40 267 endothelial functions, reduction of blood cholesterol concentration, and nicotinamide  
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42 268 adenine dinucleotide phosphate oxidase activity are also associated with a reduced risk of  
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44 269 T2D mellitus.(40) Flavonoids are known to interact with molecular targets and affect NF-  
45  
46 270  $\kappa$ B and MAPK signaling pathways.(34) Furthermore, flavonoids modulate postprandial  
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48 271 glucose levels by reducing the activities of digestive enzymes ( $\alpha$ -amylase and  $\alpha$ -glucosidase),  
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50 272 decreasing the active transport of glucose across the intestinal brush border membrane, and  
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52 273 inhibiting glucose transporters.(31) Antioxidant-rich fruits and vegetables contain relatively  
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54 274 high fiber content, which can influence the beneficial effects of antioxidants against T2D.(41)

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3 275 Furthermore, it has been reported that flavonoids inhibit  $\alpha$ -glucosidase activity to alleviate  
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5 276 hyperglycemia.(42, 43)  
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8 277 The effect of each type of flavonoid intake on the risk of T2D varies by sex. In this  
9  
10 278 study, there was a correlation between anthocyanidin and proanthocyanidin intake and the  
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12 279 risk of developing T2D in men. However, there was a greater correlation between the risk  
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14 280 of T2D and intake of flavonoids, such as anthocyanidins, proanthocyanidins, flavonols,  
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16 281 flavones, and flavanones, in women than in men. These sex-specific results are often seen  
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18 282 in other phytochemical-related studies. In a previous study conducted using 2008–2011 data  
19  
20 283 from the Korea National Health and Nutrition Examination Survey, a high intake of  
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22 284 flavonoids did not reduce the incidence of obesity and abdominal obesity in men but  
23  
24 285 significantly reduced obesity (18%) in women. In addition, high flavonoid intake was  
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26 286 reported to reduce the incidence of abdominal obesity (19%) in that study.(2, 44, 45) The  
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28 287 variations in these results appear to be due to differences between the dietary intake patterns  
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30 288 of South Korean men and women. Sex-specific dietary patterns have been reported in  
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32 289 previous studies; namely, men consume the recommended amount of vegetables more than  
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34 290 women, whereas women consume the recommended amount of fruit more than men.(46) In  
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36 291 addition, women generally consume higher amounts of dietary antioxidants than men.(2, 47)  
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38 292 Higher intake of dietary antioxidants can induce high plasma concentrations of antioxidants  
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40 293 and more beneficial effects on preventing development of T2D. Furthermore, gonadal  
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42 294 hormones (menopausal estrogen and testosterone) have been implicated in sex-specific  
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44 295 differences in glucose homeostasis.(48) Healthy women have lower skeletal muscle mass,  
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46 296 higher adipose tissue mass, more circulating free fatty acids, and higher intramyocellular  
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48 297 lipid content than men of the same age. These are all factors that could promote increased  
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50 298 insulin resistance in women compared with men.(48)  
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3 299 Various factors, such as age and lifestyle, are known to contribute to the development  
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5 300 and progression of T2D.(17) The prevalence of T2D in South Koreans increases rapidly with  
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7  
8 301 age.(4) Unhealthy lifestyle habits, such as smoking, excessive alcohol consumption, and  
9  
10 302 inactivity, are known to contribute to the development of diabetes.(3, 49) We found that men  
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12 303 with T2D were older and more likely to be current drinkers and current smokers than those  
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14 304 without diabetes. However, our stratified analysis showed that there was no correlation  
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16 305 between these factors except for current alcohol consumption. On the other hand, women  
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18 306 with T2D were significantly older and had significantly higher BMI than those without  
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20 307 diabetes. Furthermore, the stratified analysis showed that antioxidant consumption was  
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22 308 inversely related to the HR of T2D in older women (> 52 years), women with a BMI > 25  
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24 309 kg/m<sup>2</sup>, regardless of alcohol consumption. Although it is difficult to fully explain these  
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26 310 variations in South Korean adults, these findings suggest that high antioxidant intake may  
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28 311 be related to a decreased risk of T2D, especially in women with specific lifestyle habits.  
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### 34 **Strengths and limitations**

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36 313 The main strength of this study was that it was conducted using a large-scale  
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38 314 community-based genomic cohort study with 5 years of follow-up on average. Stratified  
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40 315 analyses were conducted in the current study to focus on one certain exposure. This study  
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42 316 had some limitations. First, although this study reported a longitudinal relationship between  
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44 317 dietary antioxidant consumption and T2D incidence, we did not assess the causality. Second,  
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46 318 we obtained dietary information and information on the intake of antioxidant components  
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48 319 using self-reported FFQ; thus, dietary measurement errors were inevitable. However, the  
49  
50 320 106-item FFQ has been previously verified.(26) In addition, further studies are needed to  
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52 321 measure the flavonoid concentration to verify the data. Third, we did not quantify the  
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54 322 amount of alcohol consumption and smoking. Nevertheless, we found no association  
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3 323 between smoking status and T2D after stratification analyses. Dietary antioxidants showed  
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5 324 a protective effect against the development of T2D only in women who were non-drinkers.  
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## 8 325 **Conclusions**

10  
11 326 The findings of this large-scale prospective cohort study suggest that dietary  
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13 327 antioxidant consumption is associated with a lower risk of T2D in South Korean adults. The  
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15 328 findings of this study can serve as a reference or guide for the modification of food intake  
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17 329 recommendations in dietary guideline policies in South Korea. However, further studies are  
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19 330 needed to validate the results of this study.  
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## 26 332 **Declarations**

### 29 333 **Ethics approval and consent to participate**

31  
32 334 All participants voluntarily signed an informed written consent form before enrollment.  
33  
34 335 This study was performed in accordance with the guidelines specified in the Declaration of  
35  
36 336 Helsinki, and the study protocol was approved by the local Institutional Review Board (IRB)  
37  
38 337 of the Ethics Committee of the Korean Genome and Epidemiology Study of the Korea  
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40 338 National Institute of Health (IRB no. 2014-08-02-3C-A).  
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### 47 340 **Consent for publication**

48  
49  
50 341 Not applicable.  
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### 56 343 **Availability of data and materials**

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3 344 The data that support the findings of this study are available from the National  
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5 345 Genome Research Institute, Korea Centers for Disease Control and Prevention. How  
6  
7  
8 346 ever, restrictions apply to the availability of these data, which were used under lice  
9  
10 347 nse for this study, and as such are not publicly available. Data are however availa  
11  
12 348 ble from the authors upon reasonable request and with permission of the National  
13  
14 349 Genome Research Institute, Korea Centers for Disease Control and Prevention.  
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17 350

### 20 351 **Competing interests**

22  
23 352 The authors declare that they have no competing interests.  
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25

26 353

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37  
38 358 collection, analysis, and interpretation of data; writing the report; and did not impose any  
39  
40 359 restrictions regarding the publication of the report.  
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44 360

### 47 361 **Authors' contributions**

48  
49  
50 362 S.S. supervised the project. S.S. contributed to the conceptualization or design of this  
51  
52 363 study. S.J. and H.J. were contributed to establish the antioxidants database. L.J.T  
53  
54 364 conducted the formal analysis. S.S. verified and validated the outcomes. L.J.T and S.B.H.  
55  
56 365 co-wrote the first draft of the manuscript. S.J. and H.J. reviewed and revised the article  
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3 366 critically. All authors approved the final version of the article for publication. S.S. and  
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5 367 L.J.T had full access to all the data in the study and take full responsibility for the integrity  
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21 373 and Prevention.  
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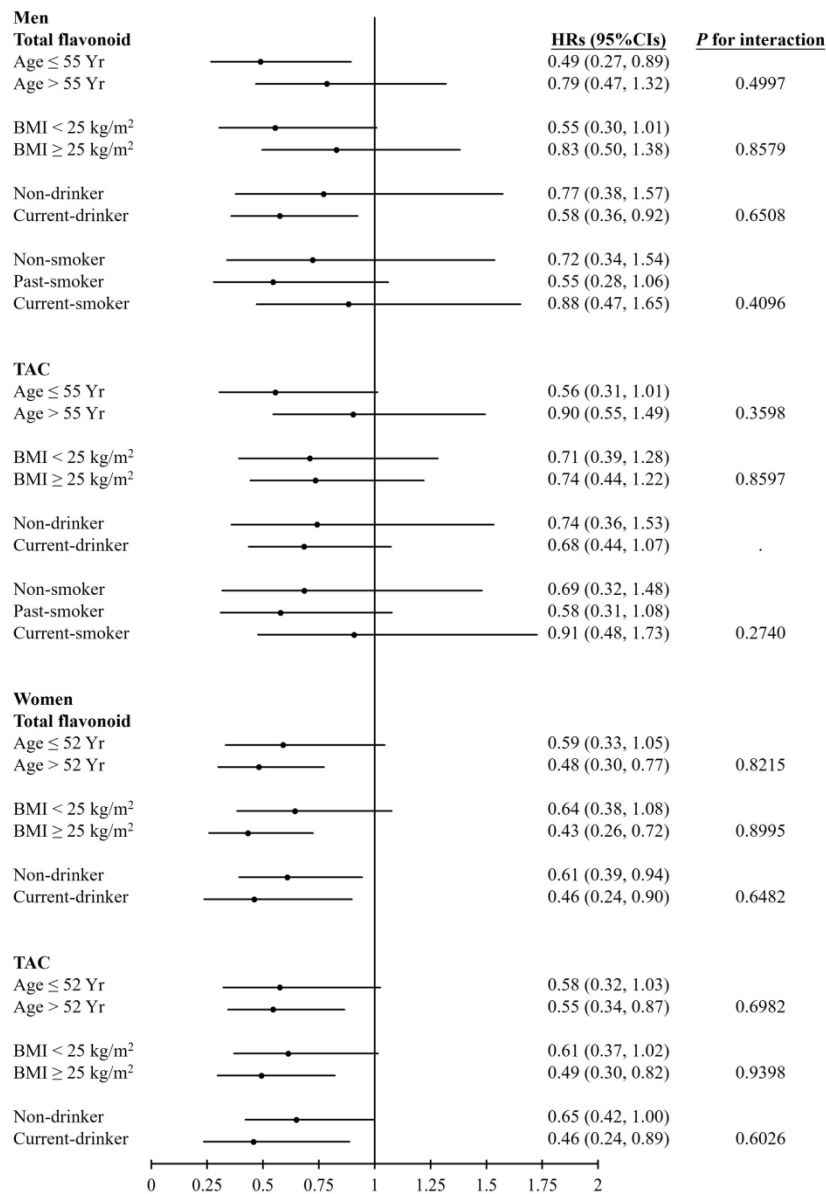
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13 502 **Figure Legend**  
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16 503 **Figure 1.** Hazard ratios (HR) with 95% confidence intervals (CIs) for type 2 diabetes  
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18 504 mellitus after comparison of antioxidant consumption in the Q5 and Q1 groups according to  
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20 505 baseline age, baseline body mass index (BMI), alcohol consumption, smoking status in the  
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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					<i>P</i> for trend	HR for a SD increment
	Q1	Q2	Q3	Q4	Q5		
<b>Men</b>							
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)
<b>Women</b>							
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					<i>P</i> for trend	HR for a SD increment
	Q1	Q2	Q3	Q4	Q5		
<b>Men</b>							
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)
<b>Women</b>							
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
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Pages 6–7
		<i>Case-control study</i> —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	
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	Pages 6–7
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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	Page 9
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	



*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy

(e) Describe any sensitivity analyses

<b>Results</b>			
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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Pages 10–14
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	Pages 10–12
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	Page 11
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 (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	Pages 12–13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 14
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://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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1 **Dietary antioxidant consumption and the risk of type 2 diabetes in South Korean adults:**  
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5 **A prospective cohort study based on the Health Examinees study**  
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3 20 **Word count:** 3,342 words  
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6 21 **ABSTRACT**  
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10 22 **Objectives:** Antioxidants are common dietary compounds with multiple health benefits.  
11  
12 23 This study aimed to identify the association between dietary antioxidant consumption and  
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14 24 the incidence of type 2 diabetes mellitus (T2D, defined using the Korean Diabetes  
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16 25 Association criteria) in South Korean adults.

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19 26 **Design:** Baseline and follow-up data from the Health Examinees (HEXA) study, a large-  
20  
21 27 scale community-based genomic cohort study conducted in South Korea  
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23 28 **Setting:** A South Korean community  
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25  
26 29 **Participants:** A total of 20,594 participants, aged 40–79 years, who participated in the  
27  
28 30 baseline and follow-up surveys of the HEXA study were included. After an average of 5  
29  
30 31 years of follow-up, there were 332 men and 360 women with T2D.  
31

32 32 **Results:** Participants with the highest total flavonoid consumption (Q5) had a lower risk of  
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34 33 T2D (men: hazard ratio [HR], 0.63; 95% confidence interval [CI], 0.42–0.93; *P* for trend =  
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36 34 0.0169]; and women: HR, 0.54; 95% CI, 0.438–0.78; *P* for trend = 0.0001) than those with  
37  
38 35 the lowest consumption (Q1). Dietary total antioxidant capacity was significantly inversely  
39  
40 36 associated with the development of T2D mellitus in women participants alone (HR, 0.58;  
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42 37 95% CI, 0.40–0.83; *P* for trend = 0.0004). Stratified analyses according to age and body  
43  
44 38 mass index showed that dietary total flavonoid consumption and total antioxidant capacity  
45  
46 39 had a negative association with the development of T2D in women aged > 52 years and  
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48 40 women with BMI > 25 kg/m<sup>2</sup>.  
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53 41 **Conclusions:** Dietary flavonoid consumption and total antioxidant capacity were associated  
54  
55 42 with a lower risk of T2D in South Korean adults, especially in women aged > 52 years and  
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3 43 overweight. The findings of this study may provide reference data for the modification of  
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5 44 dietary guidelines for South Koreans.  
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9 **45 Strengths and limitations of the study**

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12 46 • This study used a large-scale community-based genomic cohort study conducted in  
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14 South Korea with 5 years of follow-up.  
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17 48 • Stratified analyses were conducted to focus on one certain exposure.  
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19 49 • Although this study reported a longitudinal relationship between antioxidant  
20  
21 consumption and diabetes incidence, we could not assess the causality.  
22  
23  
24 51 • Dietary measurement errors were inevitable due to using self-reported FFQ.  
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27 **52 Keywords:** Cohort study, Diabetes, Dietary antioxidant, Flavonoid, Health Examinees  
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29 53 study, South Korean adults, Total antioxidant capacity  
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## 54 INTRODUCTION

55 Diabetes is a metabolic disease characterized by high blood glucose levels, impaired  
56 glucose tolerance, impaired insulin secretion, and insulin resistance.(1, 2) Currently,  $\geq 400$   
57 million people are living with type 2 diabetes (T2D) mellitus worldwide.(3) The prevalence  
58 of T2D mellitus increases with age. The 2018 Korean Diabetes Association diabetes fact  
59 sheet reported that the prevalence of T2D in the total population aged  $\geq 65$  years was  
60 29.8%.(4) It is projected that T2D will be the seventh leading cause of death by 2030.(3)  
61 Given that T2D is accompanied by various serious complications, including cardiovascular  
62 disease, peripheral vascular disease, retinopathy, nephropathy, neuropathy, and recently,  
63 sarcopenia, its prevention and treatment are extremely important.(3, 5) Both genetic and  
64 environmental factors contribute to the development and progression of T2D mellitus.  
65 However, its growing prevalence is the result of result of changing dietary habits and  
66 lifestyles observed in modern societies.(6)

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

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

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3 78 which is involved in the pathogenesis of T2D mellitus, by promoting the transportation of  
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5 79 GLUT4 through the regulation of the insulin-signaling pathway.(16, 17)  
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8 80 Previous studies have investigated the correlation between dietary antioxidants and  
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10 81 obesity, dyslipidemia, and metabolic syndrome.(18-21) Azad et al. (22) showed that a diet  
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12 82 high in antioxidants had protective effects against the development of T2D in the Iranian  
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14 83 population. However, few studies have been conducted to determine the association between  
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16 84 dietary antioxidant intake and T2D in South Korean populations. In addition, whether there  
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18 85 is a dose-response relationship between dietary antioxidants and T2D is unclear. It is  
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20 86 pertinent to determine whether a relationship exists between dietary antioxidant intake and  
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22 87 T2D in South Korean adults. Moreover, the effect of dietary antioxidants on T2D has not  
23  
24 88 been investigated according to the flavonoid subclasses, antioxidant capacities of flavonoids,  
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26 89 or total antioxidant capacity (TAC), which is an index to indicate whole dietary antioxidant  
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28 90 content.(23) Therefore, we conducted this study to explore the association between dietary  
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30 91 antioxidant and the incidence of T2D by analyzing data from the Health Examinees (HEXA)  
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32 92 study.  
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## 42 94 **METHODS**

### 43 44 45 95 **Patient and public involvement**

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48 96 Patients and public were not involved in the design of the study.  
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### 51 97 **Study population**

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54 98 This study was based on the baseline and follow-up data from the HEXA study, a large-  
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56 99 scale community-based genomic cohort study conducted in South Korea. More specific  
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58 100 details of the HEXA study design are described elsewhere.(24) A total of 173,357  
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3 101 participants aged  $\geq 40$  years were initially included in the baseline survey, which was  
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5 102 conducted from 2003 to 2014; 65,642 of these participants were included in the follow-up  
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7 103 survey, which was conducted from 2012 to 2016. At baseline, we excluded participants who  
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9 104 had T2D mellitus or had no information on fasting plasma glucose or HbA<sub>1C</sub> levels (n =  
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11 105 41,311) and those with a history of diseases closely related to T2D mellitus (i.e.,  
12  
13 106 hyperlipidemia, stroke, transient ischemic attacks, angina pectoris, and myocardial  
14  
15 107 infarction) (n = 3,082). At follow-up, we excluded those with missing information on  
16  
17 108 biomarkers for T2D mellitus (fasting plasma glucose, HbA<sub>1C</sub>) (n = 11), those who had an  
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19 109 implausible energy intake ( $< 3,349$  or  $\geq 16,743$  kJ/day for men and  $< 2,093$  or  $\geq 14,650$   
20  
21 110 kJ/day for women; n = 630 (25)), and those who were missing values for covariables such  
22  
23 111 as drinking (n = 9) and body mass index (BMI) (n = 5). Ultimately, a total of 20,594  
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25 112 participants (6,327 men and 14,267 women) were included in this study.  
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### 31 **Dietary assessment and estimation of antioxidant components**

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34 114 Dietary intake was assessed using the self-administered, 106-item, food frequency  
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36 115 questionnaire (FFQ) developed for the Korean Genome Epidemiologic Study.(24)  
37  
38 116 Participants reported the frequencies and average portions of food or beverage items  
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40 117 consumed during the last year before participating in the HEXA study. The reproducibility  
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42 118 and validity of the FFQ have been assessed in a previous study using a reference method by  
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44 119 collecting information on 12-day dietary records.(26) The median correlation coefficient for  
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46 120 all nutrients was 0.39 between the FFQ and 12-day dietary record, and the researchers  
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48 121 concluded that the FFQ could be an acceptable tool for dietary assessment.(26)  
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53 122 In this study, we estimated the participants' intake of antioxidant components using  
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55 123 self-reported dietary data linked to the TAC database for common South Korean foods.(11,  
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57 124 27) Dietary TAC and intake of each flavonoid component were expressed as vitamin C  
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3 125 equivalent antioxidant capacity (mg VCE/100 g). The intake of individual antioxidant  
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5 126 components from a food item was calculated by multiplying the antioxidant component per  
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7 127 gram of food item by the total weight in grams of daily intake of this food item. The daily  
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9 128 intake of individual total dietary antioxidant components was calculated as the sum of the  
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11 129 intake of each antioxidant component from all the food sources reported in the HEXA FFQ  
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13 130 data (mg VCE/day). After summing all individual total dietary antioxidant components, we  
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15 131 obtained the dietary TAC per person per day.

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20 132 Total flavonoid intake was classified into seven categories: anthocyanidins (cyanidin,  
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22 133 delphinidin, pelargonidin, malvidin, peonidin, and petunidin), isoflavones (daidzein,  
23  
24 134 genistein, and glycitein), proanthocyanidins (proanthocyanidin-dimer, proanthocyanidin-  
25  
26 135 trimer, proanthocyanidin-4-6mers, proanthocyanidin-7-10mers, and proanthocyanidin-  
27  
28 136 polymers), flavonols (quercetin, kaempferol, myricetin, and isorhamnetin), flavones  
29  
30 137 (luteolin and apigenin), flavanones (eriodictyol, hesperetin, and naringenin), and flavan-3-  
31  
32 138 ols (catechin, epicatechin, epigallocatechin, theaflavin, theaflavin-3-gallate, theaflavin-3'-  
33  
34 139 gallate, and theaflavin-3-3-digallate).

## 35 36 37 38 39 140 **Definition of type 2 diabetes**

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42 141 T2D was determined in accordance with the definition provided by the Korean Diabetes  
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44 142 Association.(28) T2D was defined as a diagnosis by a physician, increased fasting plasma  
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46 143 glucose level  $\geq 6.99$  mmol/L (126 mg/dL), or elevated HbA<sub>1C</sub> level  $\geq 47.5$  mmol/mol (6.5%).  
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## 49 144 **Covariables**

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52 145 In the HEXA study, the sociodemographic information of each participant was  
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54 146 collected using a questionnaire. Our covariables of interest included age, BMI, level of  
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56 147 education (middle school or lower, high school, or college or higher), and health-related  
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3 148 behaviors, such as smoking (current smoker, past smoker, or non-smoker), alcohol  
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5 149 consumption (never or current drinker), level of physical activity (inactive or active), and  
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8 150 total energy intake (kJ/day). BMI was calculated as the quotient of the body weight (kg) and  
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10 151 height (m) squared (kg/m<sup>2</sup>).<sup>(29)</sup> Smoking status was categorized into three groups based on  
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12 152 the participants' responses to the question, "Have you smoked  $\geq$  20 packs (400 cigarettes)  
13  
14 153 so far?" Participants who answered "never" were classified as "non-smokers," those who  
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16 154 answered "yes" and were still smoking at the time of the survey were classified as "current  
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18 155 smokers," and those who answered "yes" but had quit smoking at the time of the survey  
19  
20 156 were classified as "past smokers." Alcohol consumption was classified based on the  
21  
22 157 responses to the following question, "Are you unable to drink or refuse to do so for religious  
23  
24 158 or other reasons?" in the HEXA survey. In the present analysis, we classified participants  
25  
26 159 who replied "yes" as "alcohol non-drinkers;" the rest were classified as "alcohol drinkers."  
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29 160 Regarding physical activity levels, participants were classified as "active" if they reported  
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31 161 that they engaged in exercises resulting in sweating for  $\geq$  30 min twice a week.<sup>(30)</sup>  
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## 36 162 **Statistical analyses**

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39 163 All statistical analyses were sex-stratified and performed using Statistical Analysis  
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41 164 Systems software version 9.4 (SAS Institute, Cary, NC, USA). Statistical significance was  
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43 165 set at  $P < 0.05$ . Continuous variables were presented as means  $\pm$  standard deviations (SD),  
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45 166 and the difference between them in the outcome groups was tested using a generalized linear  
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47 167 model (GLM). The categorical variables were presented as numbers (percentages), and the  
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49 168 difference between them in the outcome groups was tested using the chi-square test. A  
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51 169 multivariable Cox proportional-hazards regression model was used to estimate the hazard  
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53 170 ratios (HRs) and 95% confidence intervals (CIs) for T2D after adjusting for categorical  
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55 171 (educational level, current drinking status, current smoking status, and physical activity) and  
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3 172 continuous (age, BMI, and energy intake) covariables. The lowest quintile (Q1) of TAC or  
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5 173 flavonoid intake served as a reference group. The median value of each quintile group was  
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8 174 modeled as a continuous variable in the Cox model to test the trend. We also estimated the  
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10 175 HRs and 95% CIs for an SD increment in dietary TAC and flavonoid intake and conducted  
11  
12 176 stratified analyses according to BMI, age, smoking status, and alcohol consumption. The  
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15 177 strata indices for continuous variables (BMI and age) were median value referred to a  
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17 178 previous study.(31)

## 179 RESULTS

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

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

	Antioxidant consumption					<i>P</i> -value
	Q1	Q2	Q3	Q4	Q5	
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 <sup>2</sup>	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 ± 7.10	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 ± 1.50	7.42 ± 2.14	<.0001
Total flavonoid, mg VCE/d	58.16 ± 15.38	97.92 ± 10.58	135.76 ± 11.78	185.20 ± 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	62.90 ± 28.55	<.0001
Isoflavones, mg VCE/d	8.63 ± 4.74	11.56 ± 6.30	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	135.10 ± 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 ± 4.40	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
<b>Women, n=14267</b>						
<b>Cases / person-years</b>	<b>89 / 11021.20</b>	<b>82 / 11303.30</b>	<b>76 / 11322.20</b>	<b>59 / 11526.80</b>	<b>54 / 11650.80</b>	
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 <sup>2</sup>	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

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

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

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

194  
 195 Table 2 shows the range of dietary antioxidant intake by quintiles. The associations  
 196 between dietary antioxidant intake and the HRs of T2D mellitus are presented in Table 3.  
 197 All participants with the highest total dietary flavonoid intake (Q5) had a lower risk of  
 198 developing T2D mellitus (men: HR, 0.63; 95% CI, 0.42–0.93 and women: HR, 0.54; 95%  
 199 CI, 0.38–0.78; both *P* for trend < 0.05) than those with the lowest flavonoid intake (Q1).  
 200 Consumption of more flavonols and proanthocyanidins had a protective effect against the  
 201 development of T2D mellitus in men participants, and consumption of anthocyanidins,  
 202 proanthocyanidins, flavonols, flavones, and flavanones showed a protective effect against  
 203 T2D mellitus in women participants (all *P* for trend < 0.05). After estimation of HRs

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

211 Table 2. Range of each dietary antioxidant intake by quintile

	Antioxidant consumption				
	Q1	Q2	Q3	Q4	Q5
<b>Men</b>					
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 – 378.83)
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 – 94.05)
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 – 30.39)
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 – 181.75)
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 – 43.23)
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 – 1.81)
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 – 18.86)
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 – 111.46)
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 – 711.92)
<b>Women</b>					
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 – 417.37)
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 – 103.83)
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 – 31.64)
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 – 210.37)
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 – 43.23)
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 – 2.05)
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 – 20.03)
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 – 89.56)
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 – 745.54)

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

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

	Antioxidant consumption					<i>P</i> for trend	HR for an SD increment
	Q1	Q2	Q3	Q4	Q5		
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)

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3 217 Results are presented as the hazard ratio (HR) for a standard deviation (SD) increment in dietary antioxidant  
4 218 capacity using a cox model.  
5 219 The multivariable Cox proportional hazards regression model was adjusted for age, body mass index (BMI),  
6 220 educational level, physical activity, drinking status, smoking status, and total energy intake.  
7 221 Total flavonoid intake was the sum of anthocyanidins, isoflavones, proanthocyanidins, flavonols, flavones,  
8 222 flavanones, and flavan-3-ols.  
9 223 Total antioxidant capacity (TAC) was obtained by combining the individual antioxidant capacity of each  
10 224 antioxidant derived from every food item.  
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14 226 We also performed stratified analyses according to age, BMI, drinking status for both  
15  
16 227 sexes, and smoking status for men participants. Figure 1 shows the HRs of T2D mellitus in  
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18 228 the Q5 and Q1 groups according to baseline age, baseline BMI, and alcohol drinking status  
19  
20 229 in the HEXA study. There was almost no significant association between T2D mellitus and  
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22 230 dietary intake of antioxidant components in men participants. However, total flavonoid  
23  
24 231 intake and dietary TAC showed a protective effect against the development of T2D mellitus  
25  
26 232 in women participants who were aged > 52 years, had a BMI  $\geq$  25 kg/m<sup>2</sup>, and regardless of  
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28 233 alcohol consumption.  
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## 30 31 32 33 234 **Discussion**

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36 235 In this study, we discovered that dietary total flavonoid consumption and TAC are both  
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38 236 associated with a reduced risk of developing T2D mellitus. After further analysis stratified  
39  
40 237 according to age, and BMI, we found that dietary total flavonoid consumption and TAC had  
41  
42 238 a protective effect against the development of type 2 diabetes mellitus in women participants  
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44 239 who were overweight or aged > 52 years.  
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48 240 Oxidative stress, which is an imbalance between the production of reactive oxygen  
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50 241 species (free radicals) and antioxidant defense mechanism, is a risk factor for T2D.(17)  
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52 242 Previous studies have shown that oxidative stress impairs the secretion of insulin by  
53  
54 243 pancreatic beta cells and interferes with the insulin signaling pathway, thereby accelerating  
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56 244 the development and progression of T2D by increasing insulin resistance.(2, 3, 6, 32, 33)  
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3 245 Oxidative stress can be regulated by antioxidants, which react with reactive oxygen  
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5 246 species.(34) The consumption of dietary flavonoids has been shown to be associated with  
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7 247 lower incidences of T2D. Several previous studies have indicated that flavonoids decrease  
8  
9 248 plasma glucose levels and improve lipid profile, insulin secretion, and insulin resistance,  
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11 249 factors which are implicated in the development of T2D.(2, 3, 8, 35) In a previous study,  
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13 250 higher flavonol intake was associated with a 26% lower incidence of T2D.(36)(35) In  
14  
15 251 addition, the authors observed a marginally significant inverse association between flavan-  
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17 252 3-ol intake and the risk of T2D, but there was no association with anthocyanin intake.(36)(35)  
18  
19 253 Knekt et al.(37) reported a marginally significant inverse association between the intake of  
20  
21 254 the flavonols quercetin, and myricetin, but not kaempferol, and the incidence of T2D in  
22  
23 255 Finnish men and women. Quercetin, in particular, is known to decrease plasma glucose  
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25 256 concentration, improve insulin concentration, preserve the integrity of pancreatic beta cells,  
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27 257 alleviate T2D symptoms, and reduce hepatic gene expression in streptozotocin-induced  
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29 258 diabetic models.(38)-Flavan-3-ol and isoflavone intake is associated with a reduced risk of  
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31 259 T2D and improved insulin resistance and serum insulin concentrations.(39) Dietary flavone  
32  
33 260 intake is negatively associated with systolic blood pressure, triglyceride level,  
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35 261 triglyceride/high-density lipoprotein-cholesterol level, and homeostatic model assessment  
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37 262 of insulin resistance. Flavone intake may have some beneficial effects in the reduction of  
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39 263 the prevalence of T2D in South Korean women.(8) Consumption of foods rich in  
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41 264 anthocyanins, particularly blueberries, apples, and pears, is also inversely associated with  
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43 265 the risk of T2D in the United States.(40)

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52 266 A key potential mechanism for the protective effect of flavonoids against T2D is the  
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54 267 protection of tissues from free oxygen radicals and lipid peroxidation through their  
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56 268 antioxidant activity.(41) In addition, anti-inflammatory functions, improvement of

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3 269 endothelial functions, reduction of blood cholesterol concentration, and nicotinamide  
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5 270 adenine dinucleotide phosphate oxidase activity are also associated with a reduced risk of  
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8 271 T2D mellitus.(41) Flavonoids are known to interact with molecular targets and affect NF-  
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10 272  $\kappa$ B and MAPK signaling pathways.(42) Furthermore, flavonoids modulate postprandial  
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12 273 glucose levels by reducing the activities of digestive enzymes ( $\alpha$ -amylase and  $\alpha$ -glucosidase),  
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14 274 decreasing the active transport of glucose across the intestinal brush border membrane, and  
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16 275 inhibiting glucose transporters.(32) Antioxidant-rich fruits and vegetables contain relatively  
17  
18 276 high fiber content, which can influence the beneficial effects of antioxidants against T2D.(43)  
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20 277 Furthermore, it has been reported that flavonoids inhibit  $\alpha$ -glucosidase activity to alleviate  
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22 278 hyperglycemia.(44, 45)  
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27 279 The effect of each type of flavonoid intake on the risk of T2D varies by sex. In this  
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29 280 study, there was a correlation between anthocyanidin and proanthocyanidin intake and the  
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31 281 risk of developing T2D in men. However, there was a greater correlation between the risk  
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33 282 of T2D and intake of flavonoids, such as anthocyanidins, proanthocyanidins, flavonols,  
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35 283 flavones, and flavanones, in women than in men. These sex-specific results are often seen  
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37 284 in other phytochemical-related studies. In a previous study conducted using 2008–2011 data  
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39 285 from the Korea National Health and Nutrition Examination Survey, a high intake of  
40  
41 286 flavonoids did not reduce the incidence of obesity and abdominal obesity in men but  
42  
43 287 significantly reduced obesity (18%) in women. In addition, high flavonoid intake was  
44  
45 288 reported to reduce the incidence of abdominal obesity (19%) in that study.(2, 46, 47) The  
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47 289 variations in these results appear to be due to differences between the dietary intake patterns  
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49 290 of South Korean men and women. Sex-specific dietary patterns have been reported in  
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51 291 previous studies; namely, men consume the recommended amount of vegetables more than  
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53 292 women, whereas women consume the recommended amount of fruit more than men.(48) In  
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3 293 addition, women generally consume higher amounts of dietary antioxidants than men.(2, 49)  
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5 294 Higher intake of dietary antioxidants can induce high plasma concentrations of antioxidants  
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7 295 and more beneficial effects on preventing development of T2D. Furthermore, gonadal  
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9 296 hormones (menopausal estrogen and testosterone) have been implicated in sex-specific  
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11 297 differences in glucose homeostasis.(50) Healthy women have lower skeletal muscle mass,  
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13 298 higher adipose tissue mass, more circulating free fatty acids, and higher intramyocellular  
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15 299 lipid content than men of the same age. These are all factors that could promote increased  
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17 300 insulin resistance in women compared with men.(50)  
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22 301 Various factors, such as age and lifestyle, are known to contribute to the development  
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24 302 and progression of T2D.(17) The prevalence of T2D in South Koreans increases rapidly with  
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26 303 age.(4) Unhealthy lifestyle habits, such as smoking, excessive alcohol consumption, and  
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28 304 inactivity, are known to contribute to the development of diabetes.(3, 51) We found that men  
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30 305 with T2D were older and more likely to be current drinkers and current smokers than those  
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32 306 without diabetes. However, our stratified analysis showed that there was no correlation  
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34 307 between these factors except for current alcohol consumption. On the other hand, women  
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36 308 with T2D were significantly older and had significantly higher BMI than those without  
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38 309 diabetes. Furthermore, the stratified analysis showed that antioxidant consumption was  
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40 310 inversely related to the HR of T2D in older women (> 52 years), women with a BMI > 25  
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42 311 kg/m<sup>2</sup>, regardless of alcohol consumption. Although it is difficult to fully explain these  
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44 312 variations in South Korean adults, these findings suggest that high antioxidant intake may  
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46 313 be related to a decreased risk of T2D, especially in women with specific lifestyle habits.  
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### 52 314 **Strengths and limitations**

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55 315 The main strength of this study was that it was conducted using a large-scale  
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57 316 community-based genomic cohort study with 5 years of follow-up on average. Stratified  
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3 317 analyses were conducted in the current study to focus on one certain exposure. This study  
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5 318 had some limitations. First, although this study reported a longitudinal relationship between  
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7 319 dietary antioxidant consumption and T2D incidence, we did not assess the causality. Second,  
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9 320 we obtained dietary information and information on the intake of antioxidant components  
10  
11 321 using self-reported FFQ; thus, dietary measurement errors were inevitable. However, the  
12  
13 322 106-item FFQ has been previously verified.(26) In addition, further studies are needed to  
14  
15 323 measure the flavonoid concentration to verify the data. Third, we did not quantify the  
16  
17 324 amount of alcohol consumption and smoking. Nevertheless, we found no association  
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19 325 between smoking status and T2D after stratification analyses. Dietary antioxidants showed  
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21 326 a protective effect against the development of T2D only in women who were non-drinkers.  
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## 27 **Conclusions**

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29 328 The findings of this large-scale prospective cohort study suggest that dietary  
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31 329 antioxidant consumption is associated with a lower risk of T2D in South Korean adults. The  
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33 330 findings of this study can serve as a reference or guide for the modification of food intake  
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35 331 recommendations in dietary guideline policies in South Korea. However, further studies are  
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37 332 needed to validate the results of this study.  
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## 45 **Declarations**

## 48 **Ethics approval and consent to participate**

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50 336 All participants voluntarily signed an informed written consent form before enrollment.  
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52 337 This study was performed in accordance with the guidelines specified in the Declaration of  
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54 338 Helsinki, and the study protocol was approved by the local Institutional Review Board (IRB)  
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3 339 of the Ethics Committee of the Korean Genome and Epidemiology Study of the Korea  
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5 340 National Institute of Health (IRB no. 2014-08-02-3C-A).  
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11 342 **Consent for publication**  
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14 343 Not applicable.  
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20 345 **Availability of data and materials**  
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23 346 The data that support the findings of this study are available from the National  
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25 347 Genome Research Institute, Korea Centers for Disease Control and Prevention. How  
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27 348 ever, restrictions apply to the availability of these data, which were used under lice  
28  
29 349 nse for this study, and as such are not publicly available. Data are however availa  
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31 350 ble from the authors upon reasonable request and with permission of the National  
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33 351 Genome Research Institute, Korea Centers for Disease Control and Prevention.  
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41 353 **Competing interests**  
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44 354 The authors declare that they have no competing interests.  
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56 359 Science and ICT. The study sponsor/funder was not involved in the design of the study; the  
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3 360 collection, analysis, and interpretation of data; writing the report; and did not impose any  
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17 365 **Authors' contributions**  
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20 366 S.S. supervised the project. S.S. contributed to the conceptualization or design of this  
21  
22 367 study. S.J. and H.J. were contributed to establish the antioxidants database. L.J.T  
23  
24 368 conducted the formal analysis. S.S. verified and validated the outcomes. L.J.T and S.B.H.  
25  
26 369 co-wrote the first draft of the manuscript. S.J. and H.J. reviewed and revised the article  
27  
28 370 critically. All authors approved the final version of the article for publication. S.S. and  
29  
30 371 L.J.T had full access to all the data in the study and take full responsibility for the integrity  
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32 372 of the data and accuracy of the data analysis.  
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46 377 and Prevention.  
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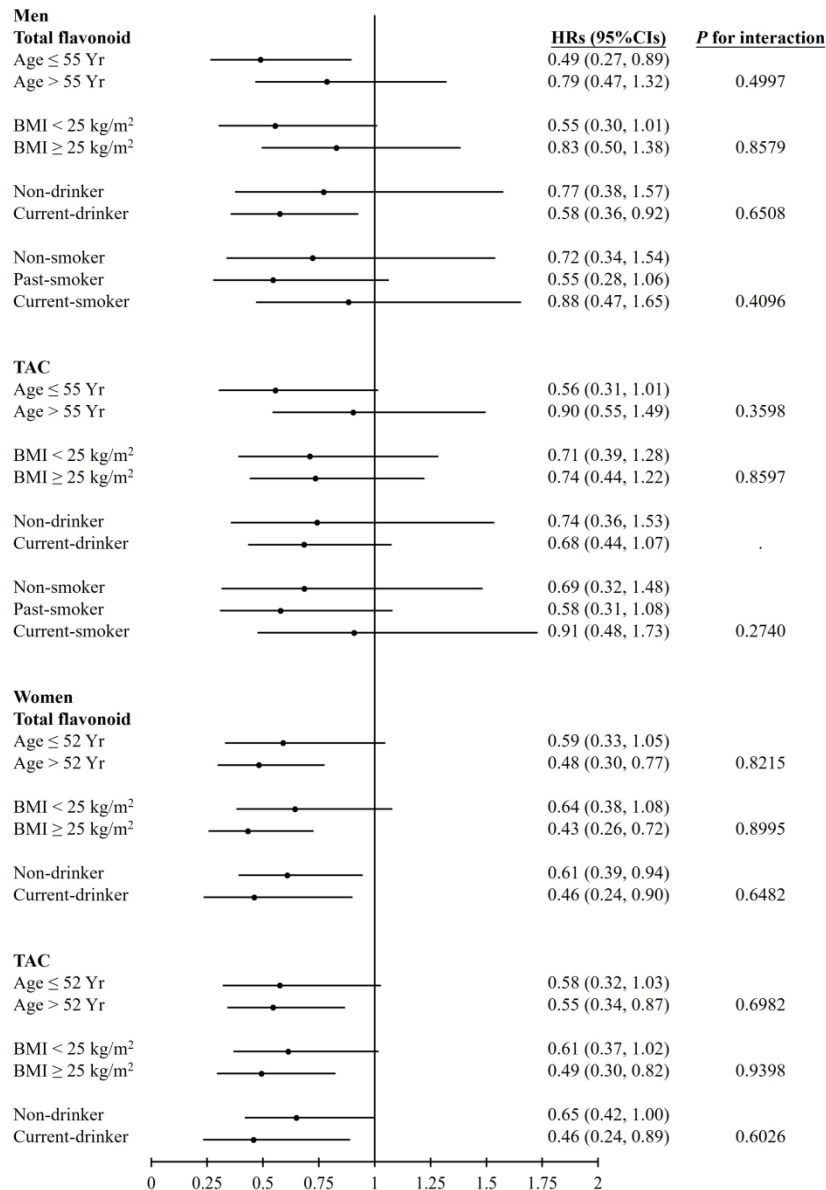
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## 30 **Figure Legend**

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32 **Figure 1.** Hazard ratios (HR) with 95% confidence intervals (CIs) for type 2 diabetes  
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34 mellitus after comparison of antioxidant consumption in the Q5 and Q1 groups according to  
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36 baseline age, baseline body mass index (BMI), alcohol consumption, smoking status in the  
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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					<i>P</i> for trend	HR for a SD increment
	Q1	Q2	Q3	Q4	Q5		
<b>Men</b>							
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)
<b>Women</b>							
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					<i>P</i> for trend	HR for a SD increment
	Q1	Q2	Q3	Q4	Q5		
<b>Men</b>							
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)
<b>Women</b>							
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
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Pages 6–7
		<i>Case-control study</i> —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	
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	Pages 6–7
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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	Page 9
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	



*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy

(e) Describe any sensitivity analyses

<b>Results</b>			
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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Pages 10–14
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	Pages 10–12
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	Page 11
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 (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	Pages 12–13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 14
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).