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Effects of dietary antioxidant vitamins on lung functions according to gender and smoking status: KNHANES 2007–2014

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4 **1 Effects of dietary antioxidant vitamins on lung functions**
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7 **2 according to gender and smoking status: KNHANES 2007–2014**
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4 **Abstract**
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8 **Objective:** Cigarette smoke-induced oxidative stress plays an important role in the pathogenesis of
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10 chronic obstructive pulmonary disease (COPD). Dietary antioxidants are thought to prevent smoke-
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12 induced oxidative damage. The aim of this study was to investigate associations between lung
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14 function and the consumption of antioxidant vitamins in Korean adults.
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17 **Methods:** In total, 21,148 participants from the Korean National Health and Nutrition Examination
18
19 Survey (2007–2014) were divided into four groups based on smoking history and gender. Multivariate
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21 regression models were used to evaluate associations between lung function and intake of dietary
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23 antioxidants.
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26 **Results:** Subjects in the highest-intake quintile (Q5) of vitamin A, carotene, and vitamin C intake had
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28 mean forced expiratory volume in 1 second (FEV₁) measurements that were 25 ml, 27 ml, and 36 ml
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30 higher than those of individuals in the lowest-intake quintile (Q1), respectively (*P* for trend; *P*=0.032,
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32 *P*=0.038, and *P*=0.004, respectively). The risks of COPD for male smokers in Q1 increased 5.42-fold
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34 (95% CI=4.09–7.18), 5.27-fold (95% CI=3.98–6.98), and 5.61-fold (4.26–7.39) for vitamin A,
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36 carotene, and vitamin C, respectively, compared to those of female non-smokers in Q5. Among COPD
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38 patients, males who smoked >20 pack years had mean FEV₁ measurements that were 124 ml, 94 ml,
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40 and 113 ml higher than those of patients in Q1 (*P* for trend; *P*=0.018, *P*=0.026, and *P*=0.047, for
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42 vitamin A, carotene, and vitamin C, respectively).
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45 **Conclusions:** These findings indicate that the influence of antioxidant vitamins on lung function
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47 depends on gender and smoking status in the Korean COPD population.
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53 Keywords: lung function, gender, smoking, antioxidant vitamins
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1 **Strengths and limitation of this study**

- 2 ■ This study revealed that the influence of antioxidant vitamins on lung function depends on
- 3 gender and smoking status in Korean patients with COPD.

- 4 ■ A cross-sectional study with a large sample size collected from a national health survey

- 5 ■ Main limitations include a possible recall bias and no further verification of nutritional intake.

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1 Introduction

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Chronic obstructive pulmonary disease (COPD) causes morbidity and mortality¹. Smoking is a primary risk factor for COPD; however, other factors also contribute as only 10–20% of smokers develop airflow limitations².

Dietary antioxidants protect against oxidative stress caused by smoking³, and multiple studies have revealed associations between the intake of antioxidant vitamins or fibers and respiratory diseases⁴⁻⁸. However, evidence supporting the benefits of vitamin supplement therapy is lacking⁹⁻¹¹.

Because micronutrient status is affected by dietary intake and metabolic turnover, which are regulated by oxidative stress, the benefits of antioxidant vitamins may vary by gender and smoking status. Multiple studies have shown that different antioxidants exhibit different effects based on smoking status. Morabia *et al.* reported an association between airway obstruction and vitamin A intake in smokers compared to former smokers, whereas Hu *et al.* reported that carotene was less strongly associated with FEV₁ in smokers compared to former smokers and non-smokers^{12 13}.

This study used KNHANES data to investigate whether dietary antioxidant vitamins were independently associated with pulmonary function and COPD in the Korean population. This study also evaluated whether the effects of antioxidant vitamins on pulmonary function differed based on gender or smoking status.

1 **Patients and Methods**

3 *Study population*

4 Participants were sampled from Korean National Health and Nutritional Examination Survey
5 (KNHANES; 2007–2014) IV–VI, a nationwide survey designed to be representative of the population
6 that is used to establish health policies. KNHANES contains a massive database with information
7 about demographic characteristics, comorbidities, lung function, nutritional status, and health
8 (<https://knhanes.cdc.go.kr/knhanes>).

9 A two-stage stratified systemic sampling method was use to select 65,973 individuals to survey
10 between February 2007 and December 2014. Of the chosen individuals, 34,278 participants over 40
11 years of age responded to questionnaires regarding diet and smoking history and underwent a medical
12 examination. After excluding subjects who omitted lung function or nutrition data, we analyzed data
13 from 21,148 (8,804 men and 12,344 women) in this study. This study was approved by the
14 Institutional Review Board of the Korean Centers for Disease Control and Prevention. All participants
15 provided informed written consent.

17 *Spirometry and airflow obstruction definitions*

18 The pulmonary function test (PFT) was performed using dry-rolling seal volume spirometers (Model
19 2130; SensorMedics, Yorba Linda, CA, USA) and standardized according to the American Thoracic
20 Society/European Respiratory Society criteria¹⁴. Qualified technicians and principal investigators
21 assessed the spirometry data for acceptability and reproducibility. The predictive equations for the
22 forced expiratory volume in 1 second (FEV₁) and the forced vital capacity (FVC) were derived from
23 survey data on non-smokers who had normal chest X-rays and no previous history of respiratory
24 diseases¹⁵. COPD was defined as a FEV₁/FVC <70 %¹⁶.

1 *Dietary assessments*

2 Food intake data were obtained using the 24-h recall method, in which participants were asked to
3 report the foods and amounts thereof consumed during the previous 24 hours. Total energy (kJ/d
4 (kcal/d)) and total intake of antioxidant vitamins were calculated using the Korean Food Composition
5 Table¹⁷ as the reference. Antioxidant vitamin consumption was adjusted for total energy intake.

6 7 *Potential confounders*

8 Data regarding demographic information, education level, household income, smoking status,
9 smoking amount, alcohol intake, body mass index (BMI), and comorbid diseases were obtained.
10 Educational level was categorized as elementary school or lower, completion of middle school,
11 completion of high school, and college or higher. Household income was divided by quartile.

12 Smokers were subjects who smoked more than 100 cigarettes in their lifetime. Participants were
13 categorized in terms of smoking status as follows: smoker, ex-smoker, or never smoked. The smoking
14 amount was determined in pack years, which was calculated by multiplying the duration of smoking
15 (years) by the number of packs of cigarettes smoked. Comorbid diseases included hypertension,
16 stroke, cardiovascular disease, arthritis, tuberculosis, asthma, diabetes mellitus, thyroid disorders,
17 renal failure, liver disease, and malignancy.

18 19 *Statistical analysis*

20 The relationship between antioxidant vitamin intake and lung function was analyzed using multiple
21 linear regression analyses. We analyzed the energy-adjusted antioxidant vitamin intake by quintiles.
22 The adjustment factors were age, sex, BMI, educational level, household income, total energy intake,
23 number of comorbid diseases, smoking history, alcohol intake, and pack years^{4 12 18}. Assessments of
24 linear trends across increasing antioxidant vitamin quintiles were also performed.

25 We estimated the odds ratios (ORs) of COPD using multivariate logistic regression analyses of
26 quintiles after adjusting for confounding factors. Participants were divided into four groups based on

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1 gender and smoking status (male smokers, male non-smokers, female smokers, female non-smokers).
2 For combined analyses between the effects of antioxidant vitamin intake, gender, and smoking status
3 on the risk of COPD, interaction tests were performed. Multiple linear regression analyses were
4 performed after categorizing COPD patients by smoking status and amount.
5 Statistical analyses were performed using PASW Statistics ver. 20 (SPSS Inc., Chicago IL, USA) and
6 SAS ver. 9.4 (SAS Institute, Cary, NC, USA) software. *P*-values <0.05 were considered statistically
7 significant.

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1 Results

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3 The baseline characteristics of the 21,148 participants are shown in Table 1. All subjects were
4 classified into four groups based on smoking history and gender. Of the 7,986 smokers, 7,178 were
5 male (mean age, 57.8±11.0 years) and 808 were female (mean age, 57.4±12.5 years). Of the 13,162
6 individuals who had never smoked, 1,626 were male (mean age, 57.9±11.3 years) and 11,536 were
7 female (mean age, 57.1±10.8 years). Among all subjects, 3,005 were diagnosed with COPD. The
8 prevalence of COPD was highest in male smokers (26.4%) and lowest in female non-smokers (6.4%).
9 The four groups differed regarding age, BMI, educational level, household income, and alcohol usage
10 ($P<0.001$). Energy intake was significantly higher in males than females (males, 2,256.5 kcal; females,
11 1,648.3 kcal; $P<0.001$). The levels of vitamin A, carotene, and vitamin C were highest in the male
12 non-smoker group and lowest in the female smoker group.

13 A statistically significant dose–response relationship was observed between lung function (FEV₁,
14 FVC) and dietary antioxidant vitamin levels (Table 2). Participants in the highest quintile (Q5) of
15 vitamin A intake had 25 ml higher FEV₁ (P for trend across quintiles = 0.032) and 31 ml higher FVC
16 (P for trend across quintiles = 0.013) compared to participants in the lowest quintile (Q1). Participants
17 in Q5 for carotene intake had 27 ml higher FEV₁ (P for trend across quintiles = 0.038) and 34 ml
18 higher FVC (P for trend across quintiles = 0.011) measurements compared to participants in Q1.
19 Participants in Q5 of vitamin C intake had 36 ml higher FEV₁ (P for trend across quintiles = 0.004)
20 and 35 ml higher FVC (P for trend across quintiles = 0.027) measurements compared to participants
21 in Q1.

22 The effects of gender, smoking, and dietary antioxidant vitamins on the risk of COPD are summarized
23 in Table 3. The risk of COPD for male smokers in Q1 for vitamin A, carotene, and vitamin C intake
24 increased by 5.42-fold (95% CI=4.09–7.18), 5.27-fold (95% CI=3.98–6.98), and 5.61-fold (95%
25 CI=4.26–7.39), respectively, which was greater than that observed for female non-smokers in Q5 for
26 antioxidant vitamin intake. The interaction effect was significant (all P -values <0.001).

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4 1 According to the multivariate logistic regression analyses, the risk of COPD was influenced by dietary
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6 2 antioxidant vitamin levels in male smokers (Figure 1). In male smokers, the risk of COPD in subjects
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8 3 in Q5 for vitamin A and vitamin C intake was significantly lower than that for subjects in Q1 (vitamin
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10 4 A, OR = 0.77, 95% CI = 0.63–0.94, $P = 0.011$; vitamin C, OR = 0.76, 95% CI = 0.62–0.93, $P =$
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12 5 0.007). Similarly, the prevalence of COPD was lower in Q5 compared to Q1 for carotene; however,
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14 6 this trend was not significant (OR = 0.82, 95% CI = 0.67–1.00, $P=0.052$). The prevalence of COPD
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16 7 did not increase significantly as the intake of dietary antioxidant vitamins increased in male non-
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18 8 smokers, female smokers, or female non-smokers. No significant interaction between the effects of
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20 9 antioxidant vitamins on COPD and smoking status was observed. The correlation between the risk of
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22 10 COPD and antioxidant vitamin intake was stronger in male smokers who smoked less than 20 pack
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24 11 years (not shown).

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29 12 We investigated the association between dietary antioxidant vitamin intake and lung function after
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31 13 limiting the analyses to individuals with COPD. The changes in FEV₁ were not statistically significant
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33 14 based on the levels of dietary antioxidant vitamins in subjects with COPD. Interestingly, only male
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35 15 smokers exhibited a beneficial association between dietary antioxidant vitamin intake and FEV₁
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37 16 (Table 4). Male smokers with COPD in Q5 for vitamin A intake had a 66-ml higher FEV₁ (P for trend
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39 17 across quintiles = 0.024) compared to those in Q1. Male smokers with COPD in Q5 of carotene and
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41 18 vitamin C intake had 65-ml higher FEV₁ (P for trend across quintiles = 0.046) and a 101-ml higher
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43 19 FEV₁ (P for trend across quintiles = 0.039), respectively, compared to individuals in Q1.

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46 20 Male COPD patients who had smoked ≥ 20 pack years exhibited a beneficial association between
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48 21 dietary antioxidant vitamin intake and FEV₁ (Figure 2). Male COPD patients in Q5 of vitamin A
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50 22 intake who had smoked ≥ 20 pack years had a 124-ml higher FEV₁ (P for trend across quintiles =
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52 23 0.018) compared to individuals in Q1. COPD patients in Q5 of carotene intake who had smoked ≥ 20
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54 24 pack years had a 94-ml higher FEV₁ (P for trend across quintiles = 0.026) compared with patients in
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1 Q1. COPD patients in Q5 of vitamin C intake who had smoked >20 pack years had a 113-ml higher
2 FEV₁ (*P* for trend across quintiles = 0.047) compared to patients in Q1.

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1 Discussion

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3 This study examined the association between the intake of antioxidant vitamins and lung functions in
4 the Korean population. Previous studies showed that antioxidant vitamins, including vitamin C, were
5 protective of the human lung^{5,13}, whereas high levels of vitamin A and carotene were also associated
6 with increased lung functions in multiple studies^{12,19-23}. In a randomized controlled trial, Keranis *et al.*
7 reported that increasing the intake of antioxidants improved lung function²⁴.

8 Cigarette smoking is the primary cause of COPD as it increases oxidative stress in the lungs and
9 activates inflammatory responses²⁵. Notably, one inhalation from a cigarette generates more than 10¹⁵
10 free radicals and other oxidants²⁶.

11 Antioxidants protect against the damage caused by smoking in multiple ways³. For example, as it is
12 water-soluble, vitamin C scavenges free radicals in the cytoplasm. Koike *et al.* reported that vitamin C
13 diminished smoke-induced oxidative stress and corrected emphysematous lungs *in vivo*²⁷.

14 Carotenoids quench singlet oxygen and inhibit lipid peroxidation³. In an animal study, the respiratory
15 epithelia of retinol-deficient animals had atrophied ciliated cells and modified lipid contents²⁸. The
16 pathologic features of the retinol-deficient animals were similar to those of human smokers²⁹.

17 Smokers exhibit nicotine-induced reductions in intestinal absorption and elevated metabolic
18 turnover³⁰. The metabolism or destruction of antioxidant vitamins increases in inflammatory
19 environments³¹⁻³⁴, which suggests that smokers with COPD require larger amounts of antioxidant
20 vitamins to achieve the same blood levels as non-smokers. A study by Sargeant found that vitamin C
21 may modify the adverse effects of smoking and the risk of COPD in the European population³⁵.
22 Additionally, Shin *et al.* reported that Korean smokers with adequate vitamin C intake had acceptable
23 pulmonary functions³⁶. Additionally, Morabia *et al.* identified that airway obstruction was reduced by
24 vitamin A in smokers¹².

25 One notable finding in the current study was that the effects of antioxidant vitamin intake on lung

1 function were stronger among male smokers. Additionally, the association between the risk of COPD
2 and antioxidant vitamin intake was clear for male but not female smokers. Male smokers with lower
3 antioxidant vitamin intakes had increased ORs of COPD compared to female smokers. After limiting
4 the analysis to subjects with COPD, a significant association between antioxidant vitamin intake and
5 FEV₁ was observed in male smokers but not in other groups. This finding was similar to that of Joshi
6 *et al.*, where changes in COPD risk and dietary vitamin C and vitamin E intake differed between
7 males and females³⁷.

8 It is not known how gender differences impact pulmonary functions based on antioxidant vitamin
9 intake; however, animal studies have revealed gender differences in antioxidant vitamin requirements.
10 Al Rejaie *et al.* reported gender-related differences in the protective roles of ascorbic acid against
11 oxidative stress³⁸, whereas Jiao *et al.* revealed gender differences in the regulation and expression of
12 oxidative genes in mice³⁹.

13 Studies detailing the effects of antioxidant vitamins on lung function in smokers and non-smokers are
14 lacking^{5,23}. In the US population, Britton *et al.* revealed that the relationship between vitamin C
15 intake and FEV₁ was stronger in ex-smokers than non- or current smokers⁵. Shahar *et al.* reported a
16 relationship between individuals in Q1 of vitamin A intake and airway obstruction among individuals
17 who smoked >41 pack years²³.

18 Among male COPD patients, those smoking ≥20 pack years had improved lung functions as
19 antioxidant vitamin intake increased. These results support that associations between antioxidants and
20 lung function may differ according to smoking status in COPD patients. However, it is unknown what
21 causes such differences. One hypothesis is that the efficacy of antioxidant vitamins is proportional to
22 the level of oxidant burden in COPD. Additional studies are required to determine whether the
23 benefits of antioxidant vitamins depend on the smoking duration or dose in COPD patients.

24 This study has several limitations that should be noted. As we used a cross-sectional design, the data
25 cannot be used to answer questions regarding causation. Additionally, because data on nutritional

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1 intake were obtained by 24-hour recall, inaccurate responses may have been offered. This study used
2 the pre-bronchodilator FEV₁ for determining COPD; however, the definition of COPD is based on
3 post-bronchodilator FEV₁¹⁶. This study failed to obtain data regarding air pollution or occupational
4 exposure and, therefore, could not associate these variables with lung function; however, the strength
5 of this study is that these data represent the Korean population.

6 **Conclusion**

7 This study supports that antioxidant vitamins have beneficial effects on pulmonary function in the
8 Korean population. The data indicate that there is a stronger association between antioxidant vitamin
9 intake and the risk of COPD in male smokers. The beneficial effects of antioxidant vitamins in COPD
10 patients differed by gender and smoking status, and future investigations should determine the roles of
11 dietary antioxidant vitamins in specific groups.

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13 **Contributors**

14 JYH and YSK equally contributed to the conception and design of the research; YSK contributed to
15 the design of the research; CYL contributed to the acquisition and analysis of the data; MGL and
16 YSK contributed to the interpretation of the data; and JYH drafted the manuscript. All authors
17 critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy
18 of the work, and read and approved the final manuscript.

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20 **Conflict of Interest Statement**

21 The authors declare no conflict of interest.

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14 **5 Competing interests**
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16 6 None declared
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20 **8 Provenance and peer review**
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22 9 Not commissioned; externally peer reviewed
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27 **11 Data sharing statement**
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7 **Table legends**8
9 **Table 1. Study population characteristics.**10
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12 ¶, numbers represent mean percentages (standard deviation).13
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1718 **Table 2. Mean values of adjusted lung function measurements across quintiles of vitamin A,**
19 **carotene, and vitamin C intake.**20
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22 Data were adjusted for age, sex, body mass index, energy intake, number of comorbid diseases,
23 alcohol consumption, smoking history, pack years (smoking amount), household income, and
24 education level.
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29 *P* values were determined using tests for linear trends across increasing quintiles (means) of
30 antioxidant vitamin intake.
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3637 **Table 3. Association between vitamin A, carotene, and vitamin C intake and COPD according to**
38 **gender and smoking status.**39
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42 OR was determined following adjustment for age, body mass index, energy intake, number of
43 comorbid diseases, alcohol consumption, household income, and education level.
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47 ¶, The risk for COPD was significantly different between Q1 and Q5.
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5253 **Table 4. Mean values of adjusted forced expiratory volume in 1-second (FEV₁) measurements**
54 **across quintiles of vitamin A, carotene, and vitamin C intake (energy-adjusted) in subjects with**
55 **COPD.**
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11 4 antioxidant vitamin intake.

12 13 14 5 **Figure Legends**

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17 6 **Figure 1. Odds ratios for the association between antioxidant vitamin intake and COPD among**
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19 7 **(a) male and (b) female smokers and non-smokers.**

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21 8 Odds ratios were adjusted for age, body mass index, energy intake, number of comorbid diseases,
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12 11 **Figure 2. Mean values of adjusted forced expiratory volume in 1-second (FEV₁) measurements**
13 12 **across quintiles of vitamin A, carotene, and vitamin C intake (energy-adjusted) in male COPD**
14 13 **patients according to smoking status.**

15 14 Values were adjusted for age, body mass index, energy intake, number of comorbid diseases, alcohol
16 15 consumption, household income, and education level. *P*-values were determined using tests for linear
17 16 trends across increasing quintiles (median) of antioxidant vitamin intake.

Table 1. Study population characteristics

	Total (n=21,148)	Male smokers (n=7,178)	Male non-smokers (n=1,626)	Female smokers (n=808)	Female non-smokers (n=11,536)	P value
Age [¶]	57.4 (10.9)	57.8 (11.0)	57.9 (11.3)	57.4 (12.5)	57.1 (10.8)	<0.001
40–49	6048 (28.6)	1998 (27.8)	464 (28.5)	273 (33.8)	3313 (28.7)	<0.001
50–59	6131 (29.0)	1981 (27.6)	431 (26.5)	199 (24.6)	3520 (30.5)	
60–69	5387 (25.5)	1913 (26.7)	430 (26.4)	158 (19.6)	2866 (25.0)	
70–	3582 (16.9)	1286 (17.9)	301 (18.5)	178 (22.0)	1817 (15.8)	
BMI [¶]	24.2 (3.0)	24.2 (2.8)	24.3 (2.8)	23.8 (3.6)	24.2 (3.2)	0.007
Education						<0.001
Elementary	7229 (34.2)	1763 (24.6)	321 (19.7)	381 (47.2)	4764 (41.3)	
Middle school	3315 (15.7)	1216 (16.9)	267 (16.4)	112 (13.9)	1720 (14.9)	
High school	6427 (30.4)	2366 (33.0)	458 (28.2)	228 (28.2)	3375 (29.3)	
More than college	4169 (19.7)	1831 (25.5)	580 (35.7)	87 (10.8)	1671 (14.5)	
Household income						<0.001
1st quartile	4763 (22.5)	1440 (20.1)	289 (17.8)	315 (39.0)	2719 (23.6)	
2nd quartile	5427 (25.7)	1874 (26.1)	391 (24.1)	223 (27.6)	2939 (25.5)	
3rd quartile	5162 (24.4)	1869 (26.1)	414 (25.5)	145 (17.9)	2734 (23.7)	
4th quartile	5780 (27.3)	1988 (27.7)	530 (32.6)	125 (15.5)	3137 (27.2)	
Comorbidity [¶]	0.9 (1.1)	0.9 (1.0)	0.8 (0.9)	1.0 (1.2)	1.0 (1.1)	<0.001
Pack years [¶]	4.7 (13.6)	13.3 (20.3)	0.2 (2.2)	3.3 (11.9)	0.0 (0.0)	<0.001
Alcohol	17554 (83.0)	6877 (95.8)	1399 (86.0)	714 (88.4)	8564 (74.2)	<0.001
Energy intake (Kcal/day) [¶]	1901.5 (797.8)	2266.5 (869.7)	2212.6 (855.9)	1538.2 (653.4)	1656.0 (630.0)	<0.001
Vitamin A (µg RE/day) [¶]	822.5 (1118.5)	881.9 (1067.5)	925.5 (1095.2)	600.3 (644.2)	786.6 (1173.9)	<0.001
Carotene (µg/day) [¶]	4337.3 (6206.0)	4596.2 (5557.8)	4803.8 (5506.6)	3143.5 (3682.6)	4194.1(6780.6)	<0.001
Vitamin C (mg/day) [¶]	111.9 (107.6)	111.8 (97.9)	128.8 (107.1)	84.8 (96.9)	111.5 (113.5)	<0.001
FEV ₁ (ml) [¶]	2.60 (0.67)	3.02 (0.68)	3.09 (0.66)	2.23 (0.56)	2.30 (0.46)	<0.001
FVC (ml) [¶]	3.38 (0.84)	4.07 (0.72)	4.04 (0.73)	2.88 (0.62)	2.89 (0.51)	<0.001
FEV1/FVC (%) [¶]	77.3 (7.9)	73.9 (9.1)	76.6 (7.9)	77.2 (8.0)	79.5 (6.1)	<0.001
COPD	3,005 (14.2)	1893 (26.4)	256 (15.7)	119 (14.7)	737 (6.4)	<0.001

¶, numbers represent mean percentages (standard deviation).

Table 2. Mean values of adjusted lung function measurements across quintiles of vitamin A, carotene, and vitamin C intake.

	Q1	Q2	Q3	Q4	Q5	Difference between Q5 and Q1 (95% CI)	<i>P</i> value for trend
Vitamin A							
Mean intake (µg RE)	151.2	353.6	573.1	893.9	2140.8		
FEV ₁ (ml)	2379	2388	2406	2395	2404	25 (5,45)	0.032
FVC(ml)	3119	3135	3156	3148	3150	31 (7,54)	0.013
Predicted FEV ₁ (%)	91.37	91.39	91.79	91.37	91.77	0.40 (-0.24,1.04)	0.393
Predicted FVC (%)	90.93	91.02	91.38	91.18	91.4	0.47 (-0.08,1.02)	0.326
Carotene							
Mean intake (µg)	691.1	1747.4	2938.9	4736.1	11574.1		
FEV ₁ (ml)	2347	2361	2373	2367	2374	27 (8,47)	0.038
FVC (ml)	3088	3115	3125	3118	3122	34(11,57)	0.011
Predicted FEV ₁ (%)	91.55	91.96	92.16	91.75	92.16	0.61 (-0.17,1.24)	0.203
Predicted FVC (%)	91.02	91.63	91.71	91.36	91.74	0.72 (0.18,1.26)	0.032
Vitamin C							
Mean intake (mg)	24.2	53.6	84.2	128.8	268.9		
FEV ₁ (ml)	2411	2421	2433	2436	2447	36 (16,56)	0.004
FVC (ml)	3117	3121	3131	3137	3152	35 (12,58)	0.027
Predicted FEV ₁ (%)	91.3	91.43	91.79	91.82	92	0.70 (0.67,1.33)	0.169
Predicted FVC (%)	91.29	91.29	91.52	91.68	91.91	0.62 (0.75,1.16)	0.118

Data were adjusted for age, sex, body mass index, energy intake, number of comorbid diseases, alcohol consumption, smoking history, pack years (smoking amount), household income, and education level. *P* values were determined using tests for linear trends across increasing quintiles (means) of antioxidant vitamin intake.

Table 3. Association between vitamin A, carotene, and vitamin C intake and COPD according to gender and smoking status.

	Intake		COPD		OR		<i>P</i> interaction
	Q5	Q1	Q5	Q1	Q5	Q1	
Vitamin A							
Female non-smokers	2096	2564	105	242	ref	1.19 (0.92,1.53)	<0.001
Female smokers	109	264	16	53	3.44 (1.86,6.34)	2.00 (1.34,2.99)	
Male non-smokers	394	225	53	47	3.29 (2.26,4.78)	3.20 (2.14,4.78)	
Male smokers	1630	1176	320	444	4.11 (3.10,5.44) [¶]	5.42 (4.09,7.18) [¶]	
Carotene							
Female non-smokers	2118	2529	108	226	ref	1.11 (0.86, 1.43)	<0.001
Female smokers	104	268	15	49	3.12 (1.66, 5.85)	1.82 (1.21, 2.74)	
Male non-smokers	397	243	55	50	3.42 (2.36, 4.94)	3.24 (2.19, 4.79)	
Male smokers	1610	1189	321	425	4.51 (3.41, 5.98)	5.27 (3.98, 6.98)	
Vitamin C							
Female non-smokers	2303	2466	112	465	ref	1.04 (0.81,1.35)	<0.001
Female smokers	107	294	12	35	2.23 (1.15,4.32)	1.87 (1.26, 2.78)	
Male non-smokers	401	191	55	55	3.33 (2.31,4.80)	3.24 (2.08, 5.03)	
Male smokers	1419	1278	317	204	4.77 (3.62,6.30) [¶]	5.61 (4.26, 7.39) [¶]	

OR (Odd ratio) was determined following adjustment for age, body mass index, energy intake, number of comorbid diseases, alcohol consumption, household income, and education level.

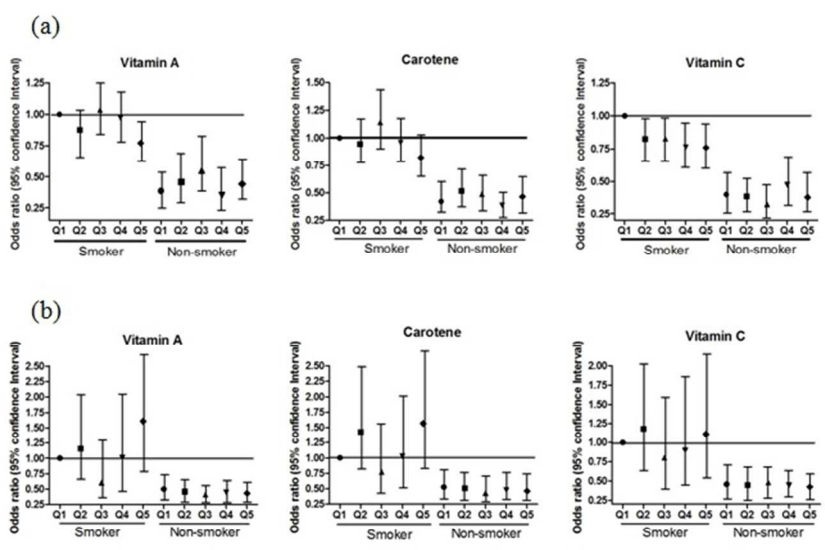
[¶], The risk for COPD was significantly different between Q1 and Q5.

Table 4. Mean values of adjusted forced expiratory volume in 1-second (FEV₁) measurements across quintiles of vitamin A, carotene, and vitamin C intake (energy-adjusted) in subjects with COPD.

	Q1	Q2	Q3	Q4	Q5	Difference between 5 and 1 (95% CI)	<i>P</i> value for trend	<i>P</i> value for interaction
Vitamin A								
COPD	1990	1999	2035	2056	2030	40 (-18,99)	0.126	0.069
Male smokers	2213	2218	2304	2303	2279	66 (-13,145)	0.024	
Male non-smokers	2334	2254	2242	2375	2280	-54 (-262,154)	0.672	
Female smokers	1639	1562	1501	1459	1628	-11(-271, 249)	0.599	
Female non-smokers	1589	1659	1565	1656	1649	60 (-38,158)	0.169	
Carotene								
COPD	1993	2022	2043	2055	2042	49 (-9,108)	0.195	0.044
Male smokers	2211	2250	2296	2317	2276	65 (-13,144)	0.046	
Male non-smokers	2329	2255	2230	2357	2341	12 (-188, 213)	0.665	
Female smokers	1689	1545	1435	1428	1626	-63 (-325,198)	0.094	
Female non-smokers	1573	1649	1628	1600	1657	84 (-14,183)	0.299	
Vitamin C								
COPD	2025	2042	2087	2090	2087	62 (5,120)	0.056	0.179
Male smokers	2235	2278	2330	2314	2336	101(25, 178)	0.039	
Male non-smokers	2402	2256	2330	2459	2256	-146 (-370,78)	0.138	
Female smokers	1603	1600	1630	1597	1563	-40 (-318,239)	0.997	
Female non-smokers	1594	1595	1618	1632	1687	93 (-11,198)	0.433	

Adjusted for age, body mass index, energy intake, number of comorbid diseases, alcohol consumption, household income, and education level. *P* values were determined using tests for linear trends across increasing quintiles (means) of antioxidant vitamin intake.

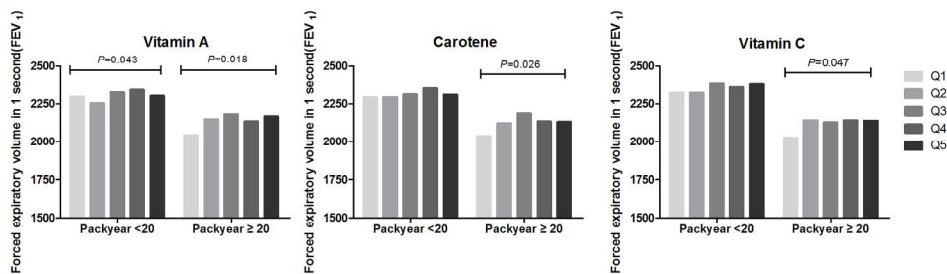
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Effects of dietary antioxidant vitamins on lung functions according to gender and smoking status in Korea: A population-based cross-sectional study

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Abstract

Objective: Cigarette smoke-induced oxidative stress plays an important role in the pathogenesis of chronic obstructive pulmonary disease (COPD). Dietary antioxidants are thought to prevent smoke-induced oxidative damage. The aim of this study was to investigate associations between lung function and the consumption of antioxidant vitamins in Korean adults.

Methods: In total, 21,148 participants from the Korean National Health and Nutrition Examination Survey (2007–2014) were divided into four groups based on smoking history and gender. Multivariate regression models were used to evaluate associations between lung function and intake of dietary antioxidants.

Results: Subjects in the highest-intake quintile (Q5) of vitamin A, carotene, and vitamin C intake had mean forced expiratory volume in 1 second (FEV₁) measurements that were 30 ml, 32 ml, and 36 ml higher than those of individuals in the lowest-intake quintile (Q1), respectively (*P* for trend; *P*=0.008, *P*=0.010, and *P*<0.001, respectively). The risks of COPD for male smokers in Q1 increased 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), for vitamin A, carotene, and vitamin C, respectively, compared to those of female non-smokers in Q5. Among COPD patients, males who smoked >20 pack years had mean FEV₁ measurements that were 192 ml, 149 ml, and 177 ml higher than those of patients in Q1 (*P* for trend; *P*=0.018, *P*=0.024, and *P*=0.043, respectively).

Conclusions: These findings indicate that the influence of antioxidant vitamins on lung function depends on gender and smoking status in the Korean COPD population.

Keywords: lung function, gender, smoking, antioxidant vitamins

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Strengths and limitation of this study

- This study revealed that the influence of antioxidant vitamins on lung function depends on gender and smoking status in Korean patients with COPD.
- A cross-sectional study with a large sample size collected from a national health survey
- Main limitations include a possible recall bias and no further verification of nutritional intake.

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2 **Introduction**

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4 Chronic obstructive pulmonary disease (COPD) causes morbidity and mortality¹. Smoking is a
5 primary risk factor for COPD; however, other factors also contribute as only 10–20% of smokers
6 develop airflow limitations².

7 Dietary antioxidants protect against oxidative stress caused by smoking³, and multiple studies have
8 revealed associations between the intake of antioxidant vitamins or fibers and respiratory diseases⁴⁻⁸.
9 However, evidence supporting the benefits of vitamin supplement therapy is lacking^{9 10}.

10 Because micronutrient status is affected by dietary intake and metabolic turnover, which are regulated
11 by oxidative stress, the benefits of antioxidant vitamins may vary by gender and smoking status.
12 Multiple studies have shown that different antioxidants exhibit different effects based on smoking
13 status. Morabia *et al.* reported an association between airway obstruction and vitamin A intake in
14 smokers compared to former smokers, whereas Hu *et al.* reported that carotene was less strongly
15 associated with FEV₁ in smokers compared to former smokers and non-smokers^{11 12}.

16 This study used KNHANES data to investigate whether dietary antioxidant vitamins were
17 independently associated with pulmonary function and COPD in the Korean population. This study
18 also evaluated whether the effects of antioxidant vitamins on pulmonary function differed based on
19 gender or smoking status.

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2 **Patients and Methods**

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4 ***Study population***

5 Participants were sampled from Korean National Health and Nutritional Examination Survey
6 (KNHANES; 2007–2014) IV–VI, a nationwide survey designed to be representative of the population
7 that is used to establish health policies. KNHANES contains a massive database with information
8 about demographic characteristics, comorbidities, lung function, nutritional status, and health
9 (<https://knhanes.cdc.go.kr/knhanes>).

10 A two-stage stratified systemic sampling method was use to select 65,973 individuals to survey
11 between February 2007 and December 2014. Of the chosen individuals, 34,278 participants over 40
12 years of age responded to questionnaires regarding diet and smoking history and underwent a medical
13 examination. After excluding subjects who omitted lung function or nutrition data, we analyzed data
14 from 21,148 (8,804 men and 12,344 women) in this study. This study was approved by the
15 Institutional Review Board of the Korean Centers for Disease Control and Prevention. All participants
16 provided informed written consent.

18 **Protocol**

19 KNHANES collects survey data through health questionnaire surveys, screening surveys, and
20 nutrition surveys. Health questionnaires were divided into household survey, health interview survey,
21 and health behavior survey. The health interview survey examined the use of medical services,
22 activity limitations, education and economic activities, and physical activity by interview method. The
23 health behavior survey examined smoking status, drinking, mental health, and safety consciousness by
24 self - filling method. The screening consisted of physical measurement, blood pressure and pulse

1 measurement, blood and urine test, oral examination, pulmonary function test, visual and refractive
2 examination, color vision test, hearing test, and muscle strength test. Nutrition surveys consisted of
3 dietary behaviors, dietary supplements, nutritional knowledge, and the contents of food intake (24-
4 hour recall method) a day before the survey.

5 6 ***Spirometry and airflow obstruction definitions***

7 The pulmonary function test (PFT) was performed using dry-rolling seal volume spirometers (Model
8 2130; Sensor Medics, Yorba Linda, CA, USA) and standardized according to the American Thoracic
9 Society/European Respiratory Society criteria¹³. Qualified technicians and principal investigators
10 assessed the spirometry data for acceptability and reproducibility. The predictive equations for the
11 forced expiratory volume in 1 second (FEV₁) and the forced vital capacity (FVC) were derived from
12 survey data on non-smokers who had normal chest X-rays and no previous history of respiratory
13 diseases¹⁴. COPD was defined as a FEV₁/FVC <70 %¹⁵.

14 15 ***Dietary assessments***

16 Food intake data were obtained using the 24-h recall method, in which participants were asked to
17 report the foods and amounts thereof consumed during the previous 24 hours. Total energy (kJ/d
18 (kcal/d)) and total intake of antioxidant vitamins were calculated using the Korean Food Composition
19 Table¹⁶ as the reference. Antioxidant vitamin consumption was adjusted for total energy intake.

20 21 ***Potential confounders***

22 Data regarding demographic information, education level, household income, smoking status,
23 smoking amount, alcohol intake, place of residence, body mass index (BMI), and comorbid diseases
24 were obtained. Educational level was categorized as elementary school or lower, completion of
25 middle school, completion of high school, and college or higher. Household income was divided by
26 quartile. Place of residence was divided to rural and urban.

1 Smokers were subjects who smoked more than 100 cigarettes in their lifetime¹⁷. Participants were
2 categorized in terms of smoking status as follows: smoker, ex-smoker, or never smoked. Those who
3 answered in the negative to the question ‘Do you currently smoke?’ were defined as ex-smokers.

4 The smoking amount was determined in pack years, which was calculated by multiplying the duration
5 of smoking (years) by the number of packs of cigarettes smoked. Comorbid diseases included
6 hypertension, stroke, cardiovascular disease, arthritis, tuberculosis, asthma, diabetes mellitus, thyroid
7 disorders, renal failure, liver disease, and malignancy.

8 9 ***Statistical analysis***

10 A total of 21,148 subjects participated in this study (Figure 1). The relationship between antioxidant
11 vitamin intake and lung function was analyzed using multiple linear regression analyses. We analyzed
12 the energy-adjusted antioxidant vitamin intake by quintiles. The adjustment factors were age, sex,
13 BMI, educational level, household income, total energy intake, place of residence, number of
14 comorbid diseases, smoking history, alcohol intake, and pack years^{4 11 18}. Assessments of linear trends
15 across increasing antioxidant vitamin quintiles were also performed.

16 We estimated the odds ratios (ORs) of COPD using multivariate logistic regression analyses of
17 quintiles after adjusting for confounding factors. Participants were divided into four groups based on
18 gender and smoking status (male smokers, male non-smokers, female smokers, female non-smokers),
19 to determine whether the relationship between COPD risk and antioxidant vitamin intake is related to
20 gender and smoking status. For combined analyses between the effects of antioxidant vitamin intake,
21 gender, and smoking status on the risk of COPD, interaction tests were performed. COPD patients and
22 male COPD patients were analyzed separately. We attempted to determine whether the association of
23 antioxidant vitamins and lung function varies with gender and smoking status in patients with COPD.
24 Multiple linear regression analyses were performed after categorizing COPD patients by smoking

1 status and amount.

2 Statistical analyses were performed using PASW Statistics ver. 20 (SPSS Inc., Chicago IL, USA) and
3 SAS ver. 9.4 (SAS Institute, Cary, NC, USA) software. *P*-values <0.05 were considered statistically
4 significant.

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1 Results

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8 The baseline characteristics of the 21,148 participants are shown in Table 1. All subjects were
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10 classified into four groups based on smoking history and gender. Of the 7,986 smokers, 7,178 were
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12 male (mean age, 57.8±11.0 years) and 808 were female (mean age, 57.4±12.5 years). Of the 13,162
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14 individuals who had never smoked, 1,626 were male (mean age, 57.9±11.3 years) and 11,536 were
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16 female (mean age, 57.1±10.8 years). Among all subjects, 3,005 were diagnosed with COPD. The
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18 prevalence of COPD was highest in male smokers (26.4%) and lowest in female non-smokers (6.4%).
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20 The four groups differed regarding age, BMI, educational level, household income, and alcohol usage
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22 ($P<0.001$). Energy intake was significantly higher in males than females (males, 2,256.5 kcal; females,
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24 1,648.3 kcal; $P<0.001$). The levels of vitamin A, carotene, and vitamin C were highest in the male
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26 non-smoker group and lowest in the female smoker group. Korean male non-smokers are pre-
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28 disposed to COPD compared to female non-smokers (incidence rate of 15.7% versus 6.4%). Age and
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30 the percentage of alcohol intake were higher in Korean male non-smokers than female non-smokers.
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33 Table 2 showed the association between lung function (FEV₁, FVC) and dietary antioxidant vitamin
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35 levels. Participants in the highest quintile (Q5) of vitamin A intake had 30 ml higher FEV₁ (P for trend
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37 across quintiles = 0.008) and 33 ml higher FVC (P for trend across quintiles = 0.007) compared to
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39 participants in the lowest quintile (Q1). Participants in Q5 for carotene intake had 32 ml higher FEV₁
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41 (P for trend across quintiles = 0.010) and 36 ml higher FVC (P for trend across quintiles = 0.005)
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43 measurements compared to participants in Q1. Participants in Q5 of vitamin C intake had 36 ml
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45 higher FEV₁ (P for trend across quintiles <0.001) and 35 ml higher FVC (P for trend across quintiles
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47 = 0.014) measurements compared to participants in Q1. A statistically significant dose–response
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49 relationship was observed (all, P for trend across quintiles <0.005), but participants in Q3 of vitamin
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51 A and carotene had comparable lung function to those in Q5.
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1 The effects of gender, smoking, and dietary antioxidant vitamins on the risk of COPD are summarized
2 in Table 3. The risk of COPD for male smokers in Q1 for vitamin A, carotene, and vitamin C intake
3 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%
4 CI=6.12-9.92), respectively, which was greater than that observed for female non-smokers in Q5 for
5 antioxidant vitamin intake. Interestingly, the risk of COPD for male non-smokers in Q5 for vitamin A,
6 carotene, and vitamin C intake increased by 3.26-fold (95% CI=2.24-4.75), 3.35-fold (95% CI=2.31-
7 4.86) and 3.28-fold (95% CI=2.27-4.73), respectively, compared with female non-smokers in Q5 for
8 antioxidant vitamin intake. The risk of COPD for male non-smokers in Q1 for vitamin A, carotene,
9 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
10 3.17-fold (95% CI=2.04-4.91), respectively, compared with female non-smokers in Q1 for antioxidant
11 vitamin intake. These results suggest that men may have other causes of COPD as well as smoking,
12 compared with women who took similar amounts of antioxidant vitamins.

13 The interaction exists between the antioxidant vitamin intake and gender/smoking status on the risk of
14 COPD (all *P*-values <0.001). The effect of the antioxidant vitamin intake depends on the
15 gender/smoking status. When assessing the risk of COPD following reduction of antioxidant intake
16 from Q5 to Q1, only male smokers showed significant difference in risk of COPD, but other three
17 groups did not. Figure 2 shows that the risk of COPD was influenced by dietary antioxidant vitamin
18 levels in male smokers, in detail. In male smokers, the risk of COPD in subjects in Q5 for antioxidant
19 vitamins intake was significantly lower than that for subjects in Q1 (vitamin A, OR = 0.77, 95% CI =
20 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,
21 95% CI = 0.61–0.91, *P* = 0.004). The dose –dependent effect of vitamin C was observed between
22 COPD risk and dietary antioxidant vitamin levels, but it was not for vitamin A and carotene. Although
23 not significant, Q3 group of carotene had increased risk to develop COPD than Q1 group of carotene.

24 The prevalence of COPD did not increase significantly as the intake of dietary antioxidant vitamins

1 increased in male non-smokers, female smokers, or female non-smokers. No significant interaction
2 between the effects of antioxidant vitamins on COPD and smoking status was observed. The
3 correlation between the risk of COPD and antioxidant vitamin intake was stronger in male smokers
4 who smoked less than 20 pack years (not shown).

5 We investigated the association between dietary antioxidant vitamin intake and lung function after
6 limiting the analyses to individuals with COPD. The changes in FEV₁ were not statistically significant
7 based on the levels of dietary antioxidant vitamins in subjects with COPD. Similar to the previous
8 results, only male smokers in subjects with COPD, exhibited a beneficial association between dietary
9 antioxidant vitamin intake and FEV₁ (Figure 3). Male smokers with COPD in Q5 for vitamin A intake
10 had a 71-ml higher FEV₁ (*P* for trend across quintiles = 0.019) compared to those in Q1. Male
11 smokers with COPD in Q5 of carotene and vitamin C intake had 71-ml higher FEV₁ (*P* for trend
12 across quintiles = 0.037) and a 109-ml higher FEV₁ (*P* for trend across quintiles = 0.026), respectively,
13 compared to individuals in Q1.

14 Additional analyzes were performed to determine if lung function was reduced by smoking amount or
15 smoking status in male smoker- COPD patients. Male COPD patients who had smoked ≥ 20 pack
16 years exhibited a beneficial association between dietary antioxidant vitamin intake and FEV₁ (Figure
17 4). Male COPD patients in Q5 of vitamin A intake who had smoked ≥ 20 pack years had a 192-ml
18 higher FEV₁ (*P* for trend across quintiles = 0.018) compared to individuals in Q1. COPD patients in
19 Q5 of carotene intake who had smoked ≥ 20 pack years had a 149-ml higher FEV₁ (*P* for trend across
20 quintiles = 0.024) compared with patients in Q1. COPD patients in Q5 of vitamin C intake who had
21 smoked >20 pack years had a 177-ml higher FEV₁ (*P* for trend across quintiles = 0.043) compared to
22 patients in Q1.

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Discussion

This study examined the association between the intake of antioxidant vitamins and lung functions in the Korean population. Previous studies showed that antioxidant vitamins, including vitamin C, were protective of the human lung^{5,12}, whereas high levels of vitamin A and carotene were also associated with increased lung functions in multiple studies^{11,19-23}. In a randomized controlled trial, Keranis *et al.* reported that increasing the intake of antioxidants improved lung function²⁴.

Cigarette smoking is the primary cause of COPD as it increases oxidative stress in the lungs and activates inflammatory responses²⁵. Notably, one inhalation from a cigarette generates more than 10¹⁵ free radicals and other oxidants²⁶.

Antioxidants protect against the damage caused by smoking in multiple ways³. For example, as it is water-soluble, vitamin C scavenges free radicals in the cytoplasm. Koike *et al.* reported that vitamin C diminished smoke-induced oxidative stress and corrected emphysematous lungs *in vivo*²⁷.

Carotenoids quench singlet oxygen and inhibit lipid peroxidation³. In an animal study, the respiratory epithelia of retinol-deficient animals had atrophied ciliated cells and modified lipid contents²⁸. The pathologic features of the retinol-deficient animals were similar to those of human smokers²⁹.

Smokers exhibit nicotine-induced reductions in intestinal absorption and elevated metabolic turnover³⁰. The metabolism or destruction of antioxidant vitamins increases in inflammatory environments³¹⁻³⁴, which suggests that smokers with COPD require larger amounts of antioxidant vitamins to achieve the same blood levels as non-smokers. A study by Sargeant found that vitamin C may modify the adverse effects of smoking and the risk of COPD in the European population³⁵. Additionally, Shin *et al.* reported that Korean smokers with adequate vitamin C intake had acceptable pulmonary functions³⁶ and Park *et al.* showed that dietary vitamin C provides protection against

1 COPD³⁷. Additionally, Morabia *et al.* identified that airway obstruction was reduced by vitamin A in
2 smokers¹¹.

3 One notable finding in the current study was that the effects of antioxidant vitamin intake on lung
4 function were stronger among male smokers. Additionally, the association between the risk of COPD
5 and antioxidant vitamin intake was clear for male but not female smokers. Male smokers with lower
6 antioxidant vitamin intakes had increased ORs of COPD compared to female smokers. Although the
7 dose-dependent effect on COPD risk was not obvious in vitamin A and carotene, contrary to vitamin
8 C (Figure 2), male smokers with Q5 intake showed a clearly reduced risk to develop COPD than male
9 smokers with Q1 intake in all three antioxidant vitamins.

10 After limiting the analysis to subjects with COPD, a significant association between antioxidant
11 vitamin intake and FEV₁ was observed in male smokers but not in other groups. This finding was
12 similar to that of Joshi *et al.*, where changes in COPD risk and dietary vitamin C and vitamin E intake
13 differed between males and females³⁸.

14 It is not known how gender differences impact pulmonary functions based on antioxidant vitamin
15 intake; however, animal studies have revealed gender differences in antioxidant vitamin requirements.
16 Al Rejaie *et al.* reported gender-related differences in the protective roles of ascorbic acid against
17 oxidative stress³⁹, whereas Jiao *et al.* revealed gender differences in the regulation and expression of
18 oxidative genes in mice⁴⁰.

19 Studies detailing the effects of antioxidant vitamins on lung function in smokers and non-smokers are
20 lacking^{5,23}. In the US population, Britton *et al.* revealed that the relationship between vitamin C
21 intake and FEV₁ was stronger in ex-smokers than non- or current smokers⁵. Shahar *et al.* reported a
22 relationship between individuals in Q1 of vitamin A intake and airway obstruction among individuals
23 who smoked >41 pack years²³.

1 Among male COPD patients, those smoking ≥ 20 pack years had improved lung functions as
2 antioxidant vitamin intake increased. These results support that associations between antioxidants and
3 lung function may differ according to smoking status in COPD patients. However, it is unknown what
4 causes such differences. One hypothesis is that the efficacy of antioxidant vitamins is proportional to
5 the level of oxidant burden in COPD. Additional studies are required to determine whether the
6 benefits of antioxidant vitamins depend on the smoking duration or dose in COPD patients.

7 This study has several limitations that should be noted. As we used a cross-sectional design, the data
8 cannot be used to answer questions regarding causation. Additionally, because data on nutritional
9 intake were obtained by 24-hour recall, inaccurate responses may have been offered. This study used
10 the pre-bronchodilator FEV₁ for determining COPD; however, the definition of COPD is based on
11 post-bronchodilator FEV₁¹⁵. This study failed to obtain data regarding air pollution or occupational
12 exposure and, therefore, could not associate these variables with lung function; however, the strength
13 of this study is that these data represent the Korean population.

14 **Conclusion**

15 This study supports that antioxidant vitamins have beneficial effects on pulmonary function in the
16 Korean population. The data indicate that there is a stronger association between antioxidant vitamin
17 intake and the risk of COPD in male smokers. The beneficial effects of antioxidant vitamins in COPD
18 patients differed by gender and smoking status, and future investigations should determine the roles of
19 dietary antioxidant vitamins in specific groups.

21 **Contributors**

22 JYH and YSK equally contributed to the conception and design of the research; YSK contributed to
23 the design of the research; CYL contributed to the acquisition and analysis of the data; MGL and

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1 YSK contributed to the interpretation of the data; and JYH drafted the manuscript. All authors
2 critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy
3 of the work, and read and approved the final manuscript.

4 **Conflict of Interest Statement**

6 The authors declare no conflict of interest.

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14 **Competing interests**

15 None declared

17 **Provenance and peer review**

18 Not commissioned; externally peer reviewed

20 **Data sharing statement**

21 No additional data are available.

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4 **1 Table legends**

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8 **3 Table 1. Study population characteristics.**

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11 4 ¶, numbers represent mean percentages (standard deviation).

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17 **6 Table 2. Mean values of adjusted lung function measurements across quintiles of vitamin A,**
18 **7 carotene, and vitamin C intake.**

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21 8 Data were adjusted for age, sex, body mass index, energy intake, number of comorbid diseases,
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23 9 alcohol consumption, place of residence, smoking history, pack years (smoking amount), household
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25 10 income, and education level.

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28 11 *P* values were determined using tests for linear trends across increasing quintiles (means) of
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30 12 antioxidant vitamin intake.

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36 **14 Table 3. Association between vitamin A, carotene, and vitamin C intake and COPD according to**
37 **15 gender and smoking status.**

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40 16 OR was determined following adjustment for age, body mass index, energy intake, number of
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42 17 comorbid diseases, alcohol consumption, place of residence, household income, and education level.

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45 18 ¶, The risk for COPD was significantly different between Q1 and Q5.

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2 **Table 1. Study population characteristics**

	Total (n=21,148)	Male smokers (n=7,178)	Male non-smokers (n=1,626)	Female smokers (n=808)	Female non-smokers (n=11,536)	P value
Age [‡]	57.4 (10.9)	57.8 (11.0)	57.9 (11.3)	57.4 (12.5)	57.1 (10.8)	<0.001
40–49	6048 (28.6)	1998 (27.8)	464 (28.5)	273 (33.8)	3313 (28.7)	<0.001
50–59	6131 (29.0)	1981 (27.6)	431 (26.5)	199 (24.6)	3520 (30.5)	
60–69	5387 (25.5)	1913 (26.7)	430 (26.4)	158 (19.6)	2866 (25.0)	
70–	3582 (16.9)	1286 (17.9)	301 (18.5)	178 (22.0)	1817 (15.8)	
BMI [‡]	24.2 (3.0)	24.2 (2.8)	24.3 (2.8)	23.8 (3.6)	24.2 (3.2)	0.007
Education						<0.001
Elementary	7229 (34.2)	1763 (24.6)	321 (19.7)	381 (47.2)	4764 (41.3)	
Middle school	3315 (15.7)	1216 (16.9)	267 (16.4)	112 (13.9)	1720 (14.9)	
High school	6427 (30.4)	2366 (33.0)	458 (28.2)	228 (28.2)	3375 (29.3)	
More than college	4169 (19.7)	1831 (25.5)	580 (35.7)	87 (10.8)	1671 (14.5)	
Household income						<0.001
1st quartile	4763 (22.5)	1440 (20.1)	289 (17.8)	315 (39.0)	2719 (23.6)	
2nd quartile	5427 (25.7)	1874 (26.1)	391 (24.1)	223 (27.6)	2939 (25.5)	
3rd quartile	5162 (24.4)	1869 (26.1)	414 (25.5)	145 (17.9)	2734 (23.7)	
4th quartile	5780 (27.3)	1988 (27.7)	530 (32.6)	125 (15.5)	3137 (27.2)	
Comorbidity [‡]	0.9 (1.1)	0.9 (1.0)	0.8 (0.9)	1.0 (1.2)	1.0 (1.1)	<0.001
Pack years [‡]	4.7 (13.6)	13.3 (20.3)	0.2 (2.2)	3.3 (11.9)	0.0 (0.0)	<0.001
Alcohol	17554 (83.0)	6877 (95.8)	1399 (86.0)	714 (88.4)	8564 (74.2)	<0.001
Energy intake (Kcal/day) [‡]	1901.5 (797.8)	2266.5 (869.7)	2212.6 (855.9)	1538.2 (653.4)	1656.0 (630.0)	<0.001
Vitamin A (µg RE/day) [‡]	822.5 (1118.5)	881.9 (1067.5)	925.5 (1095.2)	600.3 (644.2)	786.6 (1173.9)	<0.001
Carotene (µg/day) [‡]	4337.3 (6206.0)	4596.2 (5557.8)	4803.8 (5506.6)	3143.5 (3682.6)	4194.1(6780.6)	<0.001
Vitamin C (mg/day) [‡]	111.9 (107.6)	111.8 (97.9)	128.8 (107.1)	84.8 (96.9)	111.5 (113.5)	<0.001
FEV ₁ (ml) [‡]	2.60 (0.67)	3.02 (0.68)	3.09 (0.66)	2.23 (0.56)	2.30 (0.46)	<0.001
FVC (ml) [‡]	3.38 (0.84)	4.07 (0.72)	4.04 (0.73)	2.88 (0.62)	2.89 (0.51)	<0.001
FEV ₁ /FVC (%) [‡]	77.3 (7.9)	73.9 (9.1)	76.6 (7.9)	77.2 (8.0)	79.5 (6.1)	<0.001
COPD	3,005 (14.2)	1893 (26.4)	256 (15.7)	119 (14.7)	737 (6.4)	<0.001

3 [‡], numbers represent mean percentages (standard deviation).

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2 **Table 2. Mean values of adjusted lung function measurements across quintiles of**
 3 **vitamin A, carotene, and vitamin C intake.**

	Q1	Q2	Q3	Q4	Q5	Difference between Q5 and Q1 (95% CI)	<i>P</i> value for trend
Vitamin A							
Mean intake (μ g RE)	151.2	353.6	573.1	893.9	2140.8		
FEV ₁ (ml)	2379	2389	2410	2397	2409	30 (10,50)	0.008
FVC(ml)	3119	3136	3158	3148	3152	33 (10,57)	0.007
Predicted FEV ₁ (%)	91.37	91.44	91.91	91.45	91.94	0.57 (-0.08,1.22)	0.185
Predicted FVC (%)	90.93	91.06	91.45	91.22	91.48	0.55 (0.00,1.10)	0.195
Carotene							
Mean intake (μ g)	691.1	1747.4	2938.9	4736.1	11574.1		
FEV ₁ (ml)	2347	2363	2376	2370	2379	32 (12,52)	0.010
FVC (ml)	3088	3117	3127	3119	3124	36(13.59)	0.005
Predicted FEV ₁ (%)	91.55	92.03	92.26	91.85	92.31	0.76 (0.12,1.39)	0.096
Predicted FVC (%)	91.02	91.68	91.78	91.41	91.82	0.80 (0.26,1.33)	0.015
Vitamin C							
Mean intake (mg)	24.2	53.6	84.2	128.8	268.9		
FEV ₁ (ml)	2411	2423	2436	2441	2453	36 (16.56)	<0.001
FVC (ml)	3117	3122	3132	3140	3154	35 (12.58)	0.014
Predicted FEV ₁ (%)	91.3	91.5	91.9	91.99	92.21	0.91 (0.27,1.55)	0.050
Predicted FVC (%)	91.29	91.33	91.58	91.77	92.0	0.71 (0.17,1.26)	0.118

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5 Data were adjusted for age, sex, body mass index, energy intake, number of comorbid diseases, alcohol
 6 consumption, place of residence smoking history, pack years (smoking amount), household income, and
 7 education level. *P* values were determined using tests for linear trends across increasing quintiles (means) of
 8 antioxidant vitamin intake.

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Table 3. Association between vitamin A, carotene, and vitamin C intake and COPD according to gender and smoking status.

	Intake		COPD		OR		<i>P</i> interaction
	Q5	Q1	Q5	Q1	Q5	Q1	
Vitamin A							
Female non-smokers	2096	2564	105	242	ref	1.16 (0.89,1.49)	<0.001
Female smokers	109	264	16	53	3.90 (2.12,7.17)	2.42 (1.63, 3.58)	
Male non-smokers	394	225	53	47	3.26 (2.24,4.75)	3.15 (2.10,4.72)	
Male smokers	1630	1176	320	444	5.54 (4.28,7.16) [¶]	7.60 (5.92, 9.76) [¶]	
Carotene							
Female non-smokers	2118	2529	108	226	ref	1.10 (0.85,1.42)	<0.001
Female smokers	104	268	15	49	3.47 (1.86,6.47)	2.16 (1.45, 3.23)	
Male non-smokers	397	243	55	50	3.35 (2.31,4.86)	3.24 (2.18,4.82)	
Male smokers	1610	1189	321	425	5.83 (4.51,7.53) [¶]	7.16 (5.58, 9.19) [¶]	
Vitamin C							
Female non-smokers	2303	2466	112	465	ref	1.00 (0.77,1.30)	<0.001
Female smokers	107	294	12	35	2.37 (1.20,4.71)	2.27 (1.55, 3.34)	
Male non-smokers	401	191	55	55	3.28 (2.27,4.73)	3.24 (2.07, 5.06)	
Male smokers	1419	1278	317	204	6.20 (4.82,7.98) [¶]	7.79 (6.12, 9.92) [¶]	

OR (Odd ratio) was determined following adjustment for age, body mass index, energy intake, number of comorbid diseases, alcohol consumption, place of residence, household income, and education level.

[¶], The risk for COPD was significantly different between Q1 and Q5.

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4 **1 Figure Legends**

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6 **2 Figure 1. The study population framework**

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12 **4 Figure 2. Odds ratios for the association between antioxidant vitamin intake and COPD among**
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14 **5 (a) male and (b) female smokers and non-smokers.**

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17 Odds ratios were adjusted for age, body mass index, energy intake, number of comorbid diseases,
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19 alcohol consumption, place of residence, household income, and education level.

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24 **9 Figure 3. Mean values of adjusted forced expiratory volume in 1-second (FEV₁) measurements**
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26 **10 across quintiles of vitamin A, carotene, and vitamin C intake (energy-adjusted) in subjects with**
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28 **11 COPD.**

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31 Adjusted for age, body mass index, energy intake, number of comorbid diseases, alcohol consumption,
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33 place of residence, household income, and education level. *P* values were determined using tests for
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35 linear trends across increasing quintiles (means) of antioxidant vitamin intake.

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41 **16 Figure 4. Mean values of adjusted forced expiratory volume in 1-second (FEV₁) measurements**
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43 **17 across quintiles of vitamin A, carotene, and vitamin C intake (energy-adjusted) in male COPD**
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45 **18 patients according to smoking status.**

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47 Values were adjusted for age, body mass index, energy intake, number of comorbid diseases, alcohol
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49 consumption, place of residence, household income, and education level. *P*-values were determined
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51 using tests for linear trends across increasing quintiles (median) of antioxidant vitamin intake.

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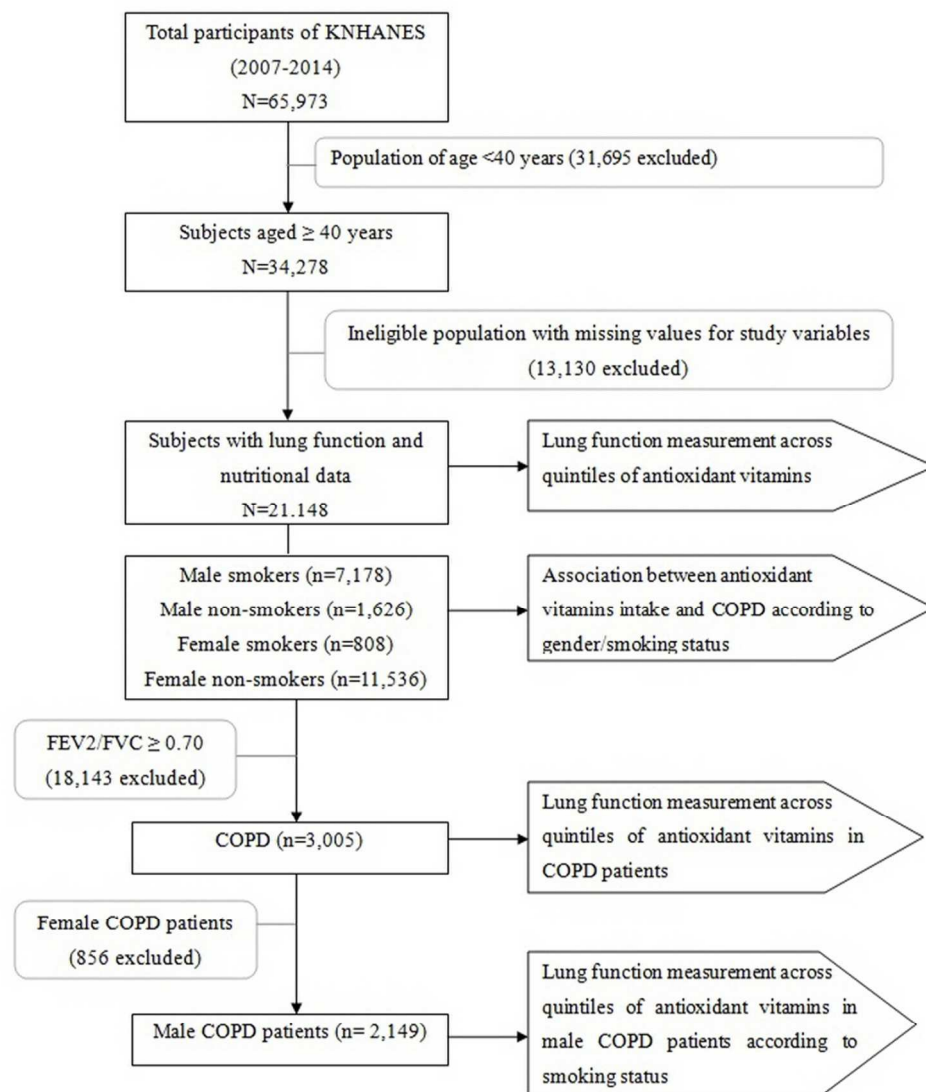


Figure 1. The study population framework

240x274mm (300 x 300 DPI)

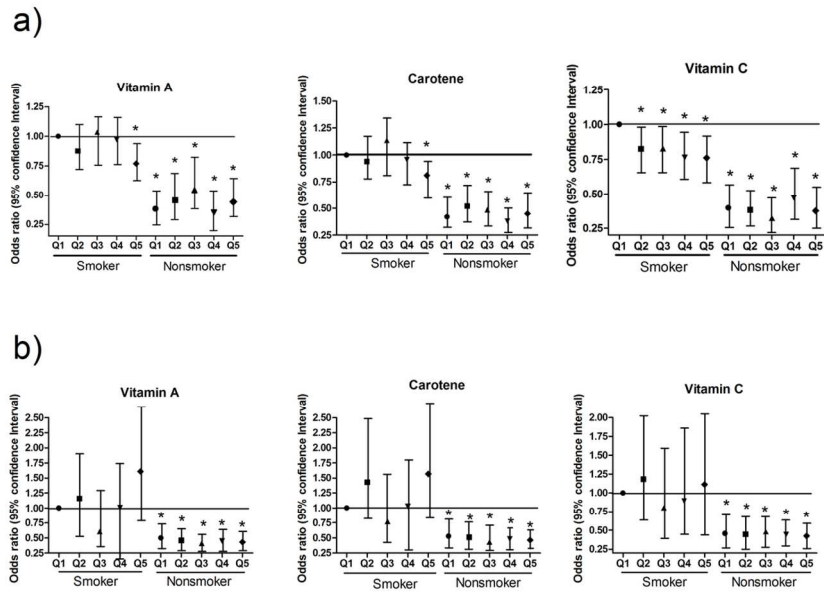


Figure 2. Odds ratios for the association between antioxidant vitamin intake and COPD among (a) male and (b) female smokers and non-smokers

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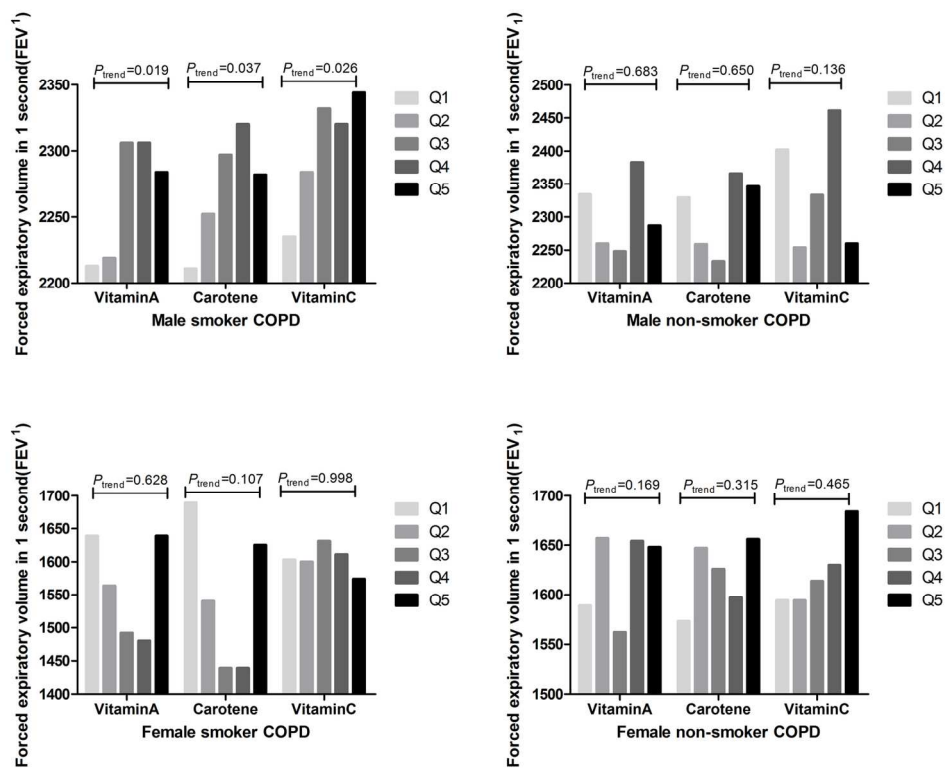


Figure 3. Mean values of adjusted forced expiratory volume in 1-second (FEV₁) measurements across quintiles of vitamin A, carotene, and vitamin C intake (energy-adjusted) in subjects with COPD.

148x121mm (300 x 300 DPI)

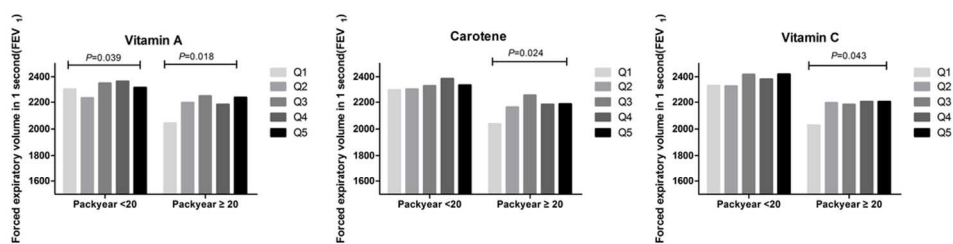


Figure 4. Mean values of adjusted forced expiratory volume in 1-second (FEV1) measurements across quintiles of vitamin A, carotene, and vitamin C intake (energy-adjusted) in male COPD patients according to smoking status.

50x14mm (600 x 600 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	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	6-7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	7
		(c) Explain how missing data were addressed	7
		(d) If applicable, describe analytical methods taking account of sampling strategy	7
		(e) Describe any sensitivity analyses	7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	Figure1
		(c) Consider use of a flow diagram	Figure1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	9
Outcome data	15*	Report numbers of outcome events or summary measures	10-11
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	9-11
		(b) Report category boundaries when continuous variables were categorized	9-11
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
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	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*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.