PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of dietary antioxidant vitamins on lung functions according to gender and smoking status in Korea: A population-based cross-sectional study
AUTHORS	Hong, Ji Young; Lee, Chang Youl; Lee, Myung Goo; Kim, Young Sam

VERSION 1 – REVIEW

REVIEWER	Yoonki Hong Kangwon National University Hospital, Internal medicine, Chuncheon City, South Korea
REVIEW RETURNED	29-Nov-2017

GENERAL COMMENTS	I am grateful to be able to review this study. This is a potentially interesting study that evaluates the influence of antioxidant vitamins on lung function in Korean COPD patients using National Health Survey. There are several key points and questions, including: Comment 1 It would be interesting to see the effect of dietary antioxidant vitamins according to smoking status (current smoking or ex-smoking). Figure 2 showed the data according to smoking amounts. Comment2 What is the evidence for criteria of smoking amount ≥20 pack years? The categories of amount of pack years are not consistent. Please unify the category with Smoking ≥20 pack years or Smoking >20 pack years.

REVIEWER	Hong Yong Peh National University of Singapore Singapore
REVIEW RETURNED	30-Nov-2017

GENERAL COMMENTS	The authors analyzed data from the previous KNHANES study conducted in 2007-2014 for this manuscript, if dietary antioxidants are beneficial to COPD patients. From the data, dietary antioxidants are probably beneficial only to male smokers. While the study is extensive, there are multiple limitations as follows: Comments: 1. The authors focused only on vitamin A, carotene and

	vitamin C, and excluded other major antioxidants such as vitamin E and NAC. Vitamin E is considerably equivalent in antioxidant potency as vitamin C. There are multiple large clinical trials that evaluated the efficacies of vitamin E and NAC as well. This should be incorporated into this study. 2. From Table 1, it seems that Korean non-smoker males are pre-disposed to COPD compared to non-smoker females (incidence rate of 15.7% versus 6.4%). Please elaborate on this. 3. In Table 2, the authors compared Q5 against Q1 groups, neglecting the fact that in certain parameters, Q3 were comparable or higher than Q5 (FEV1 for vitamin A and carotene). 4. Comparing Q5 male non-smokers to Q5 female non-smokers, it seems that males have approximately 3 (3.29, 3.42, 3.33) folds elevated risk to develop COPD. Similar to comment 3, please elaborate on this. Furthermore, the authors quoted that Q1 male smokers have approximately 5 (5.42, 5.27, 5.61) folds increased risk to develop COPD, but they did not account the fact that Q1 male non-smokers have 3 folds increased risk to develop COPD. While they used Q5 female non-smokers as the reference, they should conduct analyses between other groups too. 5. For Figure 1, the authors stated that Q5 male smokers had reduced risk to develop COPD as compared to Q1 male smokers. From the data, in Figure 1A, the dose-dependent effects of vitamin C can be observed, but this is not the case for vitamin A and carotene. While it may not be significant, it seems that Q3 group had increased risk to develop COPD than Q1 group in the carotene graph. This should be discussed in the results and discussion. 6. The citations used in this manuscript are relatively old (generally 10 years or more). Please update the citations, or justify that there are no updated references in the past decade.

REVIEWER	Cristina Menni King's College London UK
REVIEW RETURNED	12-Dec-2017

GENERAL COMMENTS	This is an interesting study with a remarkable sample size. The authors investigate the association between lung function and anti-oxidant intake in four groups based on gender and smoking status. I have few comments: 1. I find the method' section confusing. A lot of comparison are performed and it is not always easy to follow what the authors are actually doing and reporting. I suggest rewriting parts of the stats section and to add a flowchart of the study design. 3. for instance, what do the authors mean by "We analyzed the energy-adjusted antioxidant vitamin intake by quintiles. The adjustment factors were age, sex, BMI, educational level, household income, total energy intake,number of comorbid diseases, smoking history, alcohol intake, and pack year", that they run multiple linear regressions for each quintile of antioxidant intake with all the covariates as independent variables or that they looked at each covariate separately? 4. What is the rationale of running the analysis in point 3, to look for potential confounders of anti-oxidant intake that may confound the anit-oxidant-COPD association? 5. again this is unclear "For combined analyses between the effects of antioxidant vitamin intake, gender, and smoking status on the risk

	of COPD, interaction tests were performed. Multiple linear regression analyses were performed after categorizing COPD patients by smoking status and amount." What do the authors mean by interaction tests. Why did they stratify COPD patients by smoking status and amount? 6. Lots of tests are performed, but the authors do not adjust for multiple comparison. 7. there are too many tables. I think the authors should consider reporting some of their results via figures 8. regarding the figures, please add * for significance 2. Did the authors consider antioxidant intake in quintile rather than as a continuous variable? 2. when the authors say they divide the individuals in 4 groups based on smoking status, do they consider smokers as individuals who smoked over 100 cigarettes in a lifetime? How do they treat ex-smokers? Can the authors provide a rationale for their definition of smokers? 3. Are the differences reported in the results section lines 3-8 significant?

VERSION 1 – AUTHOR RESPONSE

Editor Comments to Author:
- Please remove the second half of the title and replace it with the study design and setting/country.

We corrected the title according to suggestions.
Effects of dietary antioxidant vitamins on lung functions according to gender and smoking status in Korea: A population-based cross-sectional study

- Please complete and include a STROBE checklist, ensuring that all points are included and state the page numbers where each item can be found. The checklist can be downloaded from here: http://www.strobe-statement.org/?id=available-checklists

Item No Recommendation
Title and abstract 1 (a) Indicate the study's design with a commonly used term in the title or the abstract Page 1
(b) Provide in the abstract an informative and balanced summary of what was done and what was found Page 2
Introduction
Background/rationale 2 Explain the scientific background and rationale for the investigation being reportedPage 4
Objectives 3 State specific objectives, including any prespecified hypotheses
Methods
Study design 4 Present key elements of study design early in the paperPage 5
Setting 5 Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page 5
Participants 6 (a) Give the eligibility criteria, and the sources and methods of selection of participantsPage5
Variables 7 Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicablePage 6
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 Page 7
Bias 9 Describe any efforts to address potential sources of bias Page 7

Study size 10 Explain how the study size was arrived at Page 7
Quantitative variables 11 Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Page 7
Statistical methods
Page 7 12 (a) Describe all statistical methods, including those used to control for confounding
(b) Describe any methods used to examine subgroups and interactions
(c) Explain how missing data were addressed
(d) If applicable, describe analytical methods taking account of sampling strategy
(e) Describe any sensitivity analyses
Results
Participants
Page 5-7, Figure 1 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
Descriptive data
Page 7,8 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
Outcome data 15* Report numbers of outcome events or summary measures
Main results
Page 8-10 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
Other analyses 17 Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion
Key results Page 12 18 Summarise key results with reference to study objectives
Limitations
Page 14 19 Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation
Page 12-14 20 Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability
21 Discuss the generalisability (external validity) of the study results
Other information
Funding Page 15 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

- Can you please provide more details in your paper about the timeline of the analysis. Did you have a study protocol?

We revised the method section.

A total of 21,148 subjects participated in this study. The relationship between antioxidant vitamin intake and lung function was analyzed using multiple linear regression analyses. We analyzed the energy-adjusted antioxidant vitamin intake by quintiles. The adjustment factors were age, sex, BMI,

educational level, household income, total energy intake, location of residence number of comorbid diseases, smoking history, alcohol intake, and packyears1-3. Assessments of linear trends across increasing antioxidant vitamin quintiles were also performed.
We estimated the odds ratios (ORs) of COPD using multivariate logistic regression analyses of quintiles after adjusting for confounding factors. Participants were divided into four groups based on gender and smoking status (male smokers, male non-smokers, female smokers, female non-smokers),to determine whether the relationship between COPD risk and antioxidant vitamin intake is related to gender and smoking status. For combined analyses between the effects of antioxidant vitamin intake, gender, and smoking status on the risk of COPD, interaction tests were performed. COPD patients and male COPD patients were analyzed separately. We attempted to determine whether the association of antioxidant vitamins and lung function varies with gender and smoking status in patients with COPD. Multiple linear regression analyses were performed after categorizing COPD patients by smoking status and amount.

We added the protocol section.

Protocol

KNHANES collects survey data through health questionnaire surveys, screening surveys, and nutrition surveys. Health questionnaires were divided into household survey, health interview survey, and health behavior survey. The health interview survey examined the use of medical services, activity limitations, education and economic activities, and physical activity by interview method. The health behavior survey examined smoking status, drinking, mental health, and safety consciousness by self - filling method. The screening consisted of physical measurement, blood pressure and pulse measurement, blood and urine test, oral examination, pulmonary function test, visual and refractive examination, color vision test, hearing test, and muscle strength test. Nutrition surveys consisted of dietary behaviors, dietary supplements, nutritional knowledge, and the contents of food intake (24-hour recall method) a day before the survey.

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Yoonki Hong
Institution and Country: Kangwon National University Hospital, Internal medicine, Chuncheon City, South Korea
Please state any competing interests or state ‘None declared’: None

Please leave your comments for the authors below
I am grateful to be able to review this study.
This is a potentially interesting study that evaluates the influence of antioxidant vitamins on lung function in Korean COPD patients using National Health Survey.
There are several key points and questions, including:

Comment 1
It would be interesting to see the effect of dietary antioxidant vitamins according to smoking status (current smoking or ex-smoking). Figure 2 showed the data according to smoking amounts.

We performed the additional analysis in male smokers with COPD.
Current smokers had improved lung function as vitamin A or vitamin C intake increased (vitamin A, P trend=0.036, vitamin C P trend= 0.044), but not carotene (P trend= 0.152)
Ex smokers showed no association between lung function and antioxidant vitamin intakes.

Comment2
What is the evidence for criteria of smoking amount ≥20 pack years?
The categories of amount of pack years are not consistent. Please unify the category with Smoking ≥20 pack years or Smoking >20 pack years.

The mean of packyear was 22.6 and the median of packyear was 18.0. Therefore, we set criterion to 20. The previous study classified the smoking amount as 20 packyear.

Hong JY, Jung JY, Lee MG, et al. Changes in the prevalence of COPD in Korea between 2001 and 2011 in the KNHANES data. Respir Med 2017;125:12-18. doi: 10.1016/j.rmed.2017.02.019 [published Online First: 2017/03/28]

Reviewer: 2
Reviewer Name: Hong Yong Peh
Institution and Country: National University of Singapore, Singapore
Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below
The authors analyzed data from the previous KNHANES study conducted in 2007-2014 for this manuscript, if dietary antioxidants are beneficial to COPD patients. From the data, dietary antioxidants are probably beneficial only to male smokers. While the study is extensive, there are multiple limitations as follows:

Comments:
1. The authors focused only on vitamin A, carotene and vitamin C, and excluded other major antioxidants such as vitamin E and NAC. Vitamin E is considerably equivalent in antioxidant potency as vitamin C. There are multiple large clinical trials that evaluated the efficacies of vitamin E and NAC as well. This should be incorporated into this study.

Unfortunately, vitamin E and NAC were not included in the KNHANES item and we could not analyze it.

2. From Table 1, it seems that Korean non-smoker males are pre-disposed to COPD compared to non-smoker females (incidence rate of 15.7% versus 6.4%). Please elaborate on this.

"Interestingly, Korean non-smoker males are pre-disposed to COPD compared to non-smoker females (incidence rate of 15.7% versus 6.4%). Age and th epercentage of alcohol intake were higher in Korean male non-smokers than female non-smokers."

3. In Table 2, the authors compared Q5 against Q1 groups, neglecting the fact that in certain parameters, Q3 were comparable or higher than Q5 (FEV1 for vitamin A and carotene).

Table 2 showed the association between lung function (FEV1, FVC) and dietary antioxidant vitamin levels. Participants in the highest quintile (Q5) of vitamin A intake had 30 ml higher FEV1 (P for trend across quintiles = 0.008) and 33 ml higher FVC (P for trend across quintiles = 0.007) compared to participants in the lowest quintile (Q1). Participants in Q5 for carotene intake had 32 ml higher FEV1 (P for trend across quintiles = 0.010) and 36 ml higher FVC (P for trend across quintiles = 0.005)

measurements compared to participants in Q1. Participants in Q5 of vitamin C intake had 36 ml higher FEV1 (P for trend across quintiles <0.001) and 35 ml higher FVC (P for trend across quintiles = 0.014) measurements compared to participants in Q1. A statistically significant dose–response relationship was observed (all, P for trend across quintiles <0.005), but participants in Q3 of vitamin A and carotene had comparable lung function to those in Q5.

4. Comparing Q5 male non-smokers to Q5 female non-smokers, it seems that males have approximately 3 (3.29, 3.42, 3.33) folds elevated risk to develop COPD. Similar to comment 3, please elaborate on this.
Furthermore, the authors quoted that Q1 male smokers have approximately 5 (5.42, 5.27, 5.61) folds increased risk to develop COPD, but they did not account the fact that Q1 male non-smokers have 3 folds increased risk to develop COPD. While they used Q5 female non-smokers as the reference, they should conduct analyses between other groups too.

The effects of gender, smoking, and dietary antioxidant vitamins on the risk of COPD are summarized in Table 3. The risk of COPD for male smokers in Q1 for vitamin A, carotene, and vitamin C intake increased by 7.60-fold (95% CI=5.92–9.76), 7.16-fold (95% CI=5.58–9.19), and 7.79-fold (95% CI=6.12-9.92), respectively, which was greater than that observed for female non-smokers in Q5 for antioxidant vitamin intake. Interestingly, the risk of COPD for male non-smokers in Q5 for vitamin A, carotene, and vitamin C intake increased by 3.26-fold (95% CI=2.24-4.75). 3.35-fold (95% CI=2.31-4.86) and 3.28-fold (95% CI=2.27-4.73), respectively, compared with female non-smokers in Q5 for antioxidant vitamin intake. The risk of COPD for male non-smokers in Q1 for vitamin A, carotene, and vitamin C intake increased by 2.80-fold (95% CI=1.90-4.12). 3.25-fold (95% CI=2.21-4.78) and 3.17-fold (95% CI=2.04-4.91), respectively, compared with female non-smokers in Q1 for antioxidant vitamin intake. These results suggest that men may have other causes of COPD as well as smoking, compared with women who took similar amounts of antioxidant vitamins.

The interaction exists between the antioxidant vitamin intake and gender/smoking status on the risk of COPD (all P-values<0.001).The effect of the antioxidant vitamin intake depends on the gender/smoking status. When assessing the risk of COPD following reduction of antioxidant intake from Q5 to Q1, only male smokers showed significant difference in risk of COPD, but other three groups did not.

Vitamin A
Male smokers, [Q1, 1.29 (1.05, 1.58), Q 5reference, P=0.014]
Male non-smokers, [Q1, 0.93 (0.56, 1.54), Q5reference, P=0.787]
Female smokers [Q1, 0.78 (0.37, 1.67), Q5 reference, P=0.525]
Female non-smokers [Q1, 1.14 (0.88, 1.49), Q5reference, P=0.327]

Carotene
Male smokers, [Q1, 1.24(1.01, 1.51), Q5reference, P=0.037]
Male non-smokers, [Q1, 0.97 (0.60, 1.58), Q5reference, P=0.912]
Female smokers [Q1, 0.80 (0.38, 1.69), Q5reference, P=0.563]
Female non-smokers [Q1, 1.13 (0.87, 1.47), Q5reference, P=0.364]

Vitamin C
Male smokers, [Q1 1.37 (1.09, 1.64), Q5 reference, P=0.005]
Male non-smokers, [Q1,1.15 (0.67, 1.96), Q5 reference, P=0.614]
Female smokers[Q1,1.28 (0.57, 2.87), Q5 reference, P=0.5511
Female non-smokers[Q1,1.03 (0.78, 1.35), Q5 reference, P=0.848]

5. For Figure 1, the authors stated that Q5 male smokers had reduced risk to develop COPD as compared to Q1 male smokers. From the data, in Figure 1A, the dose-dependent effects of vitamin C can be observed, but this is not the case for vitamin A and carotene. While it may not be significant, it seems that Q3 group had increased risk to develop COPD than Q1 group in the carotene graph. This should be discussed in the results and discussion.

“The dose –dependent effect of vitamin C was observed between COPD risk and dietary antioxidant vitamin levels, but it was not for vitamin A and carotene. Although not significant, Q3 group of carotene had increased risk to develop COPD than Q1 group of carotene.”

Discussion
“Although the dose-dependent effect on COPD risk was not obvious in vitamin A and carotene, contrary to vitamin C (Figure 2), male smokers with Q5 intake showed a clearly reduced risk to develop COPD than male smokers with Q1 intake in all three antioxidant vitamins.”

6. The citations used in this manuscript are relatively old (generally 10 years or more). Please update the citations, or justify that there are no updated references in the past decade.

We updated the citation as suggested.

8. Rodriguez-Rodriguez E, Ortega RM, Andres P, et al. Antioxidant status in a group of institutionalised elderly people with chronic obstructive pulmonary disease. Br J Nutr 2016;115(10):1740-7. doi: 10.1017/S0007114516000878 [published Online First: 2016/03/24]
9. Wu TC, Huang YC, Hsu SY, et al. Vitamin E and vitamin C supplementation in patients with chronic obstructive pulmonary disease. Int J Vitam Nutr Res 2007;77(4):272-9. doi: 10.1024/0300-9831.77.4.272 [published Online First: 2008/02/15]
37. Park HJ, Byun MK, Kim HJ, et al. Dietary vitamin C intake protects against COPD: the Korea National Health and Nutrition Examination Survey in 2012. Int J Chron Obstruct Pulmon Dis 2016;11:2721-28. doi: 10.2147/COPD.S119448 [published Online First: 2016/11/16]

Reviewer: 3
Reviewer Name: Cristina Menni
Institution and Country: King's College London, UK
Please state any competing interests or state ‘None declared’: None declared
Please leave your comments for the authors below
This is an interesting study with a remarkable sample size. The authors investigate the association between lung function and anti-oxidant intake in four groups based on gender and smoking status. I have few comments:

1. I find the method' section confusing. A lot of comparison are performed and it is not always easy to follow what the authors are actually doing and reporting. I suggest rewriting parts of the stats section and to add a flowchart of the study design.

We rewrite the method section and added a flowchart of the study design.(Figure 1)

3. for instance, what do the authors mean by "We analyzed the energy-adjusted antioxidant vitamin intake by quintiles. The adjustment factors were age, sex, BMI, educational level, household income, total energy intake,number of comorbid diseases, smoking history, alcohol intake, and pack year", that they run multiple linear regressions for each quintile of antioxidant intake with all the covariates as independent variables or that they looked at each covariate separately?

We performed the multivariate linear regression analysis and all the covariables (age, sex, BMI, educational level, household income, total energy intake, place of residence, number of comorbid diseases, smoking history, alcohol intake, and pack year) were used at the same time in the analysis.

4. What is the rationale of running the analysis in point 3, to look for potential confou(nders of anti-oxidant intake that may confound the anit-oxidant-COPD association?

The adjustment factors were age, sex, BMI, educational level, household income, total energy intake, place of residence ,number of comorbid diseases, smoking history, alcohol intake, and packyears1-3

These variables were included as confounders because they were presented as risk factors for COPD at the reference below. Also, most variables showed $P<0.05$ in the univariate analysis.

Kan H, Stevens J, Heiss G, et al. Dietary fiber, lung function, and chronic obstructive pulmonary disease in the atherosclerosis risk in communities study. Am J Epidemiol 2008;167(5):570-8. doi: 10.1093/aje/kwm343
Morabia A, Sorenson A, Kumanyika SK, et al. Vitamin A, cigarette smoking, and airway obstruction. Am Rev Respir Dis 1989;140(5):1312-6. doi: 10.1164/ajrccm/140.5.1312
Hong JY, Kim SY, Chung KS, et al. Factors associated with the quality of life of Korean COPD patients as measured by the EQ-5D. Qual Life Res 2015;24(10):2549-58. doi: 10.1007/s11136-015-0979-6

5. again this is unclear "For combined analyses between the effects of antioxidant vitamin intake, gender, and smoking status on the risk of COPD, interaction tests were performed. Multiple linear regression analyses were performed after categorizing COPD patients by smoking status and amount." What do the authors mean by interaction tests. Why did they stratify COPD patients by smoking status and amount?

“The interaction exists between the antioxidant vitamin intake and gender/smoking status on the risk of COPD. The effect of the antioxidant vitamin intake depends on the gender/smoking status. When assessing the risk of COPD following reduction of antioxidant intake from Q5 to Q1, only male smokers showed significant difference in risk of COPD, but other three groups did not.”

Similarly, when analyzing only COPD patients, only male smokers showed improved lung function as antioxidant vitamin intake increased.

“Similar to the previous results, only male smokers in subjects with COPD exhibited a beneficial association between dietary antioxidant vitamin intake and FEV1 (Figure 3).”
“Additional analyzes were performed to determine if lung function was reduced by smoking amount or smoking status in male smoker- COPD patients.”

6. Lots of tests are performed, but the authors do not adjust for multiple comparison.

We described the multiple comparisons in detail.

“The effects of gender, smoking, and dietary antioxidant vitamins on the risk of COPD are summarized in Table 3. The risk of COPD for male smokers in Q1 for vitamin A, carotene, and vitamin C intake increased by 7.60-fold (95% CI=5.92–9.76), 7.16-fold (95% CI=5.58–9.19), and 7.79-fold (95% CI=6.12-9.92), respectively, which was greater than that observed for female non-smokers in Q5 for antioxidant vitamin intake. Interestingly, the risk of COPD for male non-smokers in Q5 for

vitamin A, carotene, and vitamin C intake increased by 3.26-fold (95% CI=2.24-4.75). 3.35-fold (95% CI=2.31-4.86) and 3.28-fold (95% CI=2.27-4.73), respectively, compared with female non-smokers in Q5 for antioxidant vitamin intake. The risk of COPD for male non-smokers in Q1 for vitamin A, carotene, and vitamin C intake increased by 2.80-fold (95% CI=1.90-4.12). 3.25-fold (95% CI=2.21-4.78) and 3.17-fold (95% CI=2.04-4.91), respectively, compared with female non-smokers in Q1 for antioxidant vitamin intake. These results suggest that men may have other causes of COPD as well as smoking, compared with women who took similar amounts of antioxidant vitamins."

The interaction exists between the antioxidant vitamin intake and gender/smoking status on the risk of COPD (all P-values<0.001).The effect of the antioxidant vitamin intake depends on the gender/smoking status. When assessing the risk of COPD following reduction of antioxidant intake from Q5 to Q1, only male smokers showed significant difference in risk of COPD, but other three groups did not."

7. there are too many tables. I think the authors should consider reporting some of their results via figures

We changed table 4 to figure 3. Figure 2 was changed to figure 4.

8. regarding the figures, please add * for significance

We revised the figures and added * for significance. (Figure 2)

2. Did the authors consider antioxidant intake in quintile rather than as a continuous variable?

The analysis was performed with reference to several previous studies.
These studies considered antioxidant intake or fiber intake in quintile ,quartile or tertile

Reference:
Kan H, Stevens J, Heiss G, et al. Dietary fiber, lung function, and chronic obstructive pulmonary disease in the atherosclerosis risk in communities study. Am J Epidemiol 2008;167(5):570-8.Quintile

Morabia A, Sorenson A, Kumanyika SK, et al. Vitamin A, cigarette smoking, and airway obstruction. Am Rev Respir Dis 1989;140(5):1312-6.Tertile

Shahar E, Folsom AR, Melnick SL, et al. Does dietary vitamin A protect against airway obstruction? The Atherosclerosis Risk in Communities (ARIC) Study Investigators. Am J Respir Crit Care Med 1994;150(4):978-82.quartile

Tian Y, Su L, Wang J, et al. Fruit and vegetable consumption and risk of the metabolic syndrome: a meta-analysis. Public Health Nutr 2017:1-10. doi: 10.1017/S136898001700310X [published Online First: 2017/11/21]

Hanson C, Lyden E, Rennard S, et al. The Relationship between Dietary Fiber Intake and Lung Function in the National Health and Nutrition Examination Surveys. Ann Am Thorac Soc 2016;13(5):643-50. doi: 10.1513/AnnalsATS.201509-609OC [published Online First: 2016/01/20]

Park HJ, Byun MK, Kim HJ, et al. Dietary vitamin C intake protects against COPD: the Korea National Health and Nutrition Examination Survey in 2012. Int J Chron Obstruct Pulmon Dis 2016;11:2721-28. doi: 10.2147/COPD.S119448 [published Online First: 2016/11/16]
4 5
2. when the authors say they divide the individuals in 4 groups based on smoking status, do they consider smokers as individuals who smoked over 100 cigarettes in a lifetime? How do they treat ex-smokers? Can the authors provide a rationale for their definition of smokers?

A never smoker was defined as someone who had smokerd fewer than 100 cigarettes during their lifetime in questionnaire of KNHANES.
Several studies defined smokers as individuals who smoked over 100 cigarettes in a lifetime.

"Those who answered in the negative to the question ' Do you currently smoke?' were defined as ex-smokers."

References:
1. Kan H, Stevens J, Heiss G, et al. Dietary fiber, lung function, and chronic obstructive pulmonary disease in the atherosclerosis risk in communities study. Am J Epidemiol 2008;167(5):570-8. doi: 10.1093/aje/kwm343
2. Morabia A, Sorenson A, Kumanyika SK, et al. Vitamin A, cigarette smoking, and airway obstruction. Am Rev Respir Dis 1989;140(5):1312-6. doi: 10.1164/ajrccm/140.5.1312
3. Hong JY, Kim SY, Chung KS, et al. Factors associated with the quality of life of Korean COPD patients as measured by the EQ-5D. Qual Life Res 2015;24(10):2549-58. doi: 10.1007/s11136-015-0979-6 [published Online First: 2015/04/07]
4. Tian Y, Su L, Wang J, et al. Fruit and vegetable consumption and risk of the metabolic syndrome: a meta-analysis. Public Health Nutr 2017:1-10. doi: 10.1017/S136898001700310X [published Online First: 2017/11/21]
5. Hanson C, Lyden E, Rennard S, et al. The Relationship between Dietary Fiber Intake and Lung Function in the National Health and Nutrition Examination Surveys. Ann Am Thorac Soc 2016;13(5):643-50. doi: 10.1513/AnnalsATS.201509-609OC [published Online First: 2016/01/20]

3. Are the differences reported in the results section lines 3-8 significant?

We analyzed the multivariate logistic regression analyses again.
The location of residence was added as the adjusting factor.
The adjusting factors are age, body mass index, energy intake, number of comorbid diseases, alcohol consumption, place of residence, household income, and education level.(Table 2,3 Figure 1,2,3)

The risk of COPD between Q1 and Q5 significantly differs in male smokers.
In male smokers, the risk of3 COPD in subjects in Q5 for antioxidant vitamins intake was significantly lower than that for subjects in Q1 (vitamin A, OR = 0.77, 95% CI = 0.63–0.94, P = 0.009; carotene, OR = 0.81, 95% CI = 0.67–0.99, P=0.041; vitamin C, OR = 0.74, 95% CI = 0.61–0.91, P = 0.004).

VERSION 2 – REVIEW

REVIEWER	Yoonki Hong Department of Internal Medicine, Kangwon National University Hospital, Chuncheon, South Korea
REVIEW RETURNED	23-Jan-2018

GENERAL COMMENTS	I think this revised manuscript is well reviewed and revised and is

	suitable for publication.

REVIEWER	Hong Yong Peh Harvard Medical School, USA National University of Singapore, Singapore
REVIEW RETURNED	25-Jan-2018

GENERAL COMMENTS	The authors have answered my previous comments satisfactorily.