PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Dietary antioxidant consumption and the risk of type 2 diabetes in South Korean adults: A prospective cohort study based on the Health Examinees study
AUTHORS	TAN, LIJUAN; Hwang, Su Bin; Jun, Shinyoung; Joung, Hyojee; Shin, Sangah

VERSION 1 – REVIEW

REVIEWER	Daneshzad, Elnaz Tehran University of Medical Sciences, Community Nutrition
REVIEW RETURNED	21-Dec-2021

GENERAL COMMENTS	- There are some newly published papers that may be beneficial for the introduction: 1. Clin Nutr ESPEN. 2020 Jun;37:187-194. DOI: 10.1016/j.clnesp.2020.03.002. Epub 2020 Mar 19.Dietary total antioxidant capacity and its association with sleep, stress, anxiety, and depression score: A cross-sectional study among diabetic women. 2. J Nutr Sci . 2021 Feb 9;10:e9. DOI: 10.1017/jns.2020.61. eCollection 2021. Interaction between Apo A-II -265T>C polymorphism and dietary total antioxidant capacity on some anthropometric indices and serum lipid profile in patients with type 2 diabetes mellitus. 3. Br J Nutr . 2021 Aug 10;1-17. DOI: 10.1017/S0007114521002993. Interaction between Apo A-II -265T > C polymorphism and dietary total antioxidant capacity on some oxidative stress and inflammatory markers in patients with type 2 diabetes mellitus - There are several methods to calculate dietary TAC, such as FRAP and TRAP. Pleases explain why you use vitamin C equivalent for DTAC calculation. - Table 1: The percent of physical activity turns to active or inactive?

REVIEWER	Go, Gwang-Woong Hanyang University, Food and Nutrition
REVIEW RETURNED	20-Jan-2022

GENERAL COMMENTS	This article is interestingly present the data, demonstrating the dose-dependent effect of antioxidant consumption on type 2 diabetes mellitus. To test the hypothesis, authors applied HEXA data with statistical analysis. Data curation and written English are descent to deliver the message. This manuscript is eligible to be

considered for the publication in this journal as it is. However, this article could be improved by correcting some minor concerns as follows.

Minor
1. Author projected the importance of pre-diabetes conditions in the introduction. However, the results and discussion were not provided in this regard.

2. Statistical analysis -> no italic

3. line 85-89: "inhibiting AKT" and "improved GLUT4" by antioxidants is contradictory in that AKT is the well-known up-streamer of GLUT4 translocation. Please fortify the discussion on this issue.

REVIEWER	Klisic, Aleksandra Primary Health Care Center, Podgorica, Montenegro, Center for Laboratory Diagnostics
REVIEW RETURNED	19-Mar-2022

GENERAL COMMENTS	# Review The manuscript is written clearly. Minor remark: Lines 269-272: The Authors should kindly re-check the following statement and reference: „Knekt et al. reported a marginally significant inverse association between the intake of the flavonols, quercetin, and myricetin, but not kaempferol, and the incidence of type 2 diabetes among Finnish men and women.[30]". It seems that it is not cited properly.

REVIEWER	Lin, Ping-Ting Chung Shan Medical University
REVIEW RETURNED	21-Mar-2022

GENERAL COMMENTS	Review comments: The manuscript was aimed to assess the association between dietary antioxidant consumption and type 2 diabetes mellitus among South Korean adults. The rationales of the present study are reasonable and interesting. However, there some criticisms may rise and need further clarification. Comments: Title: - I suggest revising the title that the dietary "total flavonoid intake" instead of "antioxidant intake" is more appropriate. Introduction: - Line 63:aged "□ "65 years. Methods: - Statistical analyses: A repeated description in lines 182-183 and lines 188-189. - I did not see the data to estimate the HR for prediabetes after adjusting for the covariates (lines 182-183). - Regarding adjusting the covariates, please try to adjust the dietary fiber intake instead of energy intake. Results: - Line 198: female participants with type 2 DM had lower intake of …carbohydrate. The data in Table 1 is

	higher, not lower, please check. - Line 216: Please check the description of line 216: according to the data in Table 1, the HR for men should be 0.621; 95CI, 0.418-0.921; Women, HR, 0.582; 95%CI, 0.406-0.836). - Line 218, Table 2, only proanthocyanidins had a protective effect against the development of type 2 diabetes mellitus in male participants. Please delete "anthocyanidins". - Line 225, HR=0.86, means approximately 14%, not 24%. Please check. - In Table 1, Please check the values for the proportions of College or above, Physical activity, Current drinker, Current smoker in men and women groups. Some miscalculate in these data. For example, college or above in men should 1518/3649=41.60% not 41.76%. please check the data carefully. - In Table 2, please add or illustrate the values for Q1-Q5 of flavonoids consumption. - Figure 1, please illustrate why it is stratified by age 55 years in male and 52 years in female. Discussion: - Lines 269-272, please check Ref #30, the authors of ref. #30 not Knekt et al. - Line 272-275, did Ref #30 indicate quercetin? Please check the ref. - Lines 275-276, Ref #30 indicates that Flavan-3-ol and "flavonol" intake, please check. - Line 288-289, has Ref # 29 investigated the effects of flavonoids on NF-☐B and mitogen-activated protein kinase signaling pathways? - Lines 303-307, according to the references, a high intake of flavonoids also "decreases" obesity in women. - Line 325: However, our stratified analysis showed that there was no correlation between drinkers and smokers. But your data presented in Figure showed that drinker is associated with type 2 DM in men. - Lines 327-329: the stratified analysis showed in women, please adds "premenopausal". - Please discuss the values for flavonoids consumption, how to achieve the intake in a practical setting. - Limitation: please add: Further study needs to measure the flavonoids concentration to verify the data.

GENERAL COMMENTS	The paper addresses the iportant question of whether the antioxidant contents of the diet correaltes with lower risk of new onset diabetes in a population-based sample from Korea. However, the study methods are described in a very incomplete manner, and essential questions about the study design cannot be answered by reading the paper. Comments: ABSTRACT - Did you identify the asociation between dietary antioxidants and incidence of diabetes?

	- What was the length of the follow-up? How many new diabetes cases were documented? - Two decimals are enough for HRs - Among women, subgroup analysis by age < or > 52 yrs, or pre vs postmenopausal are almost identical. - There are no formal statistical tests to support the conclusions about subgroups INTRODUCTION - The introduction is a bit too long - The sentence "Furthermore, diabetes can be divided into prediabetes and diabetes" is incorrect. - At the end, the authors must specify if they are looking for the association between antioxidant consumption and diabetes... prevalence? incidence? risk? etc. METHODS - The biggest question about the study´s methods is whether the quality of food composition data are high enough to provide reliable estimates of dietary intake for each of the individual flavonoids. The authors present no evidence to support this case. - It is unclear why individuals with hyperlipidemia, stroke, TIA, etc were excluded. They may or may not have diabetes at baseline. - The description of the FFQ is too cursory and incomplete, especially as it pertains to flavonoid intake estimation. - When was the FFQ administered? By whom? Were there any data quality checks? - When was the occurrence of the primary outcome (diabetes) ascertained? How? By whom? - The authors used survival methods to analyze the time to diabetes onset. How many contacts were there per participants? How were they spaced in time? at which point was diabetes ascertained? - Line 187...did you mean "...the median value of each quintile group was modelled as a continuous variable in the Cox model to test the trend"? RESULTS - Crude incidences should be reported, in cases/person/yr - Lines 196-200. Check writing. It reads as if you were comparing participants with vs without diabetes at baseline. - Table 1 should show baseline characteristics - Line 213, did you mean hazards or probabilities? - The rationale for the choice of the particular subgroups studied is unclear, and is not presented by the authors.

VERSION 1 – AUTHOR RESPONSE

Reviewer Reports:

Reviewer: 1
Dr. Elnaz Daneshzad, Tehran University of Medical Sciences

Comments to the Author:
- There are some newly published papers that may be beneficial for the introduction:

1. Clin Nutr ESPEN. 2020 Jun;37:187-194. DOI: 10.1016/j.clnesp.2020.03.002. Epub 2020 Mar 19.Dietary total antioxidant capacity and its association with sleep, stress, anxiety, and depression score: A cross-sectional study among diabetic women.

2. J Nutr Sci . 2021 Feb 9;10:e9. DOI: 10.1017/jns.2020.61. eCollection 2021. Interaction between Apo A-II -265T>C polymorphism and dietary total antioxidant capacity on some anthropometric indices and serum lipid profile in patients with type 2 diabetes mellitus. 3. Br J Nutr . 2021 Aug 10;1-17. DOI: 10.1017/S0007114521002993. Interaction between Apo A-II -265T > C polymorphism and dietary total antioxidant capacity on some oxidative stress and inflammatory markers in patients with type 2 diabetes mellitus

Response: Thank you for your comments. We have carefully reviewed these journal articles you mentioned and cited them in our revised manuscript.

[page 5, lines 96–99]
Moreover, the effect of dietary antioxidants on T2D has not been investigated according to the flavonoid subclasses, antioxidant capacities of flavonoids, or total antioxidant capacity (TAC), which is an index to indicate whole dietary antioxidant content.(23)

[page 5, lines 79–84]
Previous studies have reported that dietary antioxidants decreased oxidative stress, an important risk factor for T2D, played a key role as anti-inflammatory factors by blocking the nuclear factor kappa-light-chain-enhancer of the activated B (NF-κB) and mitogen-activated protein kinase (MAPK) cell signaling pathways. MAPK pathway was associated with the induction of proinflammatory genes and the promotion of Akt/protein kinase B, an insulinsignaling pathway.(12–15)

[page 5, lines 88–90]
Azad et al (22) showed that a diet high in antioxidants had protective effects against the development of diabetes in the Iranian population.

- There are several methods to calculate dietary TAC, such as FRAP and TRAP. Pleases explain why you use vitamin C equivalent for DTAC calculation.

Response: Thank you for your comments. It is a fact that many methods have been developed to assess dietary total antioxidant capacity. (Pisoschi et al., 2012) Among these, the vitamin C equivalent method has been suggested to be more familiar and easily understood by Kim et al. (2002), and we adopted this method since the Korean TAC database was established in a community-based cohort study. Its validity and precision have been proven by our previous study. (Kim et al., 2019)

References:
Pisoschi, Aurelia Magdalena and Gheorghe Petre Negulescu. "Methods for Total Antioxidant Activity Determination: A Review." Biochemistry & Analytical Biochemistry 01 (2012): 110.
Kim, Dae-Ok et al. "Vitamin C equivalent antioxidant capacity (VCEAC) of phenolic phytochemicals." Journal of agricultural and food chemistry vol. 50,13 (2002): 3713-7.
Kim, Seong-Ah et al. "Dietary pattern, dietary total antioxidant capacity, and dyslipidemia in Korean adults." Nutrition journal vol. 18,1 37. 13 Jul. 2019.

- Table 1: The percent of physical activity turns to active or inactive?

Response: The percent of physical activity has been changed to "physical active" in Table 1. Furthermore, after considering all reviewers' comments, we have altered Table 1 to show the baseline general characteristics of participants.

Reviewer: 2
Dr. Gwang-Woong Go, Hanyang University

Comments to the Author:
This article is interestingly present the data, demonstrating the dose-dependent effect of antioxidant consumption on type 2 diabetes mellitus. To test the hypothesis, authors applied HEXA data with statistical analysis. Data curation and written English are descent to deliver the message. This manuscript is eligible to be considered for the publication in this journal as it is. However, this article could be improved by correcting some minor concerns as follows.

Minor
1. Author projected the importance of pre-diabetes conditions in the introduction. However, the results and discussion were not provided in this regard.

Response: Thank you for your comment. Considering all comments of reviewers together, we have deleted all content on pre-diabetes and revised Table 1 in our revised manuscript.

[pages 5–6, lines 99–105]
Furthermore, diabetes can be divided into prediabetes and diabetes. Given that prediabetes has a high probability of progressing into diabetes (up to 50% within seven years, 83% over a lifetime), it is also necessary to focus on the association of dietary antioxidants with prediabetes for the effective prevention of diabetes.(6) However, most existing epidemiological studies on diabetes have focused on comparisons between diabetic and nondiabetic participants. Thus, more detailed studies are needed to comprehensively clarify the association between dietary antioxidant intake and diabetes.

[page 8, lines 155–160]
Definition of type 2 diabetes and prediabetes
Type 2 diabetes was determined in accordance with the definition provided by the Korean Diabetes Association.(28) Diabetes was defined as a diagnosis of type 2 diabetes by a physician, increased fasting plasma glucose level ≥ 6.99 mmol/L (126 mg/dL), or elevated HbA1C level ≥ 47.5 mmol/mol (6.5%). ~~Prediabetes was defined as a fasting plasma glucose level between ≥ 5.55 mmol/L (100 mg/dL) and < 6.99 mmol/L (126 mg/dL).~~

2. Statistical analysis -> no italic Response: We have revised the format of this subheading.

[page 9, line 179]
Statistical analyses

3. line 85-89: "inhibiting AKT" and "improved GLUT4" by antioxidants is contradictory in that AKT is the well-known up-streamer of GLUT4 translocation. Please fortify the discussion on this issue.

Response: We have revised the citation.

[page 5, lines 79–86]
Previous studies have reported that dietary antioxidants decreased oxidative stress, an important risk factor for T2D, played a key role as anti-inflammatory factors by blocking the nuclear factor kappa-light-chain-enhancer of the activated B (NF-κB) and mitogen-activated protein kinase (MAPK) cell signaling pathways. MAPK pathway was associated with the induction of proinflammatory genes and the promotion of Akt/protein kinase B, an insulinsignaling pathway.(12-15) As a result, antioxidants improve insulin resistance, which is involved in the pathogenesis of T2D mellitus, by promoting the transportation of GLUT4 through the regulation of the insulin-signaling pathway.(16,17)

Reviewer: 3
Dr. Aleksandra Klisic, Primary Health Care Center, Podgorica, Montenegro

Comments to the Author:
Review
The manuscript is written clearly.
Minor remark:
Lines 269-272: The Authors should kindly re-check the following statement and reference: „Knekt et al. reported a marginally significant inverse association between the intake of the flavonols, quercetin, and myricetin, but not kaempferol, and the incidence of type 2 diabetes among Finnish men and women.[30]". It seems that it is not cited properly.

Response: We have revised the citation.

[page 15, lines 278–280]
Knekt et al.(36) reported a marginally significant inverse association between the intake of the flavonols quercetin, and myricetin, but not kaempferol, and the incidence of T2D in Finnish men and women.

Reviewer: 4
Dr. Ping-Ting Lin, Chung Chou Univ Sci

Comments to the Author:
Review comments:
The manuscript was aimed to assess the association between dietary antioxidant consumption and type 2 diabetes mellitus among South Korean adults. The rationales of the present study are reasonable and interesting. However, there some criticisms may rise and need further clarification.

Comments:
Title:
- I suggest revising the title that the dietary "total flavonoid intake" instead of "antioxidant intake" is more appropriate.

Response: Thank you for your suggestion. In the current study, we assessed the association between dietary total antioxidant capacity (TAC) and the development of type 2 diabetes at first, and we further discussed the association between dietary flavonoid (one subgroup of dietary TAC) intake and type 2 diabetes development. We primarily aimed to focus on TAC rather than the impact of flavonoid on development of type 2 diabetes.

Introduction: - Line 63:aged "≥ "65 years.

Response: We have revised this symbol in our revised manuscript.

[page 4, lines 59–60] ≥ 65 years was 29.8%.(4)

Methods: - Statistical analyses: A repeated description in lines 182-183 and lines 188-189.

Response: Thank you for your comment. In lines 182-183, we described the main analysis method by grouping participants into quintiles in current research, and in lines 188-189, we depicted the method

of analysis of assess risk for T2D development as one SD increment in TAC intake. We have revised our manuscript to improve clarity regarding statistical analyses.

[page 9, lines 185–194]
A multivariable Cox proportional-hazards regression model was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for T2D and prediabetes after adjusting for categorical (educational level, current drinking status, current smoking status, and physical activity) and continuous (age, BMI, and energy intake) covariables. The lowest quintile (Q1) of TAC or flavonoid intake served as a reference group. The median value of each quintile group was modeled as a continuous variable in the Cox model to test the trend. We also estimated the HRs and 95% CIs for an SD increment in dietary TAC and flavonoid intake and conducted stratified analyses according to BMI, age, smoking status, and alcohol consumption.

- I did not see the data to estimate the HR for prediabetes after adjusting for the covariates (lines 182-183).

Response: Thank you for your comment. In response to the other reviewers' comments, we have deleted mentions of pre-diabetes and revised Table 1 in our manuscript.

- Regarding adjusting the covariates, please try to adjust the dietary fiber intake instead of energy intake.

Response: Thank you for your comment. We have reanalyzed the association after adjusting the dietary fiber intake instead of energy intake. Results are shown in the following table.

		Antioxidant consumption					
	Q1	Q2	Q3	Q4	Q5	P for trend	HR for a SD increment
Men							
Total flavonoid	Ref	1.00 (0.72, 1.39)	0.94 (0.66, 1.34)	0.98 (0.68, 1.40)	0.71 (0.45, 1.13)	0.1553	0.89 (0.76, 1.04)
Anthocyanidins	Ref	0.82 (0.58, 1.15)	1.06 (0.76, 1.47)	0.96 (0.67, 1.37)	0.85 (0.56, 1.30)	0.6471	0.92 (0.79, 1.08)
Isoflavones	Ref	1.53 (1.08, 2.18)	1.22 (0.84, 1.76)	1.31 (0.90, 1.89)	1.61 (1.09, 2.38)	0.0731	1.12 (0.99, 1.26)
Proanthocyanidins	Ref	1.06 (0.77, 1.46)	1.02 (0.72, 1.43)	0.83 (0.58, 1.20)	0.81 (0.54, 1.22)	0.1640	0.92 (0.79, 1.06)
Flavonols	Ref	1.54 (1.12, 2.13)	0.96 (0.66, 1.39)	1.05 (0.72, 1.54)	0.97 (0.62, 1.52)	0.3271	0.88 (0.74, 1.05)
Flavones	Ref	1.06 (0.76, 1.48)	1.09 (0.77, 1.54)	0.95 (0.65, 1.38)	1.07 (0.69, 1.65)	0.9493	0.96 (0.83, 1.11)
Flavanones	Ref	0.85 (0.61, 1.21)	1.29 (0.94, 1.79)	1.03 (0.73, 1.47)	0.95 (0.64, 1.40)	0.8985	0.98 (0.87, 1.11)
Flavan-3-ols	Ref	0.93 (0.66, 1.29)	1.19 (0.86, 1.66)	0.85 (0.59, 1.23)	0.84 (0.57, 1.23)	0.2206	0.92 (0.81, 1.05)
TAC	Ref	1.13 (0.81, 1.57)	1.02 (0.71, 1.45)	0.98 (0.67, 1.44)	0.88 (0.55, 1.40)	0.3967	0.88 (0.75, 1.04)

	Q1	Q2	Q3	Q4	Q5	P	
Women Total flavonoid	Ref	0.90 (0.66, 1.23)	0.82 (0.59, 1.13)	0.62 (0.43, 0.89)	0.54 (0.35, 0.83)	0.0015	0.79 (0.68, 0.93)
Anthocyanidins	Ref	0.93 (0.69, 1.25)	0.64 (0.46, 0.90)	0.73 (0.52, 1.04)	0.58 (0.39, 0.86)	0.0054	0.88 (0.77, 1.02)
Isoflavones	Ref	1.01 (0.74, 1.39)	0.75 (0.53, 1.06)	0.88 (0.63, 1.23)	0.89 (0.62, 1.27)	0.4969	0.97 (0.86, 1.10)
Proanthocyanidins	Ref	0.91 (0.67, 1.25)	1.05 (0.78, 1.43)	0.67 (0.47, 0.96)	0.51 (0.34, 0.77)	0.0003	0.80 (0.69, 0.92)
Flavonols	Ref	0.83 (0.61, 1.14)	0.69 (0.49, 0.97)	0.58 (0.40, 0.85)	0.62 (0.41, 0.96)	0.0355	0.92 (0.78, 1.09)
Flavones	Ref	0.81 (0.60, 1.11)	0.75 (0.54, 1.03)	0.55 (0.38, 0.79)	0.57 (0.38, 0.85)	0.0029	0.82 (0.70, 0.96)
Flavanones	Ref	0.74 (0.55, 1.00)	0.57 (0.42, 0.79)	0.58 (0.42, 0.81)	0.58 (0.40, 0.82)	0.0038	0.86 (0.74, 0.99)
Flavan-3-ols	Ref	0.85 (0.62, 1.17)	0.83 (0.60, 1.15)	0.69 (0.48, 0.98)	0.87 (0.61, 1.23)	0.7719	0.96 (0.84, 1.09)
TAC	Ref	0.82 (0.60, 1.12)	0.86 (0.62, 1.19)	0.51 (0.34, 0.75)	0.57 (0.36, 0.89)	0.0039	0.80 (0.67, 0.95)

Results:

- Line 198: female participants with type 2 DM had lower intake of …carbohydrate. The data in Table 1 is higher, not lower, please check.

Response: Thank you for your comment. The data indeed indicate a higher consumption of carbohydrate in female participants with T2D than in non-diabetes participants. In addition, we have deleted content on pre-diabetes and revised Table 1 to show general characteristics at baseline according to the quintile of TAC intake.

- Line 216: Please check the description of line 216: according to the data in Table 1, the HR for men should be 0.621; 95CI, 0.418-0.921; Women, HR, 0.582; 95%CI, 0.406-0.836).

Response: We have reanalyzed our data and revised this part.
[page 11, lines 220–222]
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).

- Line 218, Table 2, only proanthocyanidins had a protective effect against the development of type 2 diabetes mellitus in male participants. Please delete "anthocyanidins".

Response: We have deleted "anthocyanidins".
[page 11, lines 223–224]
Consumption of more flavonols and proanthocyanidins had a protective effect against the development of T2D mellitus in men participants,

- Line 225, HR=0.86, means approximately 14%, not 24%. Please check.

Response: Thank you; we have revised this portion.

[page 12, lines 229–231]
However, although the TAC Q5 group of men participants did not show any significant association with T2D mellitus, they had an approximately 15% reduced risk of developing T2D mellitus for an SD increment in TAC (HR, 0.85; 95% CI, 0.75–0.96).

- In Table 1, Please check the values for the proportions of College or above, Physical activity, Current drinker, Current smoker in men and women groups. Some miscalculate in these data. For example, college or above in men should 1518/3649=41.60% not 41.76%.
please check the data carefully.

Response: When we calculated the frequency and percentage in each category of covariates, we removed all missing values, because in the Cox model, all risk assessments were conducted after removing missing values. We have revised the text in the methods section and updated Table 1, accordingly in revised manuscript.

- In Table 2, please add or illustrate the values for Q1-Q5 of flavonoids consumption.

Response: We have added the range of flavonoid intake in each quintile in Table 2 of revised manuscript.

- Figure 1, please illustrate why it is stratified by age 55 years in male and 52 years in female.

Response: We conducted a stratified analysis using the median age, which was 55 years for male and 52 for female participants.

Discussion:
- Lines 269-272, please check Ref #30, the authors of ref. #30 not Knekt et al.
- Line 272-275, did Ref #30 indicate quercetin? Please check the ref.
- Lines 275-276, Ref #30 indicates that Flavan-3-ol and "flavonol" intake, please check.

Response: Thank you for your comments. And we are sorry for the citation mistakes. We have revised this part.
[page 15, lines 274–284]
In a previous study, higher flavonol intake was associated with a 26% lower incidence of T2D.(35) In addition, the authors observed a marginally significant inverse association between flavan-3-ol intake and the risk of T2D, but there was no association with anthocyanin intake.(35) Knekt et al.(36) reported a marginally significant inverse association between the intake of the flavonols quercetin, and myricetin, but not kaempferol, and the incidence of T2D in Finnish men and women. Quercetin, in particular, is known to decrease plasma glucose concentration, improve insulin concentration, preserve the integrity of pancreatic beta cells, alleviate T2D symptoms, and reduce hepatic gene expression in streptozotocin-induced diabetic models.(37) Flavan-3-ol and isoflavone intake is associated with a reduced risk of T2D and improved insulin resistance and serum insulin concentrations.(38)

35. Jacques P. F., Cassidy A., Rogers G., et al. Higher dietary flavonol intake is associated with lower incidence of type 2 diabetes. J Nutr 2013; 143(9): 1474-80.
36. Knekt P., Kumpulainen J., Jarvinen R., et al. Flavonoid intake and risk of chronic diseases. Am J Clin Nutr 2002; 76(3): 560-8.

37. Dhanya R. Quercetin for managing type 2 diabetes and its complications, an insight into multitarget therapy. Biomed Pharmacother 2022; 146: 112560.

38. Curtis P. J., Sampson M., Potter J., et al. Chronic ingestion of flavan-3-ols and isoflavones improves insulin sensitivity and lipoprotein status and attenuates estimated 10-year CVD risk in medicated postmenopausal women with type 2 diabetes: a 1-year, double-blind, randomized, controlled trial. Diabetes Care 2012; 35(2): 226-32.

- Line 288-289, has Ref # 29 investigated the effects of flavonoids on NF-κB and mitogenactivated protein kinase signaling pathways?

Response: Reference #29 indeed reported NF-κB and MAPK signaling pathways. We have altered this portion to include the abbreviations.
[pages 15–16 , lines 296–297]
Flavonoids are known to interact with molecular targets and affect NF-κB and MAPK signaling pathways.(34)

- Lines 303-307, according to the references, a high intake of flavonoids also "decreases" obesity in women.

Response: We have revised this sentence.
[page 16, lines 309–312]
In a previous study conducted using 2008–2011 data from the Korea National Health and Nutrition Examination Survey, a high intake of flavonoids did not reduce the incidence of obesity and abdominal obesity in men but significantly reduced obesity (18%) in women.

- Line 325: However, our stratified analysis showed that there was no correlation between drinkers and smokers. But your data presented in Figure showed that drinker is associated with type 2 DM in men.

Response: We have revised this sentence.
[page 17 , lines 331–332]
However, our stratified analysis showed that there was no correlation between these factors except for current alcohol consumption.

- Lines 327-329: the stratified analysis showed in women, please adds "premenopausal".

Response: Thank you for your comments. The distribution of female participants according to median age or menopausal status was almost the same, so we deleted the stratified analyses according to menopausal status.

- Please discuss the values for flavonoids consumption, how to achieve the intake in a practical setting.

Response: Thank you for your comments. We have added this information to Table 2 of the revised manuscript.

- Limitation: please add: Further study needs to measure the flavonoids concentration to verify the data.

Response: Thank you for your comments. We have revised this part. [page 18, lines 346–348]
However, the 106-item FFQ has been previously verified. (26) In addition, further studies are needed to measure the flavonoid concentration to verify the data.

Reviewer: 5
Dr. Carlos O Mendivil, Universidad de los Andes, Fundacion Santa Fe de Bogota

Comments to the Author:
The paper addresses the important question of whether the antioxidant contents of the diet correlates with lower risk of new onset diabetes in a population-based sample from Korea. However, the study methods are described in a very incomplete manner, and essential questions about the study design cannot be answered by reading the paper.

Comments:
ABSTRACT
- Did you identify the association between dietary antioxidants and incidence of diabetes?

Response: Thank you for your comments. We have revised this sentence. [page 2, lines 23–25]
This study aimed to identify the association between dietary antioxidant consumption and the incidence of type 2 diabetes mellitus (T2D, defined using the Korean Diabetes Association criteria) in South Korean adults.

- What was the length of the follow-up? How many new diabetes cases were documented?

Response: Thank you for your comment. The number of incident cases and person-years are shown in Table 1 of the revised manuscript. [page 10, lines 196–198
After an average of 5 years of follow-up, the incidence of type 2 diabetes mellitus was 5.25% in men and 2.52% in women.

- Two decimals are enough for HRs
Response: Thank you for your comment. We have altered all HR values to include two decimals.

- Among women, subgroup analysis by age < or > 52 yrs, or pre vs postmenopausal are almost identical.

Response: Thank you for your comment. We have deleted analyses related to menopausal status.

- There are no formal statistical tests to support the conclusions about subgroups

Response: Thank you for your comment. We have added p for interaction in Figure 1.

INTRODUCTION
- The introduction is a bit too long

Response: Thank you for your comment. We have revised the introduction section in the manuscript.

- The sentence "Furthermore, diabetes can be divided into prediabetes and diabetes" is incorrect.

Response: Thank you for your comment. After reviewing all reviewers' suggestions, we have deleted the content on prediabetes.

- At the end, the authors must specify if they are looking for the association between antioxidant consumption and diabetes... prevalence? incidence? risk? etc.

12

Response: We have changed the description.
[page 6, lines 105–107]
Therefore, we conducted this study to explore the association between dietary antioxidant consumption and the incidence of diabetes by analyzing data from the Health Examinees (HEXA) study.

METHODS
- The biggest question about the study´s methods is whether the quality of food composition data are high enough to provide reliable estimates of dietary intake for each of the individual flavonoids. The authors present no evidence to support this case.

Response: We have revised this part.
[page 7, lines 132–136]
The reproducibility and validity of the FFQ have been assessed in a previous study using a reference method by collecting information on 12-day dietary records.(26) The median correlation coefficient for all nutrients was 0.39 between the FFQ and 12-day dietary record, and the researchers have reported that the FFQ could be an acceptable tool for dietary assessment.(26)

-        It is unclear why individuals with hyperlipidemia, stroke, TIA, etc were excluded. They may or may not have diabetes at baseline.

Response: Lifestyle change, including dietary habits, is an effective protective and preventive way to delay T2D progression. Other metabolic disorders such as hyperlipidemia, stroke, TIA may also affect dietary habits. Therefore, to minimize the impact of medical history on dietary behavior and focus on most health participants as much as possible, we excluded those participants.

-        The description of the FFQ is too cursory and incomplete, especially as it pertains to flavonoid intake estimation.

Response: Thank you for your comment. Our calculation is divided into three steps: 1) link the antioxidant database to HEXA FFQ data, 2) calculate how many each antioxidant item be intake through each food item intake per person, 3) obtain the individual total daily antioxidant intake by summing all food items. We have re-described this part in method section.
[page 7, lines 140–146]
The intake of individual antioxidant components from a food item was calculated by multiplying the antioxidant component per gram of food item by the total weight in grams of daily intake of this food item. The daily intake of individual total dietary antioxidant components was calculated as the sum of the intake of each antioxidant component from all the food sources reported in the HEXA FFQ data(mg VCE/day). After summing all individual total dietary antioxidant components, we obtained the dietary TAC per person per day.

- When was the FFQ administered? By whom? Were there any data quality checks?

Response: We have revised this part.
[page 7, lines 129–136]
Dietary intake was assessed using the self-administered, 106-item, food frequency questionnaire (FFQ) developed for the Korean Genome Epidemiologic Study.(24) Participants reported the frequencies and average portions of food or beverage items consumed during the last year before participating in the HEXA study. The reproducibility and validity of the FFQ have been assessed in a previous study using a reference method by collecting information on 12-day dietary records. (26) The

median correlation coefficient for all nutrients was 0.39 between the FFQ and 12-day dietary record, and the researchers reported that the FFQ could be an acceptable tool for dietary assessment.(26)

- When was the occurrence of the primary outcome (diabetes) ascertained? How? By whom?

Response: The endpoint of the present study was the occurrence of T2D determined by the Korean Diabetes Association. Diabetes was defined as a diagnosis of type 2 diabetes by a physician, increased fasting plasma glucose level ≥ 6.99 mmol/L (126 mg/dL), or elevated HbA1C level ≥ 47.5 mmol/mol (6.5%).

- The authors used survival methods to analyze the time to diabetes onset. How many contacts were there per participants? How were they spaced in time? at which point was diabetes ascertained?

Response: Participants were recruited from the National Health Examinee Registry in South Korea, and participants could get fully paid biannual health check-ups.

- Line 187...did you mean "...the median value of each quintile group was modelled as a continuous variable in the Cox model to test the trend"?

Response: We have revised this sentence.
[page 9, lines 190–191]
The median value of each quintile group was modeled as a continuous variable in the Cox model to test the trend.

RESULTS
- Crude incidences should be reported, in cases/person/yr

Response: We have added this information in Table 2 of the revised manuscript.

- Lines 196-200. Check writing. It reads as if you were comparing participants with vs without diabetes at baseline.

Response: We have changed Table 1 in the revised manuscript, and the description of the results has been changed.
[page 10, lines 204–208]
The baseline general characteristics of participants according to quintiles of total flavonoid intake are shown in Table 1. Among both male and female participants, the highest consumption group (Q5) included more non-smokers, more participants with higher education, and more participants who engaged in physical activity (all p value < 0.05).

- Table 1 should show baseline characteristics Response: We have changed Table 1 in the revised manuscript.

- Line 213, did you mean hazards or probabilities?
Response: Thank you; we have revised this sentence.
[page 4, lines 218–219]
The associations between dietary antioxidant intake and the HRs of T2D mellitus are presented in Table 3.

- The rationale for the choice of the particular subgroups studied is unclear, and is not presented by the authors.

Response: We aimed to identify whether there are interactions between covariates and dietary antioxidants affecting the HRs of T2D. Therefore, we conducted stratified analyses by grouping participants according to the characteristics of each covariate.

VERSION 2 – REVIEW

REVIEWER	Mendivil, Carlos O Universidad de los Andes, Medicine
REVIEW RETURNED	31-May-2022

GENERAL COMMENTS	My comments have been addressed successfully

REVIEWER	Lin, Ping-Ting Chung Shan Medical University
REVIEW RETURNED	08-Jun-2022

GENERAL COMMENTS	The authors almost answered the inquiries. Only one reference needs to clarify. Ref. #34: Dietary flavonoids intake and risk of type 2 diabetes: a meta-analysis of prospective cohort studies, this study used meta-analysis to investigate the association between flavonoid intake and the risk of type 2 diabetes, and the study found that consumption of dietary total flavonoids is associated with a reduced risk of type 2 diabetes. It does not appear to provide data or information on the NF-kB and MAPK signaling pathways. Please check. After the minor revision, I suggest this manuscript could be considered for publication in the journal.

VERSION 2 – AUTHOR RESPONSE

Reviewer Reports:

Reviewer: 1

Dr. Carlos O Mendivil, Universidad de los Andes, Fundacion Santa Fe de Bogota

Comments to the Author:

My comments have been addressed successfully

Reviewer: 2

Dr. Ping-Ting Lin, Chung Shan Medical University

The authors almost answered the inquiries.

Only one reference needs to clarify.

Ref. #34: Dietary flavonoids intake and risk of type 2 diabetes: a meta-analysis of prospective cohort studies, this study used meta-analysis to investigate the association between flavonoid intake and the risk of type 2 diabetes, and the study found that consumption of dietary total flavonoids is associated with a reduced risk of type 2 diabetes. It does not appear to provide data or information on the NF-kB and MAPK signaling pathways. Please check.

After the minor revision, I suggest this manuscript could be considered for publication in the journal.

Response: Thank you for your comments, and we have revised the reference.

[Page 14, Lines 269–270]

Flavonoids are known to interact with molecular targets and affect NF-κB and MAPK signaling pathways.(41)

[Page 24, Lines 477–478]

41. Mansuri M. L., Parihar P., Solanki I., Parihar M. S. Flavonoids in modulation of cell survival signalling pathways. Genes Nutr 2014; 9(3): 400.

Reviewer: 1

Competing interests of Reviewer: No competing interests to declare

Reviewer: 2

Competing interests of Reviewer: I have no competing interests.