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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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## 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 ($FEV_1$) measurements that were 25 ml, 27 ml, and 36 ml higher than those of individuals in the lowest-intake quintile (Q1), respectively (*P* for trend; *P*=0.032, *P*=0.038, and *P*=0.004, respectively). The risks of COPD for male smokers in Q1 increased 5.42-fold (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, 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 $FEV_1$ measurements that were 124 ml, 94 ml, and 113 ml higher than those of patients in Q1 (*P* for trend; *P*=0.018, *P*=0.026, and *P*=0.047, for vitamin A, carotene, and vitamin C, 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

**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.

## Introduction

Chronic obstructive pulmonary disease (COPD) causes morbidity and mortality[1]. Smoking is a primary risk factor for COPD; however, other factors also contribute as only 10–20% of smokers develop airflow limitations[2].

Dietary antioxidants protect against oxidative stress caused by smoking[3], and multiple studies have revealed associations between the intake of antioxidant vitamins or fibers and respiratory diseases[4-8]. However, evidence supporting the benefits of vitamin supplement therapy is lacking[9-11].

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 $FEV_1$ 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.

## Patients and Methods

### *Study population*

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

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

### *Spirometry and airflow obstruction definitions*

The pulmonary function test (PFT) was performed using dry-rolling seal volume spirometers (Model 2130; SensorMedics, Yorba Linda, CA, USA) and standardized according to the American Thoracic Society/European Respiratory Society criteria[14]. Qualified technicians and principal investigators assessed the spirometry data for acceptability and reproducibility. The predictive equations for the forced expiratory volume in 1 second ($FEV_1$) and the forced vital capacity (FVC) were derived from survey data on non-smokers who had normal chest X-rays and no previous history of respiratory diseases[15]. COPD was defined as a $FEV_1/FVC < 70\ \%$[16].

***Dietary assessments***

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

***Potential confounders***

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

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

***Statistical analysis***

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, number of comorbid diseases, smoking history, alcohol intake, and pack years[4 12 18]. 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). 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.

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

## Results

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

A statistically significant dose–response relationship was observed between lung function ($FEV_1$, FVC) and dietary antioxidant vitamin levels (Table 2). Participants in the highest quintile (Q5) of vitamin A intake had 25 ml higher $FEV_1$ ($P$ for trend across quintiles = 0.032) and 31 ml higher FVC ($P$ for trend across quintiles = 0.013) compared to participants in the lowest quintile (Q1). Participants in Q5 for carotene intake had 27 ml higher $FEV_1$ ($P$ for trend across quintiles = 0.038) and 34 ml higher FVC ($P$ for trend across quintiles = 0.011) measurements compared to participants in Q1. Participants in Q5 of vitamin C intake had 36 ml higher $FEV_1$ ($P$ for trend across quintiles = 0.004) and 35 ml higher FVC ($P$ for trend across quintiles = 0.027) measurements compared to participants in Q1.

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 5.42-fold (95% CI=4.09–7.18), 5.27-fold (95% CI=3.98–6.98), and 5.61-fold (95% CI=4.26-7.39), respectively, which was greater than that observed for female non-smokers in Q5 for antioxidant vitamin intake. The interaction effect was significant (all $P$-values <0.001).

According to the multivariate logistic regression analyses, the risk of COPD was influenced by dietary antioxidant vitamin levels in male smokers (Figure 1). In male smokers, the risk of COPD in subjects in Q5 for vitamin A and vitamin C intake was significantly lower than that for subjects in Q1 (vitamin 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* = 0.007). Similarly, the prevalence of COPD was lower in Q5 compared to Q1 for carotene; however, this trend was not significant (OR = 0.82, 95% CI = 0.67–1.00, *P*=0.052). The prevalence of COPD did not increase significantly as the intake of dietary antioxidant vitamins increased in male non-smokers, female smokers, or female non-smokers. No significant interaction between the effects of antioxidant vitamins on COPD and smoking status was observed. The correlation between the risk of COPD and antioxidant vitamin intake was stronger in male smokers who smoked less than 20 pack years (not shown).

We investigated the association between dietary antioxidant vitamin intake and lung function after limiting the analyses to individuals with COPD. The changes in $FEV_1$ were not statistically significant based on the levels of dietary antioxidant vitamins in subjects with COPD. Interestingly, only male smokers exhibited a beneficial association between dietary antioxidant vitamin intake and $FEV_1$ (Table 4). Male smokers with COPD in Q5 for vitamin A intake had a 66-ml higher $FEV_1$ (*P* for trend across quintiles = 0.024) compared to those in Q1. Male smokers with COPD in Q5 of carotene and vitamin C intake had 65-ml higher $FEV_1$ (*P* for trend across quintiles = 0.046) and a 101-ml higher $FEV_1$ (*P* for trend across quintiles = 0.039), respectively, compared to individuals in Q1.

Male COPD patients who had smoked ≥20 pack years exhibited a beneficial association between dietary antioxidant vitamin intake and $FEV_1$ (Figure 2). Male COPD patients in Q5 of vitamin A intake who had smoked ≥ 20 pack years had a 124-ml higher $FEV_1$ (*P* for trend across quintiles = 0.018) compared to individuals in Q1. COPD patients in Q5 of carotene intake who had smoked ≥20 pack years had a 94-ml higher $FEV_1$ (*P* for trend across quintiles = 0.026) compared with patients in

Q1. COPD patients in Q5 of vitamin C intake who had smoked >20 pack years had a 113-ml higher $FEV_1$ (*P* for trend across quintiles = 0.047) compared to patients in Q1.

## 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 13], whereas high levels of vitamin A and carotene were also associated with increased lung functions in multiple studies[12 19-23]. In a randomized controlled trial, Keranis *et al*. reported that increasing the intake of antioxidants improved lung function[24].

Cigarette smoking is the primary cause of COPD as it increases oxidative stress in the lungs and activates inflammatory responses[25]. Notably, one inhalation from a cigarette generates more than $10^{15}$ free radicals and other oxidants[26].

Antioxidants protect against the damage caused by smoking in multiple ways[3]. 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 peroxidation[3]. In an animal study, the respiratory epithelia of retinol-deficient animals had atrophied ciliated cells and modified lipid contents[28]. The pathologic features of the retinol-deficient animals were similar to those of human smokers[29].

Smokers exhibit nicotine-induced reductions in intestinal absorption and elevated metabolic turnover[30]. The metabolism or destruction of antioxidant vitamins increases in inflammatory environments[31-34], 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 population[35]. Additionally, Shin *et al.* reported that Korean smokers with adequate vitamin C intake had acceptable pulmonary functions[36]. Additionally, Morabia *et al.* identified that airway obstruction was reduced by vitamin A in smokers[12].

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

function were stronger among male smokers. Additionally, the association between the risk of COPD and antioxidant vitamin intake was clear for male but not female smokers. Male smokers with lower antioxidant vitamin intakes had increased ORs of COPD compared to female smokers. After limiting the analysis to subjects with COPD, a significant association between antioxidant vitamin intake and $FEV_1$ was observed in male smokers but not in other groups. This finding was similar to that of Joshi *et al.,* where changes in COPD risk and dietary vitamin C and vitamin E intake differed between males and females [37].

It is not known how gender differences impact pulmonary functions based on antioxidant vitamin intake; however, animal studies have revealed gender differences in antioxidant vitamin requirements. Al Rejaie *et al.* reported gender-related differences in the protective roles of ascorbic acid against oxidative stress[38], whereas Jiao *et al*. revealed gender differences in the regulation and expression of oxidative genes in mice [39].

Studies detailing the effects of antioxidant vitamins on lung function in smokers and non-smokers are lacking [5 23]. In the US population, Britton *et al.* revealed that the relationship between vitamin C intake and $FEV_1$ was stronger in ex-smokers than non- or current smokers[5]. Shahar *et al*. reported a relationship between individuals in Q1 of vitamin A intake and airway obstruction among individuals who smoked >41 pack years [23].

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

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

intake were obtained by 24-hour recall, inaccurate responses may have been offered. This study used the pre-bronchodilator $FEV_1$ for determining COPD; however, the definition of COPD is based on post-bronchodilator $FEV_1$[16]. This study failed to obtain data regarding air pollution or occupational exposure and, therefore, could not associate these variables with lung function; however, the strength of this study is that these data represent the Korean population.

## Conclusion

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

## Contributors

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

## Conflict of Interest Statement

The authors declare no conflict of interest.

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**Competing interests**

None declared

**Provenance and peer review**

Not commissioned; externally peer reviewed

**Data sharing statement**

No additional data are available.

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## Table legends

**Table 1. Study population characteristics.**

¶, 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.**

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.**

OR 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 ($FEV_1$) measurements across quintiles of vitamin A, carotene, and vitamin C intake (energy-adjusted) in subjects with COPD.**

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.

**Figure Legends**

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

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

**Figure 2. Mean values of adjusted forced expiratory volume in 1-second ($FEV_1$) measurements across quintiles of vitamin A, carotene, and vitamin C intake (energy-adjusted) in male COPD patients according to smoking status.**

Values were 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 (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) | *P* 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 | | *P* interaction |
|---|---|---|---|---|---|---|---|
| | Q5 | Q1 | Q5 | Q1 | Q5 | Q1 | |
| Vitamin A | | | | | | | <0.001 |
| Female non-smokers | 2096 | 2564 | 105 | 242 | ref | 1.19 (0.92,1.53) | |
| 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)¶ | |

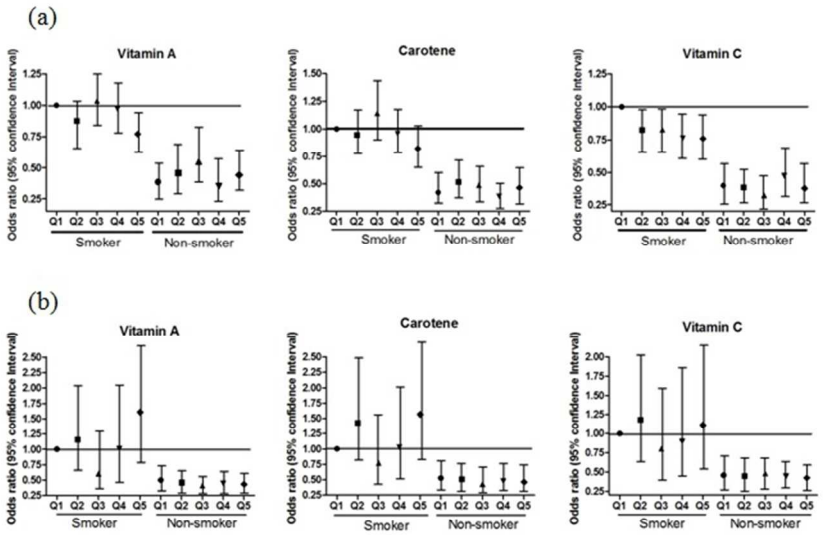
OR (Odd ratio) was determined following adjustment for age, body mass index, energy intake, number of comorbid diseases, alcohol consumption, household income, and education level.

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

**Table 4. Mean values of adjusted forced expiratory volume in 1-second ($FEV_1$) 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) | *P* value for trend | *P* 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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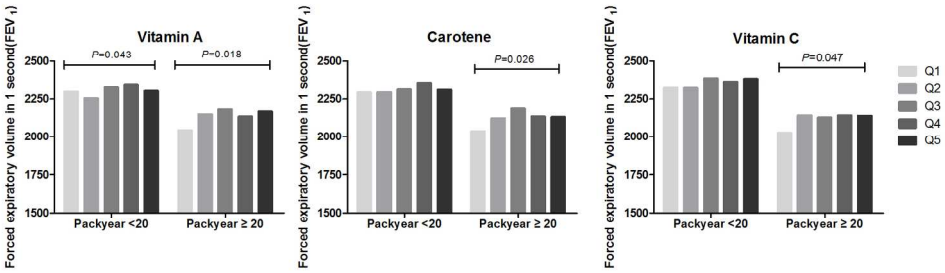


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# Effects of dietary antioxidant vitamins on lung functions according to gender and smoking status in Korea: A population-based cross-sectional study



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# 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 ($FEV_1$) 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 $FEV_1$ 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, for vitamin A, carotene, and vitamin C, 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

**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.

## Introduction

Chronic obstructive pulmonary disease (COPD) causes morbidity and mortality[1]. Smoking is a primary risk factor for COPD; however, other factors also contribute as only 10–20% of smokers develop airflow limitations[2].

Dietary antioxidants protect against oxidative stress caused by smoking[3], and multiple studies have revealed associations between the intake of antioxidant vitamins or fibers and respiratory diseases[4-8]. However, evidence supporting the benefits of vitamin supplement therapy is lacking[9 10].

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 $FEV_1$ in smokers compared to former smokers and non-smokers[11 12].

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.

## Patients and Methods

### *Study population*

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

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

### 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.

***Spirometry and airflow obstruction definitions***

The pulmonary function test (PFT) was performed using dry-rolling seal volume spirometers (Model 2130; Sensor Medics, Yorba Linda, CA, USA) and standardized according to the American Thoracic Society/European Respiratory Society criteria[13]. Qualified technicians and principal investigators assessed the spirometry data for acceptability and reproducibility. The predictive equations for the forced expiratory volume in 1 second ($FEV_1$) and the forced vital capacity (FVC) were derived from survey data on non-smokers who had normal chest X-rays and no previous history of respiratory diseases[14]. COPD was defined as a $FEV_1/FVC < 70\ \%$[15].

***Dietary assessments***

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

***Potential confounders***

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

Smokers were subjects who smoked more than 100 cigarettes in their lifetime[17]. Participants were categorized in terms of smoking status as follows: smoker, ex-smoker, or never smoked. Those who answered in the negative to the question 'Do you currently smoke?' were defined as ex-smokers.

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

***Statistical analysis***

A total of 21,148 subjects participated in this study (Figure 1). 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, place of residence, number of comorbid diseases, smoking history, alcohol intake, and pack years[4 11 18]. 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.

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

## Results

The baseline characteristics of the 21,148 participants are shown in Table 1. All subjects were classified into four groups based on smoking history and gender. Of the 7,986 smokers, 7,178 were male (mean age, 57.8±11.0 years) and 808 were female (mean age, 57.4±12.5 years). Of the 13,162 individuals who had never smoked, 1,626 were male (mean age, 57.9±11.3 years) and 11,536 were female (mean age, 57.1±10.8 years). Among all subjects, 3,005 were diagnosed with COPD. The prevalence of COPD was highest in male smokers (26.4%) and lowest in female non-smokers (6.4%).

The four groups differed regarding age, BMI, educational level, household income, and alcohol usage ($P$<0.001). Energy intake was significantly higher in males than females (males, 2,256.5 kcal; females, 1,648.3 kcal; $P$<0.001). The levels of vitamin A, carotene, and vitamin C were highest in the male non-smoker group and lowest in the female smoker group. Korean male non-smokers are pre-disposed to COPD compared to female non-smokers (incidence rate of 15.7% versus 6.4%). Age and the percentage of alcohol intake were higher in Korean male non-smokers than female non-smokers.

Table 2 showed the association between lung function ($FEV_1$, FVC) and dietary antioxidant vitamin levels. Participants in the highest quintile (Q5) of vitamin A intake had 30 ml higher $FEV_1$ ($P$ 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 $FEV_1$ ($P$ 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 $FEV_1$ ($P$ 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.

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. Figure 2 shows that the risk of COPD was influenced by dietary antioxidant vitamin levels in male smokers, in detail. In male smokers, the risk of 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). 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.

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

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

We investigated the association between dietary antioxidant vitamin intake and lung function after limiting the analyses to individuals with COPD. The changes in $FEV_1$ were not statistically significant based on the levels of dietary antioxidant vitamins in subjects with COPD. Similar to the previous results, only male smokers in subjects with COPD, exhibited a beneficial association between dietary antioxidant vitamin intake and $FEV_1$ (Figure 3). Male smokers with COPD in Q5 for vitamin A intake had a 71-ml higher $FEV_1$ (*P* for trend across quintiles = 0.019) compared to those in Q1. Male smokers with COPD in Q5 of carotene and vitamin C intake had 71-ml higher $FEV_1$ (*P* for trend across quintiles = 0.037) and a 109-ml higher $FEV_1$ (*P* for trend across quintiles = 0.026), respectively, compared to individuals in Q1.

Additional analyzes were performed to determine if lung function was reduced by smoking amount or smoking status in male smoker- COPD patients. Male COPD patients who had smoked ≥20 pack years exhibited a beneficial association between dietary antioxidant vitamin intake and $FEV_1$ (Figure 4). Male COPD patients in Q5 of vitamin A intake who had smoked ≥ 20 pack years had a 192-ml higher $FEV_1$ (*P* for trend across quintiles = 0.018) compared to individuals in Q1. COPD patients in Q5 of carotene intake who had smoked ≥20 pack years had a 149-ml higher $FEV_1$ (*P* for trend across quintiles = 0.024) compared with patients in Q1. COPD patients in Q5 of vitamin C intake who had smoked >20 pack years had a 177-ml higher $FEV_1$ (*P* for trend across quintiles = 0.043) compared to patients in Q1.

## 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 function[24].

Cigarette smoking is the primary cause of COPD as it increases oxidative stress in the lungs and activates inflammatory responses[25]. Notably, one inhalation from a cigarette generates more than $10^{15}$ free radicals and other oxidants[26].

Antioxidants protect against the damage caused by smoking in multiple ways[3]. 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 peroxidation[3]. In an animal study, the respiratory epithelia of retinol-deficient animals had atrophied ciliated cells and modified lipid contents[28]. The pathologic features of the retinol-deficient animals were similar to those of human smokers[29].

Smokers exhibit nicotine-induced reductions in intestinal absorption and elevated metabolic turnover[30]. The metabolism or destruction of antioxidant vitamins increases in inflammatory environments[31-34], 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 population[35]. Additionally, Shin *et al.* reported that Korean smokers with adequate vitamin C intake had acceptable pulmonary functions[36] and Park et al showed that dietary vitamin C provides protection against

COPD[37]. Additionally, Morabia *et al.* identified that airway obstruction was reduced by vitamin A in smokers[11].

One notable finding in the current study was that the effects of antioxidant vitamin intake on lung function were stronger among male smokers. Additionally, the association between the risk of COPD and antioxidant vitamin intake was clear for male but not female smokers. Male smokers with lower antioxidant vitamin intakes had increased ORs of COPD compared to female smokers. 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.

After limiting the analysis to subjects with COPD, a significant association between antioxidant vitamin intake and $FEV_1$ was observed in male smokers but not in other groups. This finding was similar to that of Joshi *et al.,* where changes in COPD risk and dietary vitamin C and vitamin E intake differed between males and females [38].

It is not known how gender differences impact pulmonary functions based on antioxidant vitamin intake; however, animal studies have revealed gender differences in antioxidant vitamin requirements. Al Rejaie *et al.* reported gender-related differences in the protective roles of ascorbic acid against oxidative stress[39], whereas Jiao *et al*. revealed gender differences in the regulation and expression of oxidative genes in mice [40].

Studies detailing the effects of antioxidant vitamins on lung function in smokers and non-smokers are lacking [5 23]. In the US population, Britton *et al.* revealed that the relationship between vitamin C intake and $FEV_1$ was stronger in ex-smokers than non- or current smokers[5]. Shahar *et al*. reported a relationship between individuals in Q1 of vitamin A intake and airway obstruction among individuals who smoked >41 pack years [23].

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

This study has several limitations that should be noted. As we used a cross-sectional design, the data cannot be used to answer questions regarding causation. Additionally, because data on nutritional intake were obtained by 24-hour recall, inaccurate responses may have been offered. This study used the pre-bronchodilator $FEV_1$ for determining COPD; however, the definition of COPD is based on post-bronchodilator $FEV_1$[15]. This study failed to obtain data regarding air pollution or occupational exposure and, therefore, could not associate these variables with lung function; however, the strength of this study is that these data represent the Korean population.

## Conclusion

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

## Contributors

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

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

## Conflict of Interest Statement

The authors declare no conflict of interest.


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## Competing interests

None declared


## Provenance and peer review

Not commissioned; externally peer reviewed


## Data sharing statement

No additional data are available.

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## Table legends

**Table 1. Study population characteristics.**

¶, 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.**

Data were adjusted for age, sex, body mass index, energy intake, number of comorbid diseases, alcohol consumption, place of residence, 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.**

OR 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.

**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) | *P* value for trend |
|---|---|---|---|---|---|---|---|
| **Vitamin A** | | | | | | | |
| Mean intake (μg 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 (μg) | 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 |

Data were adjusted for age, sex, body mass index, energy intake, number of comorbid diseases, alcohol consumption, place of residence 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 | | *P* interaction |
|---|---|---|---|---|---|---|---|
| | Q5 | Q1 | Q5 | Q1 | Q5 | Q1 | |
| Vitamin A | | | | | | | <0.001 |
| Female non-smokers | 2096 | 2564 | 105 | 242 | ref | 1.16 (0.89,1.49) | |
| 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.

## Figure Legends

**Figure 1. The study population framework**

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

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

**Figure 3. Mean values of adjusted forced expiratory volume in 1-second ($FEV_1$) measurements across quintiles of vitamin A, carotene, and vitamin C intake (energy-adjusted) in subjects with COPD.**

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

**Figure 4. Mean values of adjusted forced expiratory volume in 1-second ($FEV_1$) measurements across quintiles of vitamin A, carotene, and vitamin C intake (energy-adjusted) in male COPD patients according to smoking status.**

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

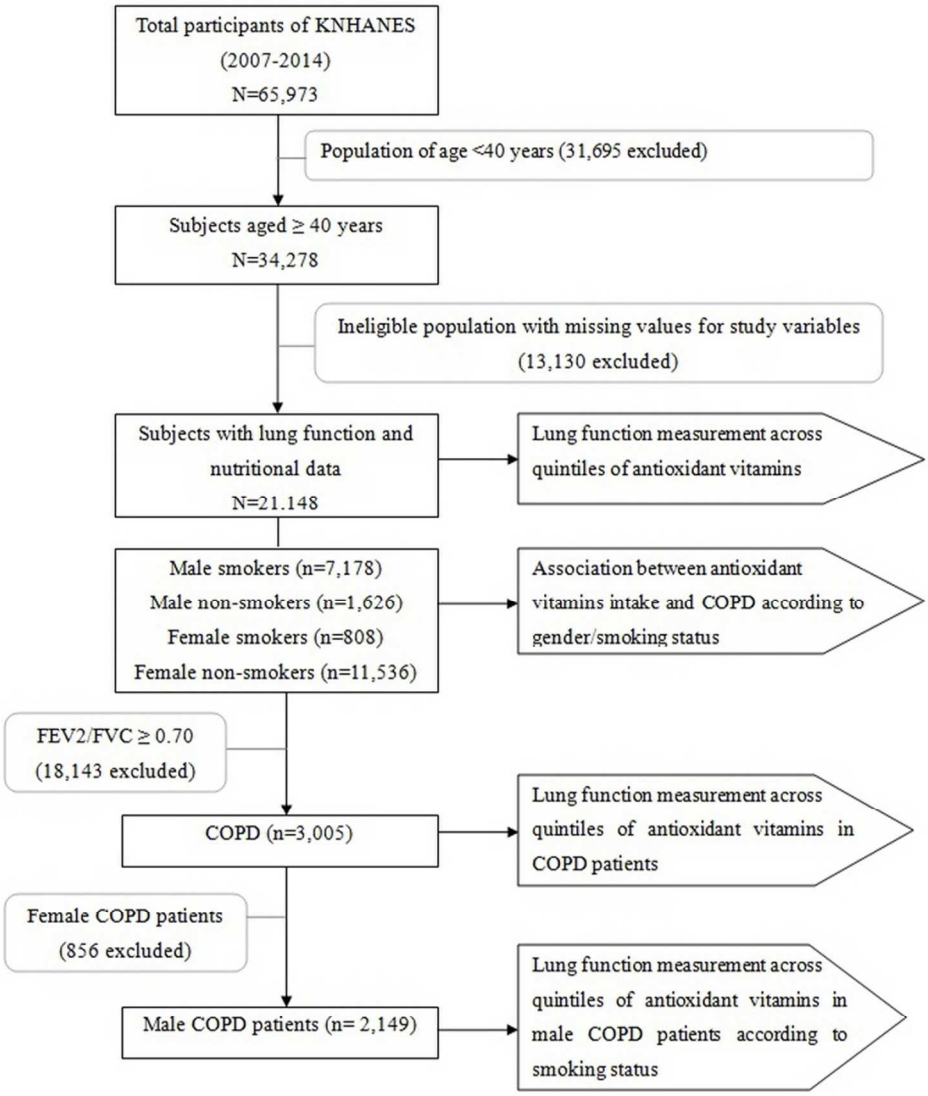


Figure 1. The study population framework

240x274mm (300 x 300 DPI)

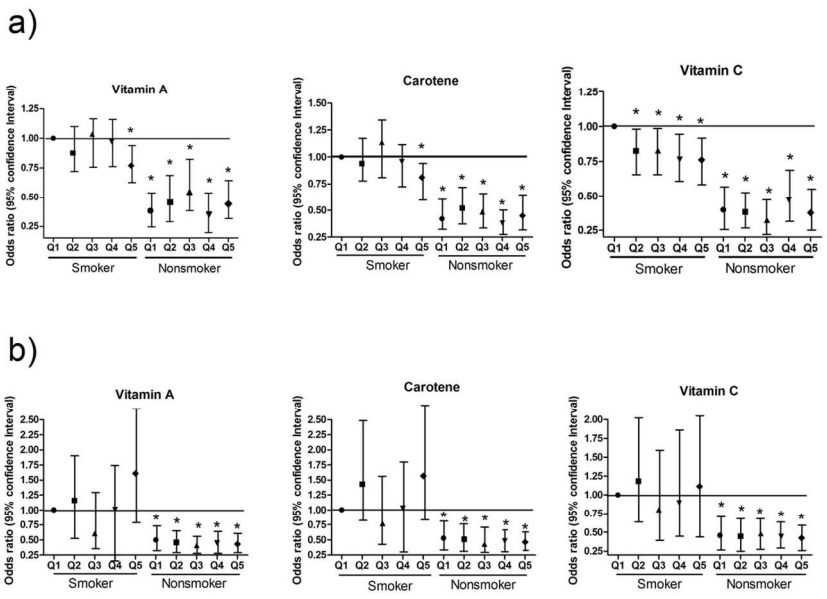


Figure 2. Odds ratios for the association between antioxidant vitamin intake and COPD among (a) male and (b) female smokers and non-smokers

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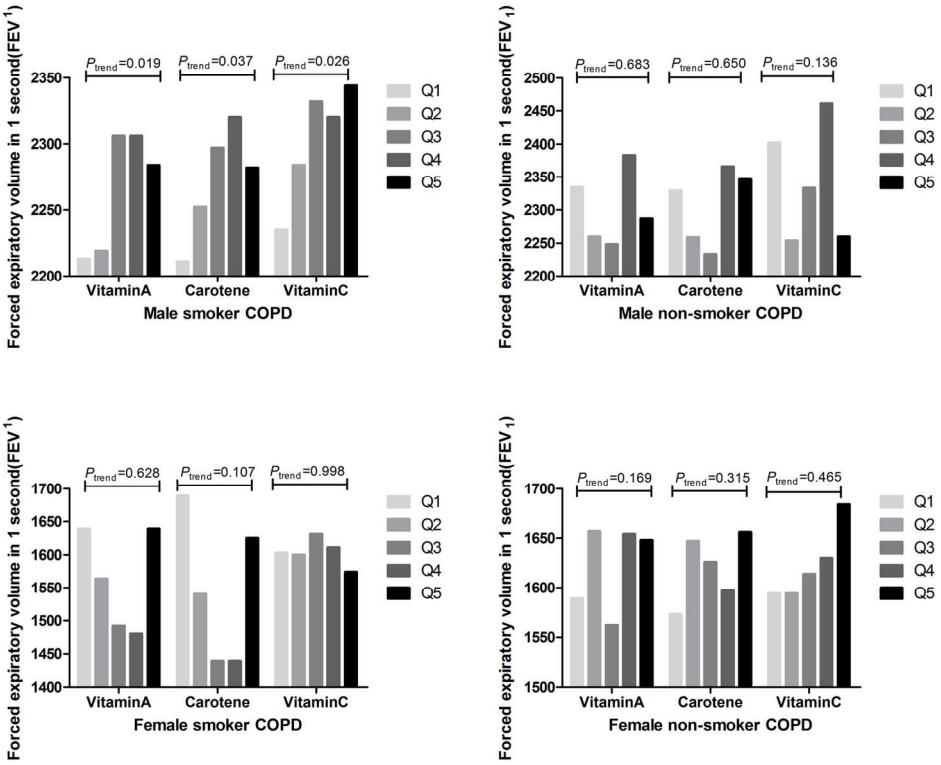


Figure 3. Mean values of adjusted forced expiratory volume in 1-second (FEV1) measurements across quintiles of vitamin A, carotene, and vitamin C intake (energy-adjusted) in subjects with COPD.

148x121mm (300 x 300 DPI)

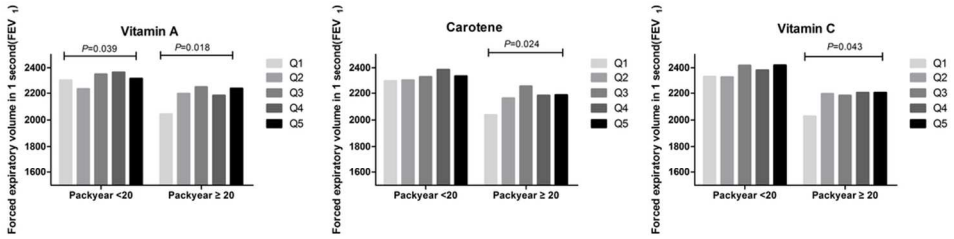


Figure 4. Mean values of adjusted forced expiratory volume in 1-second (FEV1) measurements across quintiles of vitamin A, carotene, and vitamin C intake (energy-adjusted) in male COPD patients according to smoking status.

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.