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# BMJ Open

## Obstructive lung function and the risk of chronic kidney disease: Analysis from the community-based prospective Ansan-Ansung cohort in Korea

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-043432
Article Type:	Original research
Date Submitted by the Author:	03-Aug-2020
Complete List of Authors:	Kim, Sang Hyuk; Republic of Korea Army Headquarters, Medical service corps of 2nd armored brigade Kim, Hyeon Sam; Eulji Hospital, Internal Medicine Min, Hyang Ki; Eulji Hospital, Internal Medicine Lee, Sung Woo; Eulji Hospital, Internal Medicine
Keywords:	Respiratory physiology < THORACIC MEDICINE, Chronic renal failure < NEPHROLOGY, Chronic airways disease < THORACIC MEDICINE

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4 1 **Obstructive lung function and the risk of chronic kidney disease: Analysis from the**  
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6 2 **community-based prospective Ansan-Ansung cohort in Korea**  
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13 4 Sang Hyuk Kim<sup>1</sup>, Hyeon Sam Kim<sup>2</sup>, Hyang Ki Min<sup>2</sup>, and Sung Woo Lee<sup>2\*</sup>  
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19 6 *<sup>1</sup>Medical Service Corps of 2<sup>nd</sup> Armored Brigade, Republic of Korea Army, Paju, Korea.*

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21 7 *<sup>2</sup>Department of Internal Medicine, Nowon Eulji Medical center, Eulji University, Seoul, Korea.*  
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28 9 **\*Corresponding author:** Sung Woo Lee, MD, PhD

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30 10 Mailing address: Division of Nephrology, Department of Internal Medicine, Eulji Medical

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32 11 Center, 68, Hangeulbiseok-ro, Nowon-gu, Seoul, 01735, Korea

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34 12 Phone: +82-2-970-8205

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36 13 Fax: +82-2-971-8212

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38 14 E-mail: neplsw@gmail.com  
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44 16 **Word count:** 4897 words.  
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51 18 **Short title:** Obstructive lung function and CKD  
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57 20 **Keywords:** Respiratory physiology, chronic renal failure, chronic airways disease  
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## 21 Abstract

22 **Objective:** There have been limited studies on the relationship between obstructive lung  
23 function and the development of chronic kidney disease (CKD). We investigated the  
24 association between obstructive lung function and incident CKD development in a large-scale  
25 prospective cohort study.

26 **Methods:** We reviewed the data of 8,035 non-CKD adults aged 40-69 years who participated  
27 in the Ansung-Ansan cohort, a prospective community-based cohort study. Pre-  
28 bronchodilation results for the ratio of forced expiratory volume per 1 second (FEV1) to forced  
29 vital capacity (FVC) were used as the primary exposure. The primary outcome was incident  
30 CKD, defined as the first event of an estimated glomerular filtration rate  $< 60$  mL/min/1.73m<sup>2</sup>.  
31 Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using multivariate  
32 Cox proportional hazard regression analysis.

33 **Results:** Over a mean follow-up period of 11.7 years, incident CKD developed in 513 subjects  
34 (6.4%). An increase of 0.1 in FEV1/FVC was associated with a decreased risk of incident CKD  
35 (HR 0.84, CI 0.75-0.94,  $P = 0.002$ ). Compared to the fourth quartile, the HR (95 % CI) of the  
36 first quartile of FEV1/FVC ratio was 1.35 (1.03-1.76,  $P = 0.028$ ). In the restricted cubic spline  
37 curve, the renal hazard associated with a decreased FEV1/FVC ratio was evident at FEV1/FVC  
38 values  $< 0.80$ , showing a U-shaped relationship. In subgroup analysis, the renal hazard  
39 associated with a decreased FEV1/FVC ratio was particularly evident in people without  
40 metabolic syndrome ( $P$  for interaction = 0.026).

41 **Conclusion:** Decreased FEV1/FVC ratio was independently associated with an increased risk  
42 of incident CKD development, particularly in people without metabolic syndrome. Future  
43 studies need to be conducted to confirm these results.

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4 **44 Strengths and limitations of the study**  
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7 45 The strength of our study is the prospective nature of this study with a large number of  
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9 46 participants.

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13 47 Our study is the only study to investigate the association between lung function and chronic  
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15 48 kidney disease development using a non-linear analytic method.

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18 49 The limitations are the observational nature of our study and only pre-bronchodilator  
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20 50 measurements were used for analysis.

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24 51 Another limitation is that generalization is limited because the study was conducted in a single  
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26 52 country.

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## 54 Introduction

55 Airway obstruction which is commonly found in chronic respiratory diseases such as chronic  
56 obstructive pulmonary disease (COPD) and bronchial asthma (BA), can be objectively  
57 measured by pulmonary function tests.[1, 2] Obstructive lung function is defined by a  
58 combination of the results of spirometry.[3] The main parameter that represents obstructive  
59 lung function is the ratio of forced expiratory volume per 1 second (FEV1) to forced vital  
60 capacity (FVC).[4] Many studies have revealed that lower FEV1/FVC ratios are associated  
61 with increased comorbidities and mortality.[5-8] Decreased FEV1/FVC ratios are also  
62 associated with increased incidence of atrial fibrillation,[5] heart failure[6] and type 2 diabetes  
63 mellitus.[7]

64 Chronic kidney disease (CKD) is one of the major chronic diseases in modern society,  
65 causing substantial medical expenses, chronic disease morbidity and mortality.[9] According  
66 to the 2011-2013 report, the total prevalence of CKD in adults aged more than 20 years was  
67 8.2% in Korea.[10] The prevalence and incidence of CKD has been increasing worldwide,  
68 particularly in developing countries.[11] In addition, CKD is related to an increased incidence  
69 of mental disorders, including depression, dementia, and Parkinson's disease.[12-14] As a  
70 result, degradation of quality of life was commonly found in the CKD population.[15]  
71 Therefore, identification of factors associated with CKD and early intervention may be helpful  
72 in promoting public health.[16]

73 Several recent studies have reported the association between obstructive airway diseases and  
74 CKD.[17-19] Furthermore, the findings of obstructive spirometry may also be associated with  
75 CKD.[20-22] Suzuki et al. reported that the prevalence of CKD increased with an increase in  
76 the obstructive spirometry grade.[20] Sumida et al. analyzed 14,946 participants of the  
77 Atherosclerosis Risk in Communities (ARIC) study and reported that the incidence of end-

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4 78 stage renal disease was higher in the lowest quartile of FEV1/FVC ratio than highest quartile  
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7 79 with a hazard ratio (HR) and 95% confidence interval (CI) of 1.33 (1.03-1.73).[21] Although  
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9 80 one Korean study also suggested that decreased FEV1/FVC ratio was associated with an  
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11 81 increased risk of incident CKD, it was based on a single-center retrospective cohort, and the  
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13 82 potential renal hazard associated with obstructive lung function needs to be tested in a  
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16 83 prospective setting.[22] The aim of this study was, therefore, to investigate the relationship  
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18 84 between FEV1/FVC ratio and incident CKD using data from the community-based prospective  
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20 85 Ansan-Ansung cohort in Korea.  
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## 86 **Methods**

### 87 **Participants**

88 The Ansan-Ansung cohort was prospectively assessed to investigate factors affecting the  
89 incidence of chronic diseases in the Ansan (urban) and Ansong (rural) areas. The enrolled  
90 subjects were aged 40-69 years and lived in these 2 cities in Korea, and baseline measurements  
91 were performed between May 2001 and February 2003. Participants were examined biennially  
92 after the baseline measurement. This community-based prospective cohort study is ongoing,  
93 and the last follow-up was conducted in 2015-2016. More detailed information about the  
94 Ansan-Ansung cohort can be found in previous reports.[23] In total, 10,030 people participated  
95 at the baseline. Out of 10,030 subjects, we excluded 252 subjects with missing spirometry  
96 results, 114 subjects with missing smoking status, and 337 subjects with missing data for  
97 metabolic disorders. Of the remaining 9,327 subjects, 186 subjects with prevalent CKD, 189  
98 with baseline proteinuria defined as  $\geq 1+$  protein in dipstick urinalysis (URISCAN Pro II; YD  
99 Diagnostic Corp) and 917 subjects missing serial creatinine measurements were further  
100 excluded. Finally, 8,035 subjects were included in this study for analysis (Figure 1).

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### 102 **Ethics statement**

103 The Ansan-Ansung cohort complied with the Declaration of Helsinki. All participants  
104 provided informed consent and ethical approval was obtained from the institutional review  
105 boards of the Nowon Eulji Medical Center, Eulji University (IRB Number: 2019-06-014). All  
106 data were completely anonymized prior to access. Our study was also checked using the  
107 Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)  
108 Statement.[24]

109

## 110 **Exposure**

111 The main exposure of this study was the FEV1/FVC ratio, which was obtained by pre-  
112 bronchodilator testing using spirometry (VMAX2130; Sensormedics Corporation, Yorba, CA,  
113 USA). FEV1 and FVC were measured 3 times and best scores were recorded by well-trained  
114 technicians. Percent-predicted FEV1 and FVC values were used to calculate the FEV1/FVC  
115 ratio, and the predicted FEV1 and FVC values used to calculate percent-predicted FEV1 and  
116 FVC values were derived from Korean formula.[25]

117

## 118 **Outcome**

119 Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney  
120 Disease Epidemiology Collaboration equation.[26] CKD was defined as eGFR < 60  
121 ml/min/1.73m<sup>2</sup>. Prevalent CKD was defined as eGFR < 60 ml/min/1.73m<sup>2</sup> at the baseline  
122 measurement and incident CKD, a main outcome of this study, was defined as the first event  
123 of eGFR < 60 ml/min/1.73m<sup>2</sup>, which was confirmed at least 2 or more times and was  
124 maintained thereafter.

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## 126 **Measurements and other definitions**

127 A standard interview regarding the participants' socio-demographic status and lifestyle was  
128 conducted by trained interviewers. High income was defined as the highest quintile of monthly  
129 household income ( $\geq 3$  million won a month). Blood pressure (BP) was measured using a  
130 standard mercury sphygmomanometer (Baumanometer-Standby; W. A. Baum Co., Inc.,

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4 131 Copiague, NY, USA), and the average BP on both arms was used as the representative BP  
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6 132 measure. Body mass index (BMI) was calculated by dividing the weight by the square of the  
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9 133 height (kg/m<sup>2</sup>). Waist circumference (WC) was measured at the narrowest point between the  
10  
11 134 lower rib and the iliac crest (measured to the nearest 0.1 cm). Blood samples were examined  
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13 135 for fasting for at least 8 hours. Hemoglobin levels and white blood cell (WBC) counts were  
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15 136 analyzed using enzymatic methods with ADVIA 120 (Bayer Diagnostics, Tarrytown, NY,  
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17 137 USA). Fasting glucose (FG), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C),  
18  
19 138 C-reactive protein (CRP), serum creatinine and blood urea nitrogen (BUN) levels were  
20  
21 139 measured using ADVIA 1650 (Siemens, Tarrytown, NY, USA). Five components of metabolic  
22  
23 140 syndrome (MetS) were defined according to the recommendations of the International Diabetes  
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25 141 Federation.[27] First, elevated BP was defined as a systolic BP  $\geq$ 130mmHg, a diastolic BP  
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27 142  $\geq$ 85mmHg, treatment with anti-hypertensive drugs, or a previous diagnosis of hypertension by  
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29 143 a physician. Second, elevated FG was defined as an FG level of  $\geq$ 100 mg/dL, treatment with  
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31 144 insulin or oral anti-diabetic drugs, or a previous diagnosis of diabetes by a physician. Third,  
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33 145 increased TG was defined as TG  $\geq$ 150 mg/dL, treatment with anti-dyslipidemic drugs, or a  
34  
35 146 previous diagnosis of dyslipidemia by a physician. Fourth, reduced HDL-C levels were defined  
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37 147 as HDL-C  $<$ 40mg/dL in men and  $<$  50mg/dL in women. Finally, central obesity was defined  
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39 148 as WC  $\geq$ 90cm in men and  $\geq$ 80cm in women. MetS was defined as three or more of the five  
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41 149 MetS components.[28]  
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## 52 151 **Statistical analyses**

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55 152 All statistical analyses were performed using R version 3.6.2 (R core Team 2019; R  
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57 153 foundation for Statistical Computing, Vienna, Austria). Histograms and Q-Q plots were used  
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59 154 to evaluate the normality of continuous variables. Normally distributed continuous variables

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4 155 were expressed as mean  $\pm$  standard deviation (SD). Non-normally distributed continuous  
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6 156 variables were described as medians with interquartile ranges (IQR). The *P*-trend was analyzed  
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9 157 using linear regression for the normally distributed continuous variables, Jonckheere-Terpstra  
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11 158 test for the non-normally distributed continuous variables, and the Cochran-Armitage test for  
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13 159 the categorical variables. Survival curves were analyzed using Kaplan-Meier estimates, and  
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16 160 differences among groups were tested using the log-rank test. Hazard ratios (HRs) and 95%  
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18 161 confidence intervals (CIs) were calculated using Cox proportional hazards regression analysis.  
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20 162 Both analyses were performed with the 'survival' package. In the Kaplan-Meier survival curve,  
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22 163 the mean survival time of each FEV1/FVC ratio quartile group was truncated at 14 years and  
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24 164 analyzed using the restricted mean survival time function with the 'survRM2' package. The  
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27 165 proportional hazards assumption was verified by goodness-of-fit tests. Two variables, age and  
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29 166 eGFR, violated proportional hazard assumption. Therefore, they were categorized by clinically  
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31 167 important cutoffs (65 years for age and 90 mL/min/1.73m<sup>2</sup> for eGFR) and incorporated as strata  
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34 168 in multivariate modeling after confirming the absence of interactions. Potential non-linear  
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36 169 relationships between obstructive lung function and incident CKD were evaluated using  
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39 170 restricted cubic spline curve analysis with the 'rms' package. A *P* value of <0.05 was  
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41 171 considered statistically significant. Subgroup analysis was performed on clinically important  
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43 172 variables, and continuous variables were divided into median values. Sensitivity analysis was  
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46 173 presented using multivariate Cox regression analysis for percent-predicted FEV1.

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## 175 **Results**

176 The 8,035 subjects had a mean  $\pm$  SD age of  $51.7 \pm 8.7$  years, and the proportions of men and  
177 current smokers were 48.3% and 41.2%, respectively. Mean  $\pm$  SD BMI, WC, systolic BP,  
178 diastolic BP, and HDL-C level were  $24.6 \pm 3.1$  kg/m<sup>2</sup>,  $82.6 \pm 8.7$  cm,  $120.9 \pm 18.1$  mmHg,  $80.2$   
179  $\pm 11.4$  mmHg, and  $44.7 \pm 9.9$  ml/dL, respectively, and median (IQR) of FG and TG levels were  
180 82 (77-90) mg/dL and 134 (99-188) mg/dL, respectively. The mean  $\pm$  SD of FEV1/FVC ratio,  
181 FEV1, and FVC were  $0.80 \pm 0.08$ ,  $96.8 \pm 14.1\%$ -predicted, and  $96.9 \pm 13.1\%$ -predicted,  
182 respectively. Mean  $\pm$  SD baseline eGFR was  $94.9 \pm 12.0$  mL/min/1.73m<sup>2</sup>. During a mean 11.7  
183 years' follow-up, incident CKD developed in 513 subjects (6.4%).

184 The first through fourth quartiles of the FEV1/FVC ratio were  $<0.76$ ,  $0.76-0.80$ ,  $0.81-0.84$ ,  
185 and  $\geq 0.85$ , respectively. The baseline characteristics of the study according to the FEV1/FVC  
186 ratio quartiles are depicted in Table 1. As the FEV1/FVC ratio quartile decreased, the  
187 proportions of men and current smokers increased, while the proportions of high-income and  
188 college graduates decreased. Although BMI and the HDL-C level decreased, systolic BP,  
189 diastolic BP, and WC increased as the FEV1/FVC ratio quartile decreased. With the reduction  
190 in the FEV1/FVC ratio quartile, WBC, CRP, hemoglobin, and FVC increased, while eGFR and  
191 FEV1 decreased.

192 We explored the potential hazard of the FEV1/FVC ratio quartile on the development of  
193 incident CKD. In the Kaplan-Meier survival curve (Figure 2), the mean (95 % CI) CKD-free  
194 survival was 13.4 (13.3-13.5) years in Q1, 13.6 (13.5-13.6) years in Q2, 13.7 (13.7-13.8) years  
195 in Q3, and 13.7 (13.6-13.8) years in Q4 (log-rank  $P < 0.001$ ). In multivariate Cox proportional  
196 hazard regression analysis (Table 2), a 0.1-unit increase in FEV1/FVC ratio was associated  
197 with decreased hazard of incident CKD development: HR (95% CI) of 0.84 (0.75-0.94,  $P =$   
198 0.002). Compared to the fourth quartile, the HR (95% CI) of the first quartile of the FEV1/FVC

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4 199 ratio was 1.35 (1.03-1.76,  $P = 0.028$ ). In restricted cubic spline curve analysis (Figure 3), as  
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6 200 FEV1/FVC ratio decreased, HR (95 % CI) for incident CKD development increased, showing  
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8 201 a U-shaped relationship and the negative relationship was obvious for FEV1/FVC < 0.80.  
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11 202 However, unlike the FEV1/FVC ratio, FEV1 was not associated with the development of  
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13 203 incident CKD in the sensitivity analysis table S1.  
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16 204 In the subgroup analysis, MetS modified the effect of the FEV1/FVC ratio on incident CKD  
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18 205 development (Figure 4). In detail, although an increased FEV1/FVC ratio was not associated  
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20 206 with incident CKD development in people with MetS, it was independently associated with  
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22 207 incident CKD development in those without MetS. There were no subgroups showing  
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24 208 statistically significant effect modification. However, nonsmokers, low baseline eGFR, low  
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26 209 CRP, low WBC, younger age, female sex, low BMI, non-raised HDL-C, BP, and FG were  
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28 210 valid subgroups for the relationship between FEV1/FVC ratio and CKD development.  
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## 211 Discussion

212 Obstructive lung disease and CKD are both important chronic diseases in the modern  
213 world.[9, 29] Several recent studies have shown the relationship between obstructive lung  
214 disease and CKD.[17, 30] Chen et al. reported that the overall incidence of CKD was higher in  
215 the COPD group (287.52 per 104 person-years vs. 470.9 per 104 person-years).[30] Huang et  
216 al. found that BA patients were more likely to develop CKD (HR 1.56, CI 1.48-1.64, P <  
217 0.001).[17] The FEV1/FVC ratio called the Tiffeneau-pinelli index, has been used worldwide  
218 as a screening index for diagnosing obstructive lung function. The FEV1/FVC ratio is an easily  
219 applicable index because it does not require calculation of the predicted value.[3, 18] Since  
220 only a few studies have evaluated the usefulness of the FEV1/FVC ratio in predicting future  
221 incident CKD development, we performed the current study and identified that a decreased  
222 FEV1/FVC ratio was independently associated with incident CKD development in a  
223 community-dwelling general population.

224 In this study, a 0.1 unit increase in the FEV1/FVC ratio was associated with a 16% lower  
225 risk of developing incident CKD. In comparison with patients showing FEV1/FVC  $\geq 0.85$   
226 (highest quartile), those with an FEV1/FVC ratio <0.76 (lowest quartile) showed a 35% higher  
227 risk of developing incident CKD. However, those in the second and third quartiles did not show  
228 a statistically significant renal hazard, suggesting a non-linear relationship between the  
229 FEV1/FVC ratio and incident CKD development. Therefore, we performed restricted cubic  
230 spline curve analysis and found that the renal hazard of association with decreased FEV1/FVC  
231 was evident at FEV1/FVC <0.80. Furthermore, the renal hazard was increased proportionally  
232 with the decrease in FEV1/FVC, suggesting that FEV1/FVC can be used not only as a  
233 screening index, but also as a severity index, particularly in predicting future CKD  
234 development.

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4 235 In contrast, however, percent-predicted FEV1 which is traditionally used as a severity index  
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6 236 for obstructive lung function, was not associated with incident CKD development. This may  
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9 237 be because of possible inaccuracies in the prediction method attribute to race, age, and  
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11 238 gender.[31] We used the formula proposed in 2005 based on the Korean population, but the  
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13 239 demographics of Korea have been changed dramatically over the last 15 years. Thus, a new  
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15 240 estimation formula based on new demographics will be needed.[32] In addition, the aging  
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17 241 process and underlying diseases can falsely reduce FEV1 values due to respiratory muscle  
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19 242 weakness, but the FEV1/FVC ratio was not affected by those confounders.[33] Therefore, for  
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21 243 a population with a low prevalence of airway obstruction, including this cohort, the FEV1/FVC  
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23 244 ratio may be a more suitable index for predicting incident CKD than absolute FEV1 values.  
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25 245 Since the FEV1/FVC ratio was particularly evident in groups without metabolic derangements,  
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27 246 we propose that this ratio can be used as a spirometric index to be associated with future CKD  
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29 247 development in a relatively healthy population.  
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35 248 To date, there have been no exact mechanisms for the potential renal hazard of airway  
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37 249 obstruction. One possible explanation is the chronic hypoxia induced by airway obstruction.  
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39 250 Chronic hypoxia may cause hypoxic renal damage, which is related to a decline in kidney  
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41 251 function.[34] Atherosclerosis, a risk factor for CKD, is also associated with chronic  
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43 252 hypoxia.[35] The systemic inflammation in obstructive lung diseases, including increased  
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45 253 levels of tumor necrosis factor  $\alpha$  and interleukin 6, may cause vascular calcification and  
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47 254 protein-energy wasting, which can ultimately result in CKD development.[36]  
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52 255 Our study has several strengths. First, to our knowledge, this is the first prospective study  
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54 256 using the FEV1/FVC ratio as the main index to predict CKD development. Second, a large  
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56 257 number of participants and many confounders for the incident CKD were adjusted in this study.  
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58 258 Third, using a non-linear analytic method, we found that incident CKD and the FEV1/FVC  
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4 259 ratio had a U-shaped relationship. This study also had several limitations. First, this was an  
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6 260 observational study. Therefore, a causal relationship could not be ascertained, and the results  
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9 261 should be interpreted with caution. Second, because of the large number of participants, we  
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11 262 only obtained pre-bronchodilator measurements. Because of the low prevalence of airway  
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13 263 diseases, however, we assumed that this limitation has little effect on the study results. Finally,  
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16 264 the generalizability of the results is limited because the study was conducted in a single country  
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18 265 with a single ethnicity.  
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21 266 In conclusion, decreased FEV1/FVC ratio was an independent risk factor for future CKD  
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23 267 development. The relationship of this findings with incident CKD development was  
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26 268 particularly valid in a relatively healthy population, suggesting that it may serve as an early  
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28 269 predictor for CKD development. Future studies need to be conducted to confirm the results of  
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30 270 this study.  
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33 271 **Author's Contribution:** Conceptualization, S.W.L.; Data curation/Formal analysis, S.H.K.;  
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35 272 Investigation/Methodology, H.S.K.; Writing – original draft, S.H.K.; Writing – review &  
36  
37 273 editing– H.K.M; Supervision/Validation – S.W.L. All authors read and approved the final  
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39 274 manuscript.  
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41 275 **Funding:** This study was supported by the National Research Foundation of Korea (Grant No:  
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43 276 NRF-2016R1A6A3A11933465).  
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46 277 **Competing Interests:** None declared.  
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49 278 **Patient consent:** Not required.  
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53 279 **Ethics approval:** Ethical Committee of Eulji Medical Center, Seoul, Korea.  
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56 280 **Data sharing statement:** No data are available.  
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4 395 **Figure legends**  
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7 396 **Figure 1. Flow chart of the study subject selection.** CKD, chronic kidney disease.  
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13 398 **Figure 2. Kaplan-Meier CKD-free survival curves among four groups defined by the**  
14 **FEV1/FVC ratio.** CKD, chronic kidney disease; FEV1, forced expiratory volume in 1 second;  
15 399 FVC, functional vital capacity; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4.  
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24 402 **Figure 3. Restricted cubic splines curve of Cox proportional hazards regression analysis**  
25 **according to the FEV1/FVC ratio.** FEV1, forced expiratory volume in 1 second; FVC,  
26 403 functional vital capacity. All covariates of model 2 shown in table 2 were used for adjustment.  
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28 404 The solid line indicates the calculated line of association between the FEV1/FVC ratio and  
29 405 estimated hazard ratio. The shaded region represents the 95% confidential intervals for value  
30 406 of hazard ratio according to the FEV1/FVC ratio.  
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42 409 **Figure 4. Subgroup analysis for the relationship between the FEV1/FVC ratio and the**  
43 **risk of incident CKD.** FEV1, forced expiratory volume in 1 second; FVC, functional vital  
44 410 capacity; CKD, chronic kidney disease; BMI, body mass index; MetS, metabolic syndrome;  
45 411 HR, hazard ratio; CI, confidence interval. Adjusted beta and 95% CI were analyzed using Cox  
46 412 proportional hazards regression analysis. All covariates of model 2 shown in table 2 were used  
47 413 to adjustment.  
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**Table 1. Clinical characteristics of the study population according to the FEV1/FVC ratio quartile.**

	FEV1/FVC ratio groups (n = 8,035)				P-trend
	1Q: <0.76 (n = 1,967)	2Q: 0.76-0.80 (n = 2,044)	3Q: 0.81-0.84 (n = 2,099)	4Q: ≥0.85 (n = 1,925)	
Age (years)	55.95 ± 8.62	52.44 ± 8.50*	50.11 ± 7.99*†	48.47 ± 7.81*†‡	<0.001
Male, n (%)	1,313 (66.75%)	1,047 (51.22%)*	860 (40.97%)*†	659 (34.23%)*†‡	<0.001
High income, n (%)	232 (11.79%)	386 (18.88%)*	435 (20.72%)*	384 (19.95%)*	<0.001
College graduate, n (%)	191 (9.71%)	283 (13.85%)*	362 (17.25%)*†	276 (14.34%)*‡	<0.001
Current smoker, n (%)	1190 (60.50%)	899 (43.98%)*	696 (33.16%)*†	526 (27.32%)*†‡	<0.001
BMI (kg/m <sup>2</sup> )	24.02 ± 3.02	24.79 ± 2.98*	24.93 ± 3.01*	24.59 ± 3.34*‡	<0.001
SBP (mmHg)	123.84 ± 18.31	121.25 ± 17.81*	119.67 ± 18.00*†	118.80 ± 17.91*†	<0.001
DBP (mmHg)	81.72 ± 11.07	80.33 ± 11.16*	79.66 ± 11.42*	78.97 ± 11.63*†	<0.001
Waist circumference (cm)	83.32 ± 8.08	83.58 ± 8.46	82.54 ± 8.74*†	80.93 ± 9.20*†‡	<0.001
Fasting glucose (mg/dL)	82 (77-90)	82 (77-91)	82 (78-90)	82 (77-89)	0.433
Triglyceride (mg/dL)	139 (102-191)	141 (104-198)	133 (98-186)* †	126 (94-176)* †‡	<0.001
HDL-cholesterol (mg/dL)	44.51 ± 9.95	44.33 ± 9.89	44.66 ± 9.73	45.52 ± 10.15*†	<0.001
BUN (mg/dL)	14.62 ± 3.66	14.42 ± 3.53	14.16 ± 3.36*	13.79 ± 3.47*†‡	<0.001
eGFR (mL/min/1.73m <sup>2</sup> )	92.38 ± 12.10	94.15 ± 11.83*	95.39 ± 11.87*†	97.92 ± 11.70*†‡	<0.001
Hemoglobin (g/dL)	13.97 ± 1.44	13.73 ± 1.57*	13.45 ± 1.63*†	13.31 ± 1.53*†	<0.001
WBC count (×10 <sup>3</sup> /μL)	6.71 ± 1.83	6.52 ± 1.81*	6.43 ± 1.73*	6.38 ± 1.73*†	<0.001
CRP (mg/dL)	0.15 (0.07-0.26)	0.14 (0.06-0.23)*	0.13 (0.06-0.24)*	0.14 (0.06-0.23)*	<0.001
FEV1 (%-predicted)	87.74 ± 14.69	97.31 ± 12.58*	100.19 ± 12.20*†	101.91 ± 12.61*†‡	<0.001
FVC (%-predicted)	98.13 ± 14.12	98.19 ± 12.91	97.15 ± 12.26	93.90 ± 12.79*†‡	<0.001

FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; WBC, white blood cells; CRP, C-reactive protein. Values are expressed as mean ± standard deviation for normally distributed continuous variables, median and interquartile range for non-normally distributed variables and percentage for categorical variables. P-trend was analyzed normally distributed continuous variables by ANOVA, for non-normally distributed continuous variable by Jonckheere-Terpstra tests, and for categorical variables by Cochran-Armitage test for trend. \*, †, and ‡ meant P < 0.05 when compared to < 0.76, 0.76-0.81, 0.81-0.85 groups of FEV1/FVC ratio, respectively, using Bonferroni post-hoc analysis of one-way ANOVA

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**Table 2. Hazard of FEV1/FVC ratio on incident CKD development.**

	Univariate	Model 1	Model 2
	HR (95% CI, <i>P</i> -value)	HR (95% CI, <i>P</i> -value)	HR (95% CI, <i>P</i> -value)
FEV1/FVC ratio: 0.1-unit increase	0.69 (0.63-0.76, < 0.001)	0.79 (0.71-0.89, < 0.001)	0.84 (0.75-0.94, 0.002)
FEV1/FVC ratio quartile			
1Q: <0.76 (n=1,967)	2.15 (1.67-2.76, < 0.001)	1.58 (1.21-2.07, < 0.001)	1.35 (1.03-1.76, 0.028)
2Q: 0.76-0.80 (n=2,044)	1.43 (1.10-1.87, 0.008)	1.18 (0.90-1.55, 0.224)	1.06 (0.81-1.39, 0.670)
3Q: 0.81-0.84 (n=2,099)	1.05 (0.79-1.39, 0.731)	0.99 (0.74-1.31, 0.926)	0.89 (0.67-1.18, 0.425)
4Q: ≥0.85 (n=1,925)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)

FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; CKD, chronic kidney disease; HR, hazard ratio; CI, confidence interval. In model 1, sex and body mass index were added as covariates and age group was used as strata. Model 2 included college graduate, high income, smoking status, triglyceride, high density lipoprotein cholesterol, C-reactive protein, blood urea nitrogen, systolic blood pressure, diastolic blood pressure, fasting glucose, white blood cells count, hemoglobin and estimated glomerular filtration rate group was used as strata in addition to the covariates in the model 1.

**Table S1. Sensitivity analysis for the relationship between the percent-predicted FEV1 and the risk of incident CKD**

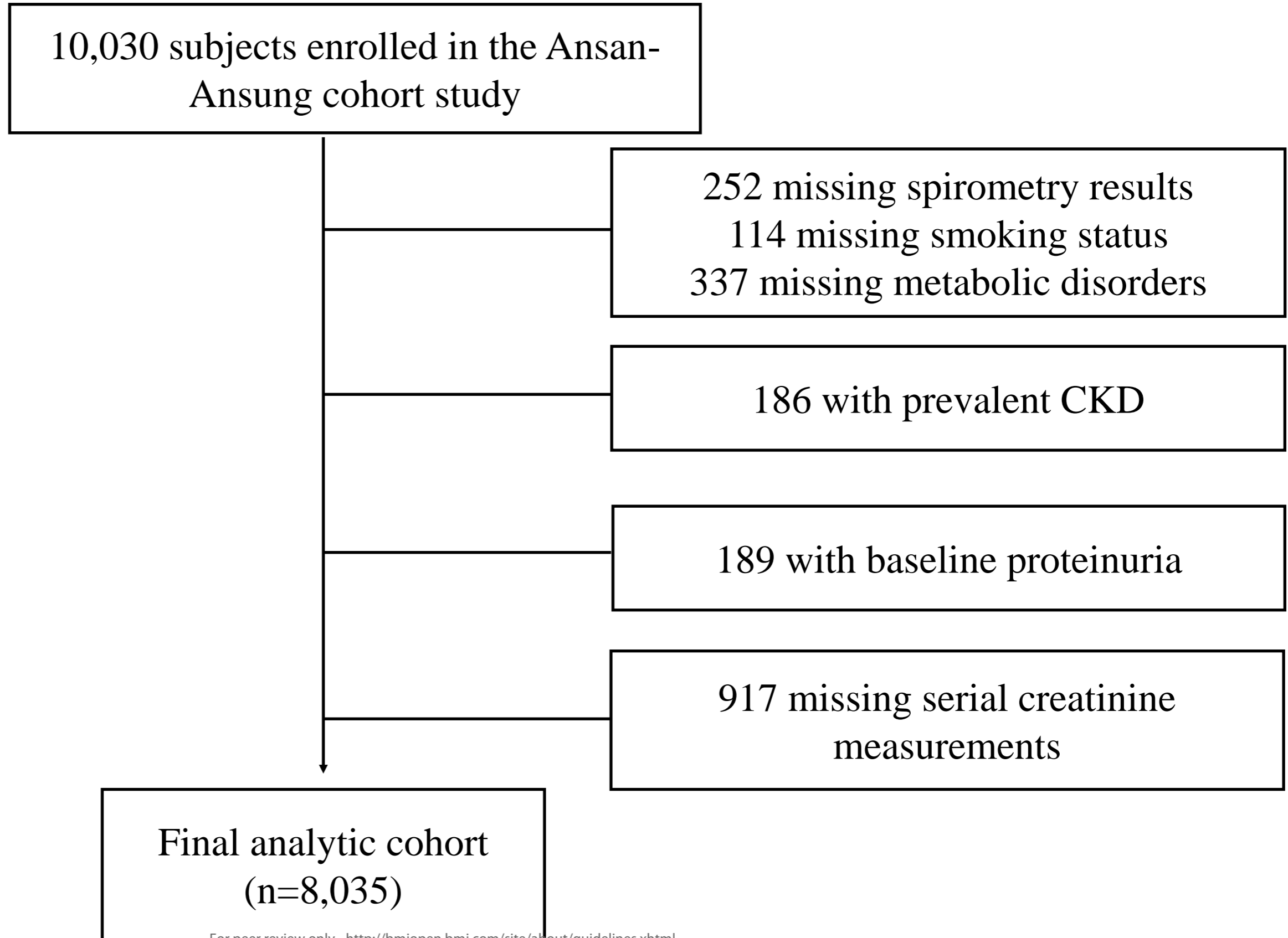
	Univariate	Model 1	Model 2
	HR (95% CI, <i>P</i> -value)	HR (95% CI, <i>P</i> -value)	HR (95% CI, <i>P</i> -value)
Percent-predicted FEV1: 10% increase	0.89 (0.84-0.95, < 0.001)	0.95 (0.87-1.05, 0.321)	0.99 (0.89-1.09, 0.798)
Percent-predicted FEV1			
1Q: < 88 %-predicted (n=1,941)	1.59 (1.24-2.04, < 0.001)	1.21 (0.92-1.77, 0.255)	1.17 (0.82-1.67, 0.397)
2Q: 88-97 %-predicted (n=2,022)	1.28 (0.99-1.65, 0.061)	1.16 (0.85-1.57, 0.354)	1.16 (0.85-1.58, 0.346)
3Q: 97-106 %-predicted (n=2,077)	1.15 (0.89-1.50, 0.279)	1.23 (0.92-1.60, 0.177)	1.24 (0.94-1.64, 0.132)
4Q: 106 %-predicted (n=1,955)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)

FEV1, forced expiratory volume in 1 second; CKD, chronic kidney disease; HR, hazard ratio; CI, confidence interval. In model 1, sex and body mass index, percent-predicted functional vital capacity were added as covariates and age group was used as strata. Model 2 included college graduate, high income, smoking status, triglyceride, high density lipoprotein cholesterol, C-reactive protein, blood urea nitrogen, systolic blood pressure, diastolic blood pressure, fasting glucose, white blood cells count, hemoglobin and estimated glomerular filtration rate group was used as strata in addition to the covariates in the model 1.

**Table S2. Additional subgroup analysis for the relationship between the FEV1/FVC ratio and the risk of CKD.**

Subgroup	No. of people	Per 0.1 increase of FEV1/FVC ratio	
		Adjusted HR (95%CI, <i>P</i> )	<i>P</i> for interaction
Age	< 65 (n=7,133)	0.83 (0.72-0.95, 0.009)	0.779
	≥ 65 (n=902)	0.91 (0.76-1.10, 0.329)	
Sex	Male (n=3,879)	0.86 (0.74-1.01, 0.065)	0.762
	Female (n=4,156)	0.83 (0.70-0.97, 0.022)	
BMI	< 25 (n=4,586)	0.80 (0.69-0.92, 0.001)	0.194
	≥ 25 (n=3,449)	0.91 (0.75-1.10, 0.308)	
Central obesity	No (n=4,996)	0.83 (0.71-0.96, 0.015)	0.455
	Yes (n=3,118)	0.87 (0.75-1.01, 0.076)	
Raised TG	No (n=4,674)	0.87 (0.74-1.01, 0.073)	0.907
	Yes (n=3,361)	0.82 (0.69-0.97, 0.020)	
Reduced HDL-C	No (n=3,737)	0.77 (0.66-0.90, 0.001)	0.416
	Yes (n=4,298)	0.92 (0.78-1.08, 0.297)	
Raised BP	No (n=4,596)	0.75 (0.62-0.90, 0.002)	0.129
	Yes (n=3,439)	0.89 (0.77-1.03, 0.131)	
Raised FG	No (n=7,087)	0.83 (0.73-0.93, 0.002)	0.075
	Yes (n=948)	1.04 (0.78-1.41, 0.776)	

FEV1, forced expiratory volume in 1 second; FVC, functional vital capacity; CKD, chronic kidney disease; BMI, body mass index; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; BP, blood pressure; FG, fasting glucose; HR, hazard ratio; CI, confidence interval. Adjusted beta and 95% CI were analyzed using multivariate Cox proportional hazards regression analysis. All covariates of model 2 shown in table 2 were used to adjustment.



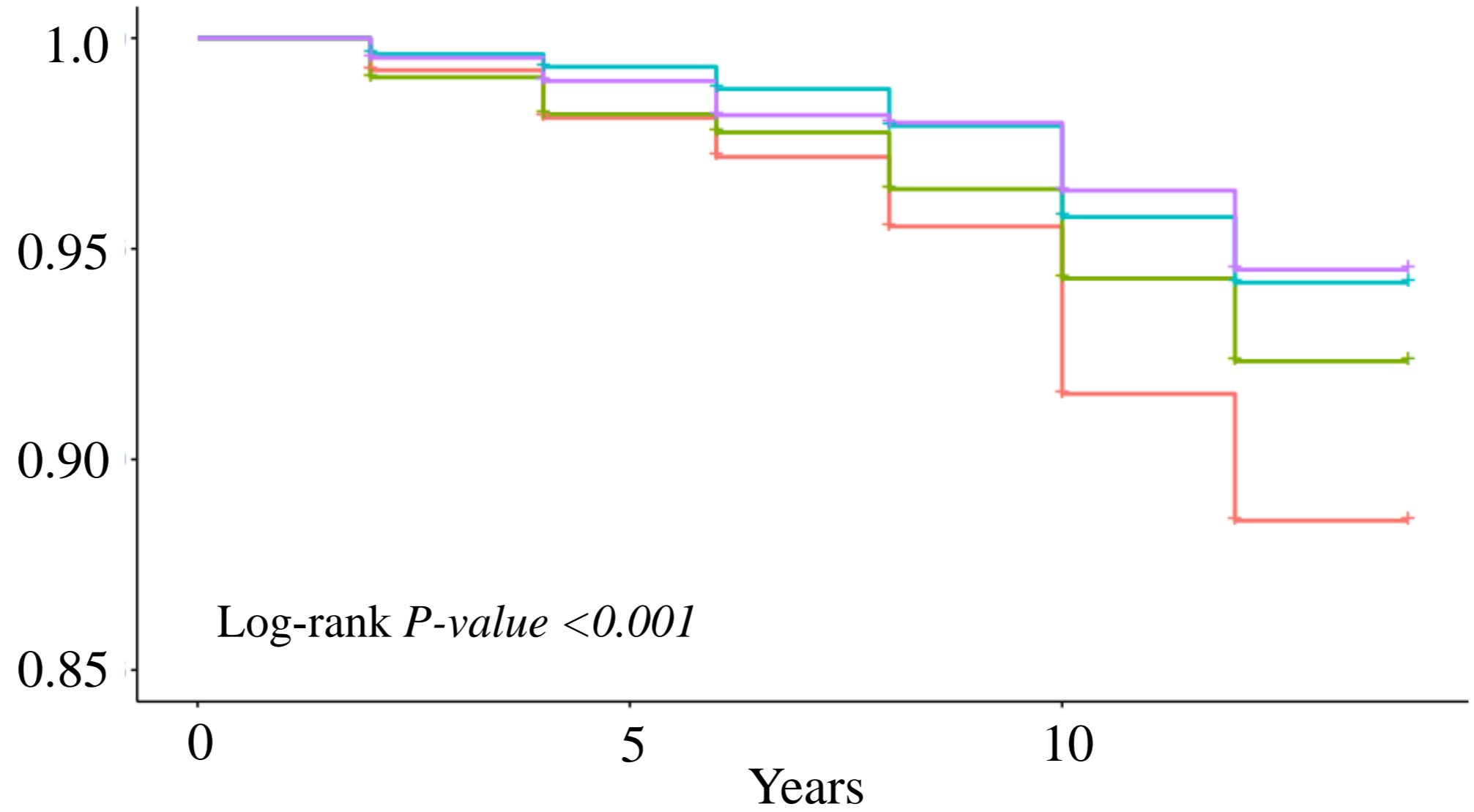
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**Figure 2.**

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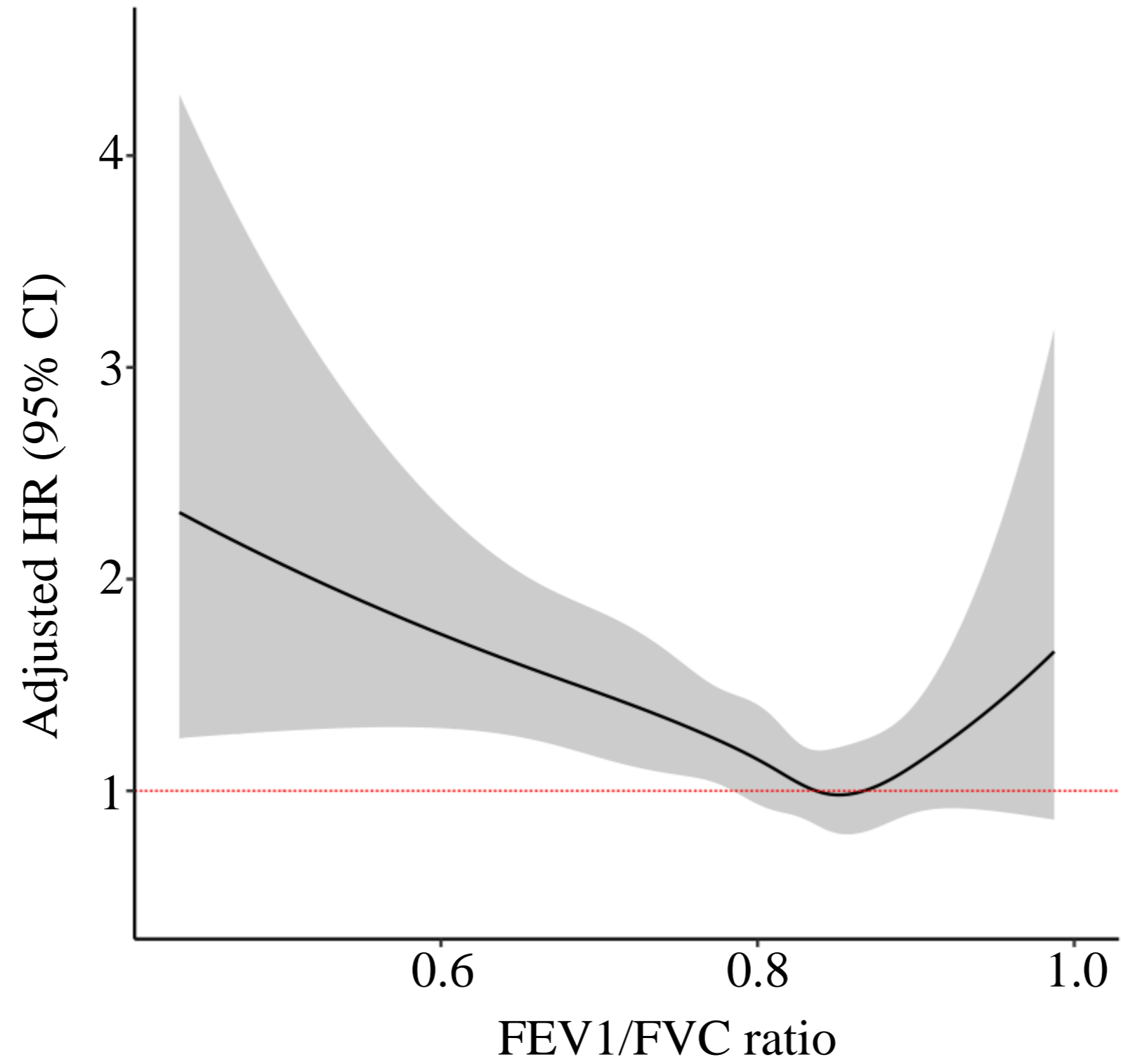
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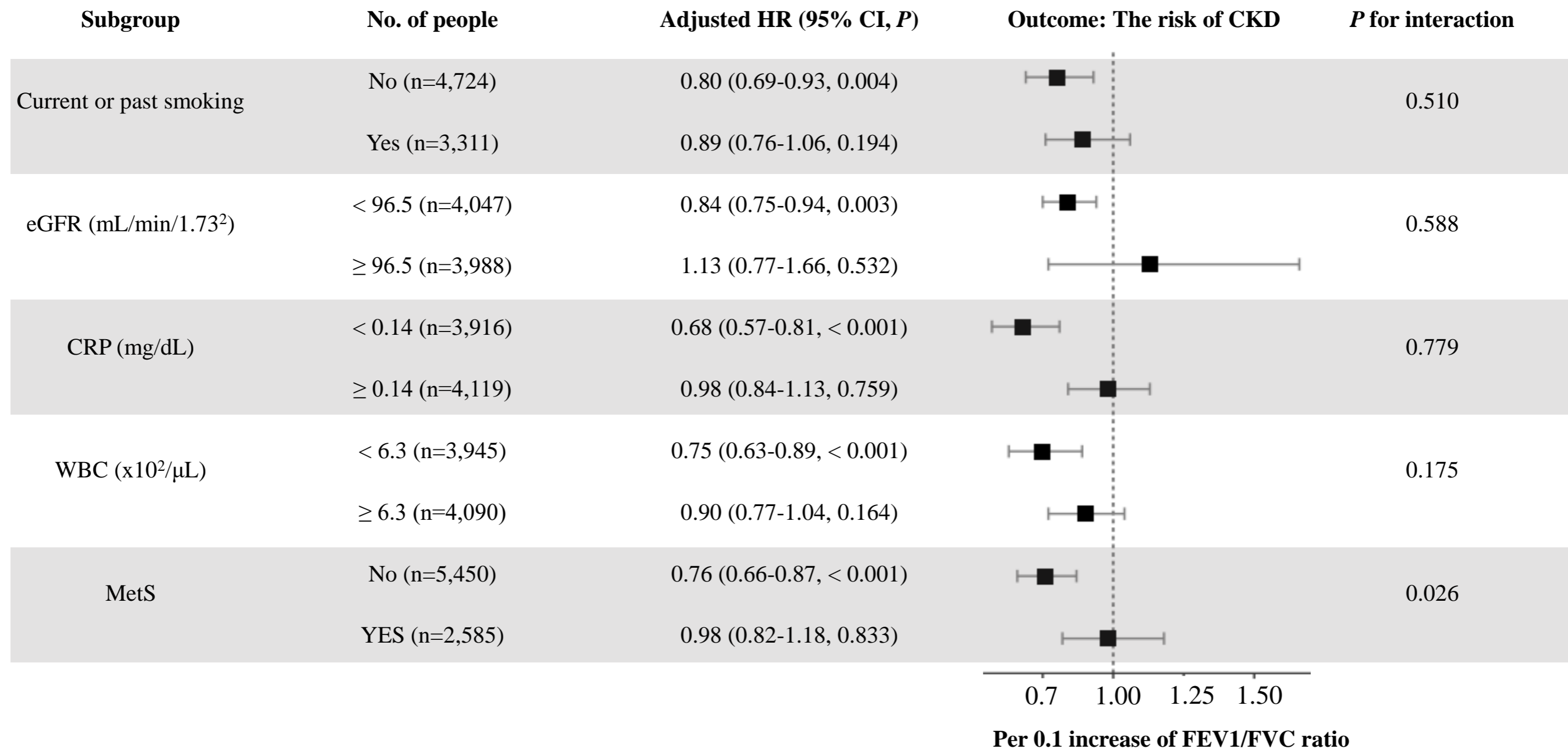


Numbers at risk

	0	5	10
Q1	1967	1690	1466
Q2	2044	1820	1635
Q3	2099	1888	1720
Q4	1925	1708	1582

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1 **Reporting checklist for cohort study.**  
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		Reporting Item	Page Number
<b>Title and abstract</b>			
Title	<a href="#">#1a</a>	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	<a href="#">#1b</a>	Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background / rationale	<a href="#">#2</a>	Explain the scientific background and rationale for the investigation being reported	4
Objectives	<a href="#">#3</a>	State specific objectives, including any prespecified hypotheses	5
<b>Methods</b>			
Study design	<a href="#">#4</a>	Present key elements of study design early in the paper	6
Setting	<a href="#">#5</a>	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Eligibility criteria	<a href="#">#6a</a>	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6
Eligibility criteria	<a href="#">#6b</a>	For matched studies, give matching criteria and number of exposed and unexposed	n/a (This is not a matched study.)
Variables	<a href="#">#7</a>	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources / measurement	<a href="#">#8</a>	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. Give information separately for for exposed and unexposed groups if applicable.	6-7
Bias	<a href="#">#9</a>	Describe any efforts to address potential sources of bias	8-9
Study size	<a href="#">#10</a>	Explain how the study size was arrived at	6
Quantitative variables	<a href="#">#11</a>	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7-9
Statistical methods	<a href="#">#12a</a>	Describe all statistical methods, including those used to control for confounding	8-9
Statistical methods	<a href="#">#12b</a>	Describe any methods used to examine subgroups and interactions	9
Statistical methods	<a href="#">#12c</a>	Explain how missing data were addressed	6



1	Statistical methods	<a href="#">#12d</a>	If applicable, explain how loss to follow-up was addressed	6
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3	Statistical methods	<a href="#">#12e</a>	Describe any sensitivity analyses	9
4				
5	<b>Results</b>			
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7	Participants	<a href="#">#13a</a>	Report numbers of individuals at each stage of study—eg numbers potentially	6
8			eligible, examined for eligibility, confirmed eligible, included in the study,	
9			completing follow-up, and analysed. Give information separately for for	
10			exposed and unexposed groups if applicable.	
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13	Participants	<a href="#">#13b</a>	Give reasons for non-participation at each stage	6
14				
15	Participants	<a href="#">#13c</a>	Consider use of a flow diagram	6
16				
17	Descriptive data	<a href="#">#14a</a>	Give characteristics of study participants (eg demographic, clinical, social) and	10
18			information on exposures and potential confounders. Give information	
19			separately for exposed and unexposed groups if applicable.	
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21	Descriptive data	<a href="#">#14b</a>	Indicate number of participants with missing data for each variable of interest	n/a (There was no
22				missing data in the
23				final analysis)
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26	Descriptive data	<a href="#">#14c</a>	Summarise follow-up time (eg, average and total amount)	10
27				
28	Outcome data	<a href="#">#15</a>	Report numbers of outcome events or summary measures over time. Give	10
29			information separately for exposed and unexposed groups if applicable.	
30				
31	Main results	<a href="#">#16a</a>	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and	10
32			their precision (eg, 95% confidence interval). Make clear which confounders	
33			were adjusted for and why they were included	
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36	Main results	<a href="#">#16b</a>	Report category boundaries when continuous variables were categorized	10
37				
38	Main results	<a href="#">#16c</a>	If relevant, consider translating estimates of relative risk into absolute risk for a	n/a (We didn't
39			meaningful time period	calculate relative
40				risk)
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43	Other analyses	<a href="#">#17</a>	Report other analyses done—e.g., analyses of subgroups and interactions, and	11
44			sensitivity analyses	
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46	<b>Discussion</b>			
47				
48	Key results	<a href="#">#18</a>	Summarise key results with reference to study objectives	11
49				
50	Limitations	<a href="#">#19</a>	Discuss limitations of the study, taking into account sources of potential bias or	13
51			imprecision. Discuss both direction and magnitude of any potential bias.	
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54	Interpretation	<a href="#">#20</a>	Give a cautious overall interpretation considering objectives, limitations,	11-12
55			multiplicity of analyses, results from similar studies, and other relevant	
56			evidence.	
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58	Generalisability	<a href="#">#21</a>	Discuss the generalisability (external validity) of the study results	14
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1 **Other**  
2 **Information**  
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4 Funding [#22](#) Give the source of funding and the role of the funders for the present study and, 14  
5 if applicable, for the original study on which the present article is based  
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For peer review only

# BMJ Open

## Obstructive spirometry pattern and the risk of chronic kidney disease: Analysis from the community-based prospective Ansan-Ansung cohort in Korea

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-043432.R1
Article Type:	Original research
Date Submitted by the Author:	25-Jan-2021
Complete List of Authors:	Kim, Sang Hyuk; Republic of Korea Army Headquarters, Medical service corps of 2nd armored brigade Kim, Hyeon Sam; Eulji Hospital, Internal Medicine Min, Hyang Ki; Eulji Hospital, Internal Medicine Lee, Sung Woo; Eulji Hospital, Internal Medicine
<b>Primary Subject Heading</b>:	Respiratory medicine
Secondary Subject Heading:	Renal medicine
Keywords:	Respiratory physiology < THORACIC MEDICINE, Chronic renal failure < NEPHROLOGY, Chronic airways disease < THORACIC MEDICINE

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4 **Obstructive spirometry pattern and the risk of chronic kidney disease: Analysis from the community-**  
5 **based prospective Ansan-Ansung cohort in Korea**  
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11 Sang Hyuk Kim<sup>1</sup>, Hyeon Sam Kim<sup>2</sup>, Hyang Ki Min<sup>2</sup>, and Sung Woo Lee<sup>2\*</sup>  
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17 *<sup>1</sup>Medical Service Corps of 2<sup>nd</sup> Armored Brigade, Republic of Korea Army, Paju, Korea.*  
18 *<sup>2</sup>Department of Internal*  
19 *Medicine, Nowon Eulji Medical center, Eulji University, Seoul, Korea.*  
20  
21

22  
23  
24 **\*Corresponding author:** Sung Woo Lee, MD, PhD  
25

26 Mailing address: Division of Nephrology, Department of Internal Medicine, Eulji Medical Center, 68,  
27 Hangeulbiseok-ro, Nowon-gu, Seoul, 01735, Korea  
28

29 Phone: +82-2-970-8205  
30

31 Fax: +82-2-971-8212  
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33 E-mail: neplsw@gmail.com  
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38 **Word count:** 2,853 words.  
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44 **Short title:** Obstructive spirometry pattern and CKD  
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50 **Keywords:** Respiratory physiology, obstructive spirometry pattern, chronic renal failure, chronic airways disease  
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## Abstract

**Objective:** There have been limited studies on the relationship between obstructive spirometry pattern and the development of chronic kidney disease (CKD). We investigated the association between obstructive spirometry pattern and incident CKD development in a large-scale prospective cohort study.

**Methods:** We reviewed the data of 7,960 non-CKD adults aged 40-69 years who participated in the Ansung-Ansan cohort, a prospective community-based cohort study. Pre-bronchodilation results for the ratio of forced expiratory volume per 1 second (FEV1) to forced vital capacity (FVC) were used as the primary exposure. The primary outcome was incident CKD, defined as the first event of an estimated glomerular filtration rate < 60 mL/min/1.73m<sup>2</sup>. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using multivariate Cox proportional hazard regression analysis.

**Results:** Over a mean follow-up period of 11.7 years, incident CKD developed in 511 subjects (6.4%). An increase of 0.1 in FEV1/FVC was associated with a decreased risk of incident CKD (HR 0.76, CI 0.68-0.84,  $P < 0.001$ ). Compared to the fourth quartile, the HR (95 % CI) of the first quartile of FEV1/FVC ratio was 1.81 (1.39-2.36,  $P < 0.001$ ). In the restricted cubic spline curve, the renal hazard associated with a decreased FEV1/FVC ratio was evident at FEV1/FVC values < 0.80, showing a U-shaped relationship. In subgroup analysis, the renal hazard associated with a decreased FEV1/FVC ratio was particularly evident in people without metabolic syndrome ( $P$  for interaction = 0.018).

**Conclusion:** Decreased FEV1/FVC ratio was independently associated with an increased risk of incident CKD development, particularly in people without metabolic syndrome. Future studies need to be conducted to confirm these results.

## Strengths and limitations of the study

The strength of our study is the prospective nature of this study with a large number of participants.

Our study is the only study to investigate the association between lung function and chronic kidney disease development using a non-linear analytic method.

The limitations are the observational nature of our study and only pre-bronchodilator measurements were used

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4 for analysis.  
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7 Another limitation is that generalization is limited because the study was conducted in a single country.  
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## 11 12 **Introduction** 13

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15 Airway obstruction which is commonly found in chronic respiratory diseases such as chronic obstructive  
16 pulmonary disease (COPD) and bronchial asthma (BA), can be objectively measured by pulmonary function  
17 tests.<sup>1 2</sup> Obstructive spirometry pattern is defined by a combination of the results of spirometry.<sup>3</sup> The main  
18 parameter that represents obstructive spirometry pattern is the ratio of forced expiratory volume per 1 second  
19 (FEV1) to forced vital capacity (FVC).<sup>4</sup> Many studies have revealed that lower FEV1/FVC ratios are associated  
20 with increased comorbidities and mortality.<sup>5-8</sup> Decreased FEV1/FVC ratios are also associated with increased  
21 incidence of atrial fibrillation,<sup>5</sup> heart failure<sup>6</sup> and type 2 diabetes mellitus.<sup>7</sup>  
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30 Chronic kidney disease (CKD) is one of the major chronic diseases in modern society, causing substantial  
31 medical expenses, chronic disease morbidity and mortality.<sup>9</sup> According to the 2011-2013 report, the total  
32 prevalence of CKD in adults aged more than 20 years was 8.2% in Korea.<sup>10</sup> The prevalence and incidence of CKD  
33 has been increasing worldwide, particularly in developing countries.<sup>11</sup> In addition, CKD is related to an increased  
34 incidence of mental disorders, including depression, dementia, and Parkinson's disease.<sup>12-14</sup> As a result,  
35 degradation of quality of life was commonly found in the CKD population.<sup>15</sup> Therefore, identification of factors  
36 associated with CKD and early intervention may be helpful in promoting public health.<sup>16</sup>  
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44 Several recent studies have reported the association between obstructive airway diseases and CKD.<sup>17-19</sup>  
45 Furthermore, the findings of obstructive spirometry pattern may also be associated with CKD.<sup>20-22</sup> Suzuki et al.  
46 reported that the prevalence of CKD increased with an increase in the obstructive spirometry grade.<sup>20</sup> Sumida et  
47 al. analyzed 14,946 participants of the Atherosclerosis Risk in Communities (ARIC) study and reported that the  
48 incidence of end-stage renal disease was higher in the lowest quartile of FEV1/FVC ratio than highest quartile  
49 with a hazard ratio (HR) and 95% confidence interval (CI) of 1.33 (1.03-1.73).<sup>21</sup> Although one Korean study also  
50 suggested that decreased FEV1/FVC ratio was associated with an increased risk of incident CKD, it was based on  
51 a single-center retrospective cohort, and the potential renal hazard associated with obstructive spirometry pattern  
52 needs to be tested in a prospective setting.<sup>22</sup> The aim of this study was, therefore, to investigate the relationship  
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4 between FEV1/FVC ratio and incident CKD using data from the community-based prospective Ansan-Ansung  
5 cohort in Korea.  
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## 11 **Methods**

### 12 **Participants**

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17 The Ansan-Ansung cohort was prospectively assessed to investigate factors affecting the incidence of chronic  
18 diseases in the Ansan (urban) and Ansung (rural) areas. The enrolled subjects were aged 40-69 years and lived in  
19 these 2 cities in Korea, and baseline measurements were performed between May 2001 and February 2003.  
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21 Participants were examined biennially after the baseline measurement. This community-based prospective cohort  
22 study is ongoing, and the last follow-up was conducted in 2015-2016. More detailed information about the Ansan-  
23 Ansung cohort can be found in previous reports.<sup>23</sup> In total, 10,030 people participated at the baseline. Out of  
24 10,030 subjects, we excluded 252 subjects with missing spirometry results, 114 subjects with missing smoking  
25 status, and 337 subjects with missing data for metabolic disorders. Of the remaining 9,327 subjects, 186 subjects  
26 with prevalent CKD, 189 subjects with baseline proteinuria defined as  $\geq 1+$  protein in dipstick urinalysis  
27 (URISCAN Pro II; YD Diagnostic Corp), 917 subjects missing serial creatinine measurements, and 75 subjects  
28 with prevalent chronic lung diseases were further excluded. Finally, 7,960 subjects were included in this study for  
29 analysis (Figure 1).  
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### 44 **Ethics statement**

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46 The Ansan-Ansung cohort complied with the Declaration of Helsinki. All participants provided informed  
47 consent and ethical approval was obtained from the institutional review boards of the Nowon Eulji Medical Center,  
48 Eulji University (IRB Number: 2019-06-014). All data were completely anonymized prior to access. Our study  
49 was also checked using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)  
50 Statement.<sup>24</sup>  
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### **Exposure**



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4 The main exposure of this study was the FEV1/FVC ratio, which was obtained by pre-bronchodilator testing  
5 using spirometry (VMAX2130; SensorMedics Corporation, Yorba, CA, USA). FEV1 and FVC were measured 3  
6 times and best scores were recorded by well-trained technicians. Percent-predicted FEV1 and FVC values were  
7 used to calculate the FEV1/FVC ratio, and the predicted FEV1 and FVC values used to calculate percent-predicted  
8 FEV1 and FVC values were derived from Korean formula.<sup>25</sup>  
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## 17 **Outcome**

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20 Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology  
21 Collaboration equation.<sup>26</sup> CKD was defined as eGFR < 60 ml/min/1.73m<sup>2</sup>. Prevalent CKD was defined as eGFR  
22 < 60 ml/min/1.73m<sup>2</sup> at the baseline measurement and incident CKD, a main outcome of this study, was defined  
23 as the first event of eGFR < 60 ml/min/1.73m<sup>2</sup>, which was confirmed at least 2 or more times and was maintained  
24 thereafter.  
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## 33 **Measurements and other definitions**

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36 A standard interview regarding the participants' socio-demographic status and lifestyle was conducted by  
37 trained interviewers. High income was defined as the highest quintile of monthly household income ( $\geq 3$  million  
38 won a month). Blood pressure (BP) was measured using a standard mercury sphygmomanometer (Baumanometer-  
39 Standby; W. A. Baum Co., Inc., Copiague, NY, USA), and the average BP on both arms was used as the  
40 representative BP measure. Body mass index (BMI) was calculated by dividing the weight by the square of the  
41 height (kg/m<sup>2</sup>). Waist circumference (WC) was measured at the narrowest point between the lower rib and the  
42 iliac crest (measured to the nearest 0.1 cm). Blood samples were examined for fasting for at least 8 hours.  
43 Hemoglobin levels and white blood cell (WBC) counts were analyzed using enzymatic methods with ADVIA 120  
44 (Bayer Diagnostics, Tarrytown, NY, USA). Fasting glucose (FG), triglyceride (TG), high-density lipoprotein  
45 cholesterol (HDL-C), C-reactive protein (CRP), serum creatinine and blood urea nitrogen (BUN) levels were  
46 measured using ADVIA 1650 (Siemens, Tarrytown, NY, USA). Five components of metabolic syndrome (MetS)  
47 were defined according to the recommendations of the International Diabetes Federation.<sup>27</sup> First, elevated BP was  
48 defined as a systolic BP  $\geq 130$ mmHg, a diastolic BP  $\geq 85$ mmHg, treatment with anti-hypertensive drugs, or a  
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4 previous diagnosis of hypertension by a physician. Second, elevated FG was defined as an FG level of  $\geq 100$   
5 mg/dL, treatment with insulin or oral anti-diabetic drugs, or a previous diagnosis of diabetes by a physician. Third,  
6 increased TG was defined as TG  $\geq 150$  mg/dL, treatment with anti-dyslipidemic drugs, or a previous diagnosis of  
7 dyslipidemia by a physician. Fourth, reduced HDL-C levels were defined as HDL-C  $< 40$  mg/dL in men and  $<$   
8 50 mg/dL in women. Finally, central obesity was defined as WC  $\geq 90$  cm in men and  $\geq 80$  cm in women. MetS was  
9 defined as three or more of the five MetS components.<sup>28</sup>  
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### 20 **Statistical analyses**

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22 All statistical analyses were performed using R version 3.6.2 (R core Team 2019; R foundation for Statistical  
23 Computing, Vienna, Austria). Histograms and Q-Q plots were used to evaluate the normality of continuous  
24 variables. Normally distributed continuous variables were expressed as mean  $\pm$  standard deviation (SD). Non-  
25 normally distributed continuous variables were described as medians with interquartile ranges (IQR). The *P*-trend  
26 was analyzed using linear regression for the normally distributed continuous variables, Jonckheere-Terpstra test  
27 for the non-normally distributed continuous variables, and the Cochran-Armitage test for the categorical variables.  
28 Survival curves were analyzed using Kaplan-Meier estimates, and differences among groups were tested using  
29 the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional  
30 hazards regression analysis. Both analyses were performed with the 'survival' package. In the Kaplan-Meier  
31 survival curve, the mean survival time of each FEV1/FVC ratio quartile group was truncated at 14 years and  
32 analyzed using the restricted mean survival time function with the 'survRM2' package. The proportional hazards  
33 assumption was verified by goodness-of-fit tests. All variables except age satisfied the proportional risk  
34 assumption. As a result, Cox proportional hazard regression analysis was performed without adjustment for age  
35 and Kaplan-Meier survival curve by age was presented (Figure S1). Potential non-linear relationships between  
36 obstructive spirometry pattern and incident CKD were evaluated using restricted cubic spline curve analysis with  
37 the 'rms' package. A *P* value of  $< 0.05$  was considered statistically significant. Subgroup analysis was performed  
38 on clinically important variables, and continuous variables were divided into median values. Sensitivity analysis  
39 was presented using multivariate Cox regression analysis for percent-predicted FEV1 and FVC.  
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### **Patient and public involvement**

Cohort data managed by the Korea Center for Disease Control and Prevention (KCDC) was provided anonymously. Patient and public were not involved in the design of this study. The result will not be disseminated to participants.

## Results

The 7,960 subjects had a mean  $\pm$  SD age of  $51.7 \pm 8.7$  years, and the proportions of men and current smokers were 48.2% and 41.1%, respectively. Mean  $\pm$  SD BMI, WC, systolic BP, diastolic BP, and HDL-C level were  $24.6 \pm 3.1$  kg/m<sup>2</sup>,  $82.6 \pm 8.7$  cm,  $120.9 \pm 18.1$  mmHg,  $80.2 \pm 11.4$  mmHg, and  $44.7 \pm 9.9$  ml/dL, respectively, and median (IQR) of FG and TG levels were 82 (77-90) mg/dL and 134 (99-187) mg/dL, respectively. The mean  $\pm$  SD of FEV1/FVC ratio, FEV1, and FVC were  $0.80 \pm 0.08$ ,  $96.9 \pm 14.1\%$ -predicted, and  $96.9 \pm 13.1\%$ -predicted, respectively. Mean  $\pm$  SD baseline creatinine was  $0.8 \pm 0.2$  mL/min/1.73m<sup>2</sup>. During a mean 11.7 years' follow-up, incident CKD developed in 511 subjects (6.4%).

The first through fourth quartiles of the FEV1/FVC ratio were  $< 0.76$ ,  $0.76-0.80$ ,  $0.81-0.84$ , and  $\geq 0.85$ , respectively. The baseline characteristics of the study according to the FEV1/FVC ratio quartiles are depicted in Table 1. As the FEV1/FVC ratio quartile decreased, the proportions of men and current smokers increased, while the proportions of high-income and college graduates decreased. Although BMI and the HDL-C level decreased, systolic BP, diastolic BP, and WC increased as the FEV1/FVC ratio quartile decreased. With the reduction in the FEV1/FVC ratio quartile, WBC, CRP, hemoglobin, creatinine and FVC increased, while FEV1 decreased.

We explored the potential hazard of the FEV1/FVC ratio quartile on the development of incident CKD. In the Kaplan-Meier survival curve (Figure 2), the mean (95% CI) CKD-free survival was 13.4 (13.3-13.5) years in Q1, 13.6 (13.5-13.6) years in Q2, 13.7 (13.7-13.8) years in Q3, and 13.7 (13.6-13.8) years in Q4 (log-rank  $P < 0.001$ ). In multivariate Cox proportional hazard regression analysis (Table 2), a 0.1-unit increase in FEV1/FVC ratio was associated with decreased hazard of incident CKD development: HR (95% CI) of 0.73 (0.66-0.82,  $P < 0.001$ ). Compared to the fourth quartile, the HR (95% CI) of the first quartile of the FEV1/FVC ratio was 1.81 (1.39-2.36,  $P < 0.001$ ). In restricted cubic spline curve analysis (Figure 3), as FEV1/FVC ratio decreased, HR (95% CI) for incident CKD development increased, showing a U-shaped relationship and the negative relationship was obvious for FEV1/FVC  $< 0.80$ . However, unlike the FEV1/FVC ratio, FEV1 was not associated with the development of incident CKD in the sensitivity analysis (Table S1).

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3 In the subgroup analysis, MetS modified the effect of the FEV1/FVC ratio on incident CKD development (Figure  
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5 4). In detail, although an increased FEV1/FVC ratio was not associated with incident CKD development in people  
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7 with MetS, it was independently associated with incident CKD development in those without MetS. There were  
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9 no subgroups showing statistically significant effect modification. However, younger age, low baseline eGFR,  
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11 and raised FG were not valid subgroups for the for the relationship between FEV1/FVC ratio and CKD  
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13 development (Table S2).  
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For peer review only

**Table 1. Clinical characteristics of the study population according to the FEV1/FVC ratio quartile.**

	FEV1/FVC ratio groups (n = 7,960)				P-trend
	1Q: <0.76 (n = 1,935)	2Q: 0.76-0.80 (n = 2,027)	3Q: 0.81-0.84 (n = 2,088)	4Q: ≥0.85 (n = 1,910)	
Age (years)	55.93 ± 8.66	52.41 ± 8.50*	50.09 ± 7.98*†	48.47 ± 7.81*†‡	<0.001
Male, n (%)	1,290 (66.67%)	1,040 (51.31%)*	854 (40.90%)*†	651 (34.08%)*†‡	<0.001
High income, n (%)	230 (11.89%)	384 (18.94%)*	433 (20.74%)*	383 (20.05%)*	<0.001
College graduate, n (%)	189 (9.77%)	283 (13.96%)*	360 (17.24%)*†	273 (14.29%)*‡	<0.001
Current smoker, n (%)	1167 (60.31%)	893 (43.06%)*	691 (33.09%)*†	519 (27.17%)*†‡	<0.001
BMI (kg/m <sup>2</sup> )	24.02 ± 3.00	24.80 ± 2.98*	24.94 ± 3.01*	24.60 ± 3.34*‡	<0.001
SBP (mmHg)	123.80 ± 18.41	121.24 ± 17.82*	119.66 ± 17.96*†	118.80 ± 17.92*†	<0.001
DBP (mmHg)	81.72 ± 11.09	80.32 ± 11.16*	79.65 ± 11.40*	78.98 ± 11.65*†	<0.001
Waist circumference (cm)	83.31 ± 8.04	83.60 ± 8.44	82.54 ± 8.73*†	80.96 ± 9.20*†‡	<0.001
Fasting glucose (mg/dL)	82 (77-90)	82 (77-91)	82 (78-90)	82 (77-89)	0.390
Triglyceride (mg/dL)	139 (103-191)	141 (104-198)	133 (98-186)*†	127 (94-177)*†‡	<0.001
HDL-cholesterol (mg/dL)	44.45 ± 9.87	44.33 ± 9.91	44.66 ± 9.72	45.50 ± 10.15*†‡	<0.001
Creatinine (mg/dL)	0.85 ± 0.17	0.84 ± 0.17	0.83 ± 0.17*	0.81 ± 0.16*†‡	<0.001
Hemoglobin (g/dL)	13.97 ± 1.45	13.74 ± 1.57*	13.45 ± 1.63*†	13.32 ± 1.53*†	<0.001
WBC count (×10 <sup>3</sup> /μL)	6.70 ± 1.83	6.51 ± 1.77*	6.43 ± 1.73*	6.38 ± 1.73*†	<0.001
CRP (mg/dL)	0.15 (0.07-0.26)	0.14 (0.06-0.23)*	0.13 (0.06-0.24)*	0.14 (0.06-0.23)*	<0.001
FEV1 (%-predicted)	87.89 ± 14.59	97.35 ± 12.58*	100.25 ± 12.18*†	101.98 ± 12.53*†‡	<0.001

FVC (%-predicted)	98.24 ± 14.05	98.24 ± 12.90	97.22 ± 12.24	93.96 ± 12.72*†‡	<0.001
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Values are expressed as mean ± standard deviation for normally distributed continuous variables, median and interquartile range for non-normally distributed variables and percentage for categorical variables. *P*-trend was analyzed normally distributed continuous variables by ANOVA, for non-normally distributed continuous variable by Jonckheere-Terpstra tests, and for categorical variables by Cochran-Armitage test for trend. \*, †, and ‡ meant *P* < 0.05 when compared to < 0.76, 0.76-0.81, 0.81-0.85 groups of FEV1/FVC ratio, respectively, using Bonferroni post-hoc analysis of one-way ANOVA for normally distributed continuous variables, Mann-Whitney U tests for non-normally distributed continuous variable, and chi-square tests for categorical variables. Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; WBC, white blood cells; CRP, C-reactive protein.

**Table 2. Hazard of FEV1/FVC ratio on incident CKD development.**

	Univariate	Model 1	Model 2
	HR (95% CI, <i>P</i> -value)	HR (95% CI, <i>P</i> -value)	HR (95% CI, <i>P</i> -value)
FEV1/FVC ratio: 0.1-unit increase	0.69 (0.63-0.76, < 0.001)	0.65 (0.59-0.72, < 0.001)	0.73 (0.66-0.82, < 0.001)
FEV1/FVC ratio quartile			
1Q: < 0.76 (n=1,935)	2.13 (1.66-2.75, < 0.001)	2.35 (1.82-3.05, < 0.001)	1.81 (1.39-2.36, < 0.001)
2Q: 0.76-0.80 (n=2,027)	1.45 (1.11-1.89, 0.006)	1.49 (1.14-1.95, 0.003)	1.31 (1.00-1.72, 0.047)
3Q: 0.81-0.84 (n=2,088)	1.05 (0.79-1.39, 0.742)	1.05 (0.79-1.40, 0.720)	0.96 (0.7-1.27, 0.765)
4Q: ≥ 0.85 (n=1,910)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)

Model 1: adjustment for sex and BMI. Model 2: model 1 + adjustment for college graduate, high income, smoking status, systolic and diastolic BP, waist circumference, fasting glucose, triglyceride, HDL-cholesterol, creatinine, hemoglobin level, WBC count, and CRP. Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; CKD, chronic kidney disease; HR, hazard ratio; CI, confidence interval; BMI, body mass index; HDL, high density lipoprotein; CRP, C-reactive protein; BP, blood pressure; WBC, white blood cell.

## Discussion

Obstructive lung disease and CKD are both important chronic diseases in the modern world.<sup>9 29</sup> Several recent studies have shown the relationship between obstructive lung disease and CKD.<sup>17 30</sup> Chen et al. reported that the overall incidence of CKD was higher in the COPD group (287.52 per 104 person-years vs. 470.9 per 104 person-years).<sup>30</sup> Huang et al. found that BA patients were more likely to develop CKD (HR 1.56, CI 1.48-1.64,  $P < 0.001$ ).<sup>17</sup> The FEV1/FVC ratio called the Tiffeneau-pinelli index, has been used worldwide as a screening index for diagnosing obstructive lung disease. The FEV1/FVC ratio is an easily applicable index because it does not require calculation of the predicted value.<sup>3 18</sup> Since only a few studies have evaluated the usefulness of the FEV1/FVC ratio in predicting future incident CKD development, we performed the current study and identified that a decreased FEV1/FVC ratio was independently associated with incident CKD development in a community-dwelling general population.

In this study, a 0.1 unit increase in the FEV1/FVC ratio was associated with a 16% lower risk of developing incident CKD. In comparison with patients showing FEV1/FVC  $\geq 0.85$  (highest quartile), those with an FEV1/FVC ratio  $< 0.76$  (lowest quartile) showed a 35% higher risk of developing incident CKD. However, those in the second and third quartiles did not show a statistically significant renal hazard, suggesting a non-linear relationship between the FEV1/FVC ratio and incident CKD development. Therefore, we performed restricted cubic spline curve analysis and found that the renal hazard of association with decreased FEV1/FVC was evident at FEV1/FVC  $< 0.80$ . Furthermore, the renal hazard was increased proportionally with the decrease in FEV1/FVC, suggesting that FEV1/FVC can be used not only as a screening index, but also as a severity index, particularly in predicting future CKD development.

In contrast, however, percent-predicted FEV1 which is traditionally used as a severity index for obstructive lung disease, was not associated with incident CKD development. This may be because of possible inaccuracies in the prediction method attribute to race, age, and gender.<sup>31</sup> We used the formula proposed in 2005 based on the Korean population, but the demographics of Korea have been changed dramatically over the last 15 years. Thus, a new estimation formula based on new demographics will be needed.<sup>32</sup> In addition, the aging process and underlying diseases can falsely reduce FEV1 values due to respiratory muscle weakness, but the FEV1/FVC ratio was not affected by those confounders.<sup>33</sup> Therefore, for a population with a low prevalence of airway obstruction, including this cohort, the FEV1/FVC ratio may be a more suitable index for predicting incident CKD than absolute

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4 FEV1 values. The FEV1/FVC ratio was particularly evident in groups without metabolic derangements. This  
5 means that spirometry patterns in individuals with metabolic disorders may differ from those in healthy population.  
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8 We propose that FEV1/FVC ratio can be used as a spirometric index to be associated with future CKD  
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10 development in a relatively healthy population.  
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13 To date, there have been no exact mechanisms for the potential renal hazard of airway obstruction. One possible  
14 explanation is the chronic hypoxia induced by airway obstruction. Chronic hypoxia may cause hypoxic renal  
15 damage, which is related to a decline in kidney function.<sup>34</sup> Atherosclerosis, a risk factor for CKD, is also associated  
16 with chronic hypoxia.<sup>35</sup> The systemic inflammation in obstructive lung diseases, including increased levels of  
17 tumor necrosis factor  $\alpha$  and interleukin 6, may cause vascular calcification and protein-energy wasting, which can  
18 ultimately result in CKD development.<sup>36</sup>  
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26 Our study has several strengths. First, to our knowledge, this is the first prospective study using the FEV1/FVC  
27 ratio as the main index to predict CKD development. Second, a large number of participants and many  
28 confounders for the incident CKD were adjusted in this study. Third, using a non-linear analytic method, we found  
29 that incident CKD and the FEV1/FVC ratio had a U-shaped relationship. The upper limit of FEV1/FVC is not  
30 clear, but most of those with FEV1/FVC above 0.9 had a decreased FVC % predicted. Neuromuscular disorders  
31 may cause high FEV1/FVC and be associated with incident CKD. Further study will be needed to clarify the  
32 clinical significance of high FEV1/FVC. This study also had several limitations. First, this was an observational  
33 study. Therefore, a causal relationship could not be ascertained, and the results should be interpreted with caution.  
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35 Second, because of the large number of participants, we only obtained pre-bronchodilator measurements. Third,  
36 age was not included in the adjustment of Cox proportional hazard regression analysis. Age cannot be adjusted  
37 due to extreme violation of the proportional risk assumption. However, age was used to adjust for incident CKD.  
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39 The superiority of further adjustment for already adjusted variable is not clear. Repeated adjustment of same  
40 variable can cause bias.<sup>37</sup> Because of the low prevalence of airway diseases, however, we assumed that this  
41 limitation has little effect on the study results. Finally, the generalizability of the results is limited because the  
42 study was conducted in a single country with a single ethnicity.  
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55 In conclusion, decreased FEV1/FVC ratio was an independent risk factor for future CKD development. The  
56 relationship of this findings with incident CKD development was particularly valid in a relatively healthy  
57 population, suggesting that it may serve as an early predictor for CKD development. Future studies need to be  
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4 conducted to confirm the results of this study.  
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**Author's Contribution:** Conceptualization, S.W.L.; Data curation/Formal analysis, S.H.K.; Investigation/Methodology, H.S.K.; Writing – original draft, S.H.K.; Writing – review & editing– H.K.M.; Supervision/Validation – S.W.L. All authors read and approved the final manuscript.

**Funding:** This study was supported by the National Research Foundation of Korea (Grant No: NRF-2016R1A6A3A11933465).

**Competing Interests:** None declared.

**Patient consent:** Not required.

**Ethics approval:** Ethics approval was obtained from Ethical Committee of Eulji Medical Center, Seoul, Korea.

**Data sharing statement:** The data of our study is fully available when manuscript is accepted for publication.

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## Figure legends

**Figure 1. Flow chart of the study subject selection.** Abbreviation: CKD, chronic kidney disease.

**Figure 2. Kaplan-Meier CKD-free survival curves among four groups defined by the FEV1/FVC ratio.**

Abbreviations: CKD, chronic kidney disease; FEV1, forced expiratory volume in 1 second; FVC, functional vital capacity; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4.

**Figure 3. Restricted cubic splines curve of Cox proportional hazards regression analysis according to the**

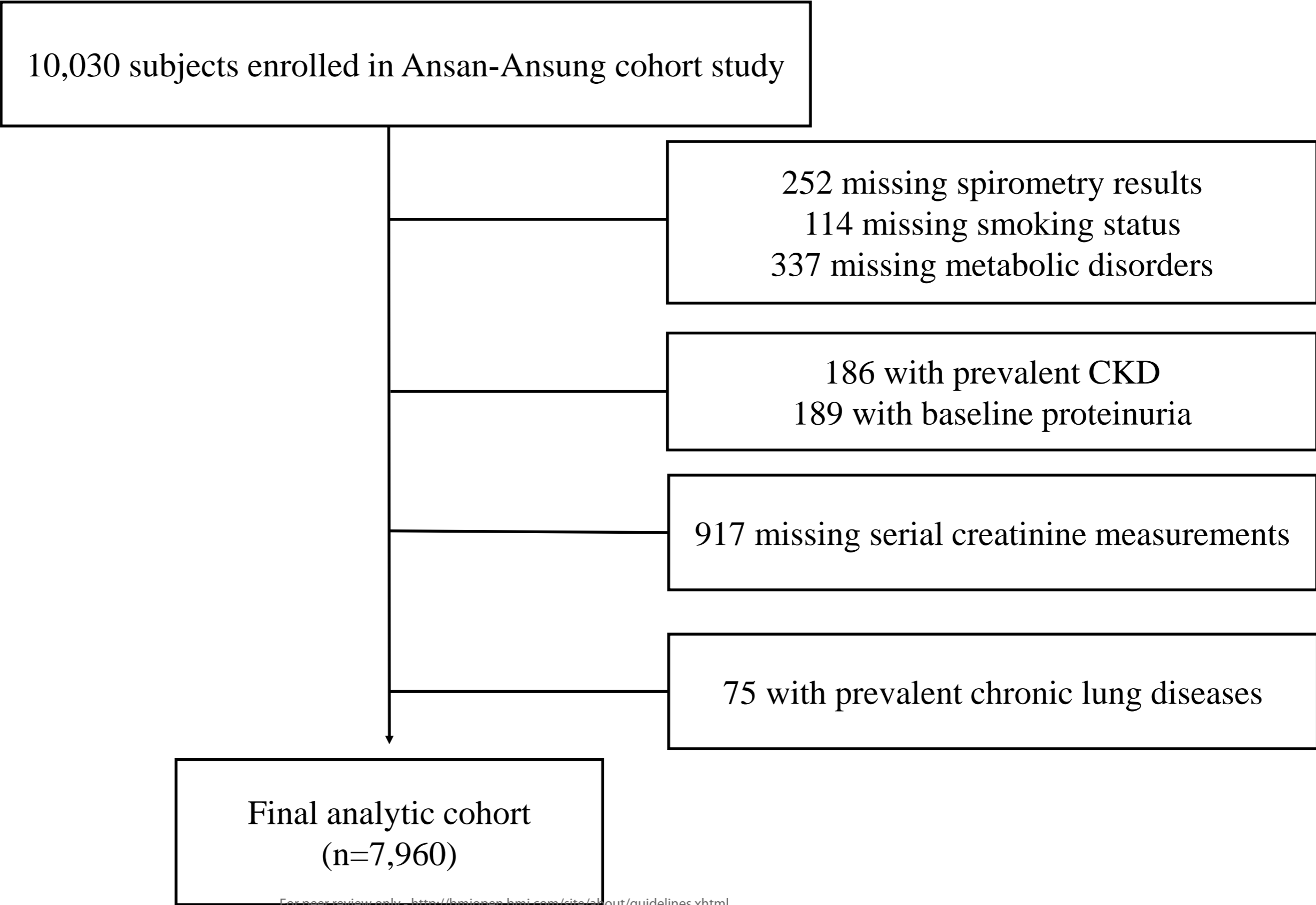
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4 **FEV1/FVC ratio.** All covariates of model 2 shown in table 2 were used for adjustment. The solid line indicates  
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6 the calculated line of association between the FEV1/FVC ratio and estimated hazard ratio. The shaded region  
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8 represents the 95% confidential intervals for value of hazard ratio according to the FEV1/FVC ratio.  
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10 Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, functional vital capacity.

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15 **Figure 4. Subgroup analysis for the relationship between the FEV1/FVC ratio and the risk of incident CKD.**

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17 Adjusted beta and 95% CI were analyzed using Cox proportional hazards regression analysis. All covariates of  
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19 model 2 shown in table 2 were used to adjustment. Abbreviations: FEV1, forced expiratory volume in 1 second;  
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21 FVC, functional vital capacity; CKD, chronic kidney disease; BMI, body mass index; MetS, metabolic syndrome;  
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23 HR, hazard ratio; CI, confidence interval.

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28 **Figure S1. Kaplan-Meier CKD-free survival curves among four groups defined by age.** Abbreviations: CKD,

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30 chronic kidney disease; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4.  
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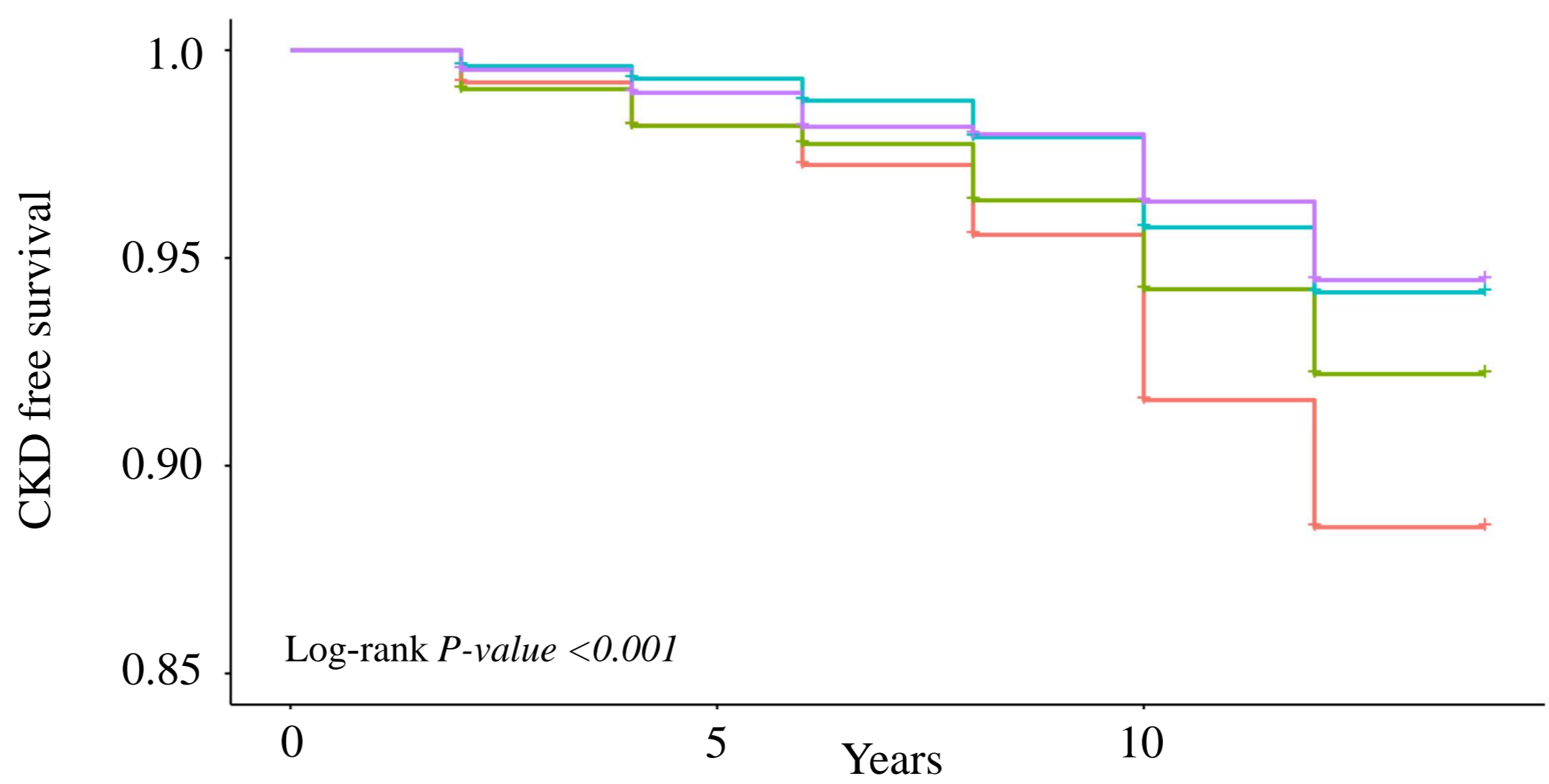


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**Figure 2.**

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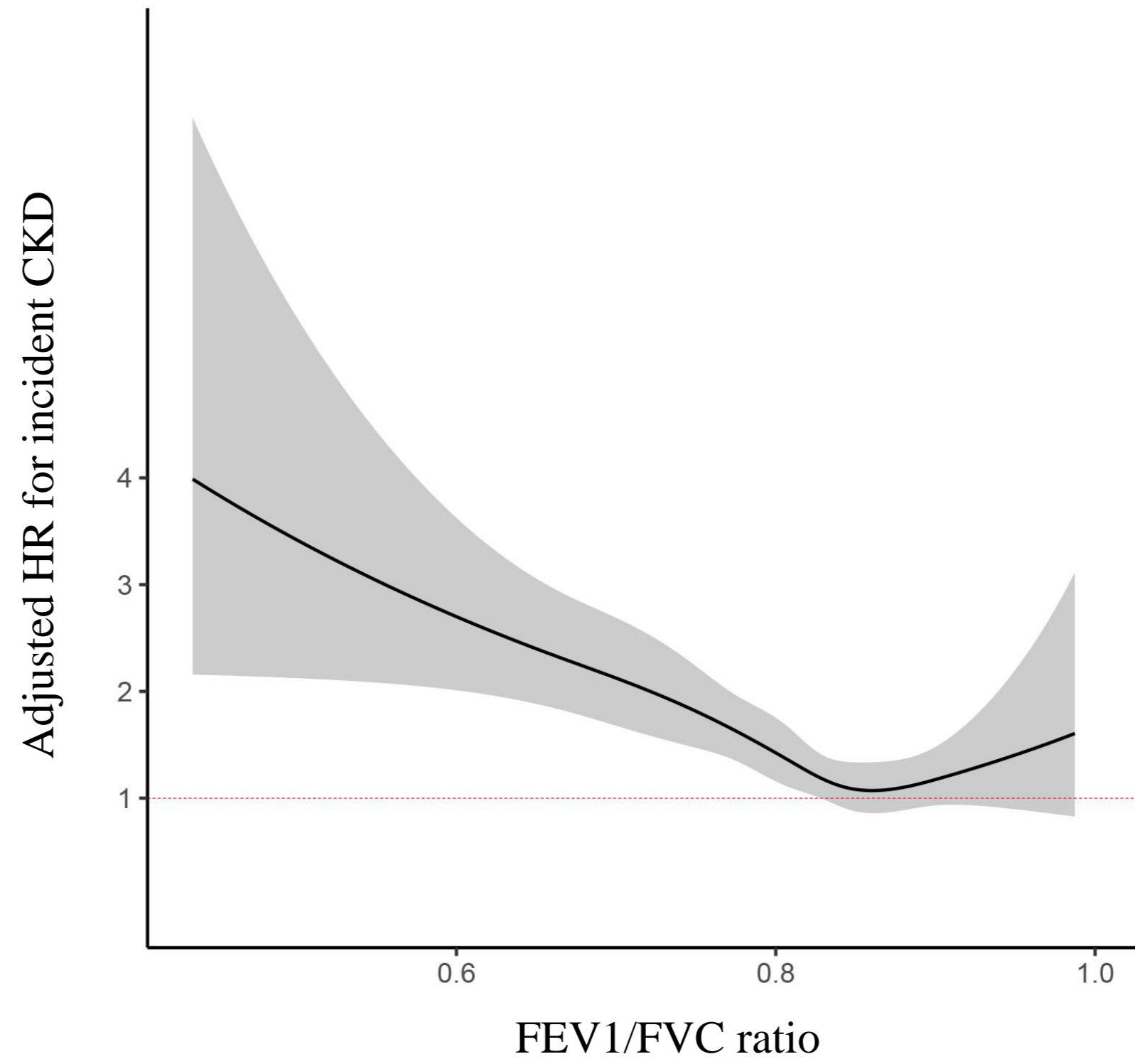


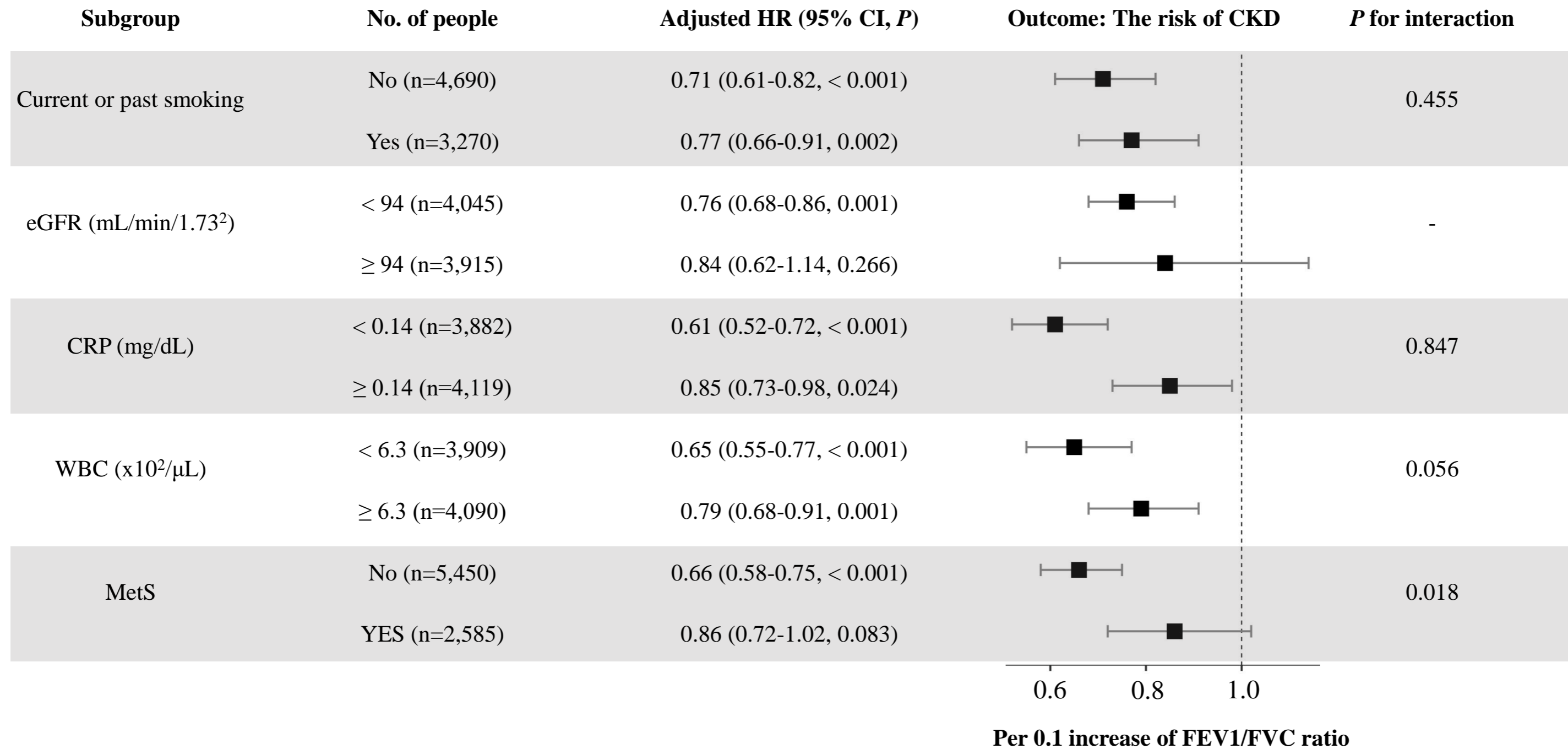
Numbers at risk

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Q1	1935	1660	1441
Q2	2027	1805	1622
Q3	2088	1880	1713
Q4	1910	1696	1572

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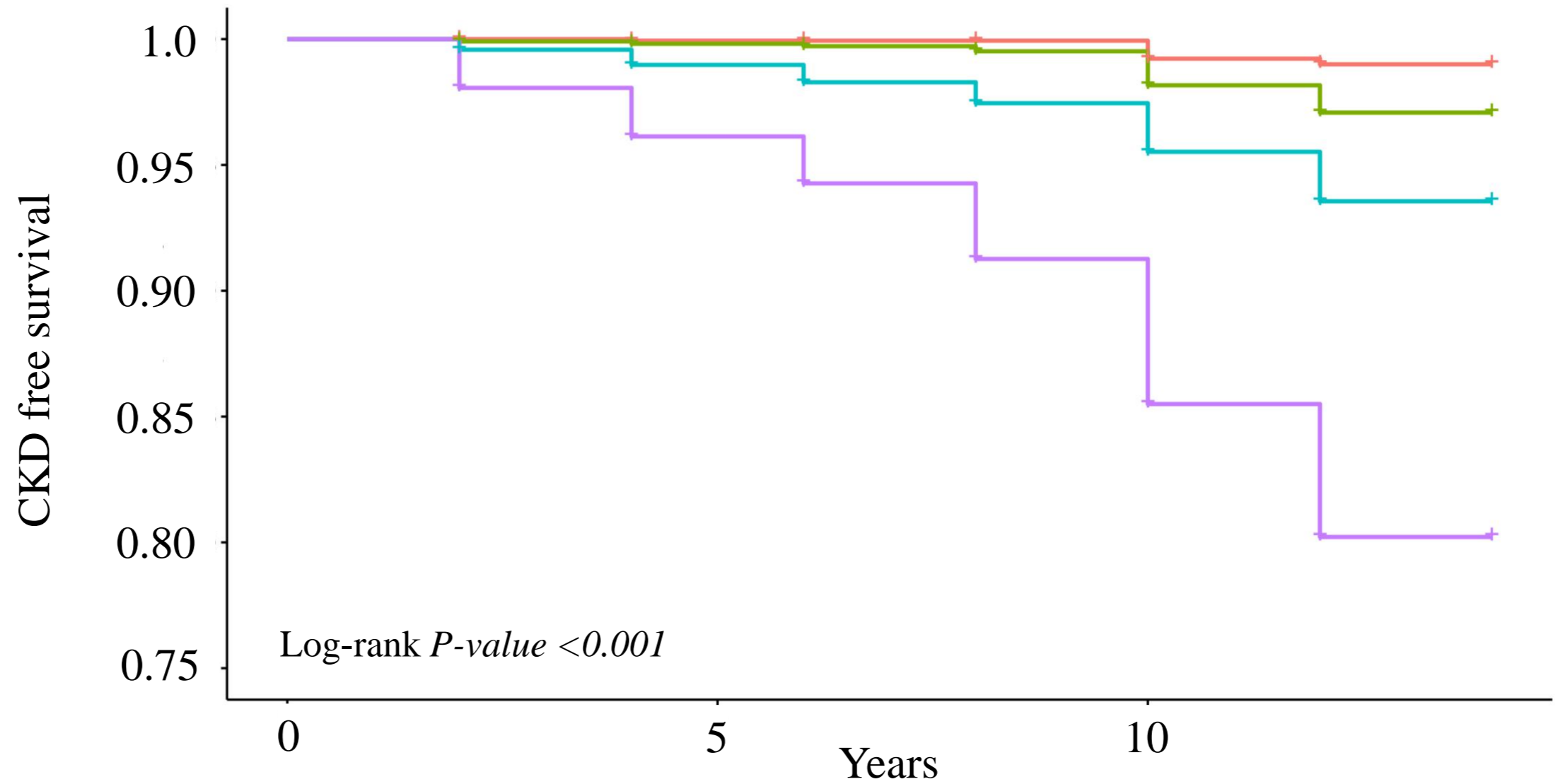






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Numbers at risk

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Q1	1729	1516	1399
Q2	2211	2051	1913
Q3	1904	1722	1564
Q4	2116	1752	1472

Years

**Table S1. Sensitivity analysis for the relationship between the %-predicted FEV1, FVC and the risk of incident CKD**

	Univariate	Model 1	Model 2
	HR (95% CI, <i>P</i> -value)	HR (95% CI, <i>P</i> -value)	HR (95% CI, <i>P</i> -value)
<b>%-predicted FEV1</b>			
1Q: < 88 %-predicted (n=1,985)	1.58 (1.23-2.03, < 0.001)	1.64 (1.25-2.08, < 0.001)	1.28 (0.99-1.65, 0.061)
2Q: 88-96 %-predicted (n=2,067)	1.26 (0.98-1.63, 0.074)	1.27 (0.98-1.65, 0.067)	1.16 (0.89-1.50, 0.277)
3Q: 97-105 %-predicted (n=2,002)	1.14 (0.88-1.48, 0.308)	1.15 (0.89-1.49, 0.296)	1.09 (0.84-1.41, 0.533)
4Q: 106 %-predicted (n=1,906)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
<b>%-predicted FVC</b>			
1Q: < 89 %-predicted (n=2,045)	2.19 (1.69-2.84, < 0.001)	2.16 (1.66-2.81, < 0.001)	1.68 (1.29-2.19, < 0.001)
2Q: 89-96 %-predicted (n=1,949)	1.71 (1.30-2.25, < 0.001)	1.70 (1.29-2.23, < 0.001)	1.52 (1.15-2.00, 0.003)
3Q: 97-104 %-predicted (n=1,911)	1.48 (1.12-1.95, 0.006)	1.48 (1.12-1.95, 0.006)	1.34 (1.01-1.77, 0.042)
4Q: 105 %-predicted (n=2,055)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)

Model 1: adjustment for sex and BMI. Model 2: model 1 + adjustment for college graduate, high income, smoking status, systolic and diastolic BP, waist circumference, fasting glucose, triglyceride, HDL-cholesterol, creatinine, hemoglobin level, WBC count, and CRP. Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; CKD, chronic kidney disease; HR, hazard ratio; CI, confidence interval; BMI, body mass index; HDL, high density lipoprotein; CRP, C-reactive protein; BP, blood pressure; WBC, white blood cell.

**Table S2. Additional subgroup analysis for the relationship between the FEV1/FVC ratio and the risk of CKD.**

Subgroup	No. of people	Per 0.1 increase of FEV1/FVC ratio	
		Adjusted HR (95%CI, <i>P</i> )	<i>P</i> for interaction
Age	< 50 (n=3,940)	0.81 (0.56-1.17, 0.267)	-
	≥ 50 (n=4,020)	0.85 (0.75-0.96, 0.007)	
Sex	Male (n=3,835)	0.74 (0.63-0.86, < 0.001)	0.632
	Female (n=4,125)	0.74 (0.63-0.86, < 0.001)	
BMI	< 25 (n=4,539)	0.68 (0.59-0.77, < 0.001)	0.054
	≥ 25 (n=3,421)	0.79 (0.65-0.95, 0.012)	
Central obesity	No (n=4,866)	0.72 (0.62-0.83, < 0.001)	0.657
	Yes (n=3,094)	0.76 (0.64-0.89, 0.001)	
Raised TG	No (n=4,627)	0.74 (0.64-0.86, < 0.001)	0.513
	Yes (n=3,333)	0.73 (0.63-0.86, < 0.000)	
Reduced HDL-C	No (n=3,695)	0.67 (0.58-0.78, < 0.001)	0.437
	Yes (n=4,265)	0.79 (0.68-0.92, 0.003)	
Raised BP	No (n=4,560)	0.63 (0.53-0.74, < 0.000)	0.028
	Yes (n=3,400)	0.80 (0.70-0.92, 0.002)	
Raised FG	No (n=7,025)	0.71 (0.63-0.79, < 0.000)	0.060
	Yes (n=935)	0.93 (0.70-1.24, 0.616)	

Adjusted beta and 95% CI were analyzed using multivariate Cox proportional hazards regression analysis. All covariates of model 2 shown in table 2 were used to adjustment. Variable used to divide subgroups was excluded from the adjustment. Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, functional vital capacity; CKD, chronic kidney disease; BMI, body mass index; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; BP, blood pressure; FG, fasting glucose; HR, hazard ratio; CI, confidence interval.

**Reporting checklist for cohort study.**

		Reporting Item	Page Number
<b>Title and abstract</b>			
Title	<a href="#">#1a</a>	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	<a href="#">#1b</a>	Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background / rationale	<a href="#">#2</a>	Explain the scientific background and rationale for the investigation being reported	4
Objectives	<a href="#">#3</a>	State specific objectives, including any prespecified hypotheses	5
<b>Methods</b>			
Study design	<a href="#">#4</a>	Present key elements of study design early in the paper	6
Setting	<a href="#">#5</a>	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Eligibility criteria	<a href="#">#6a</a>	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6
Eligibility criteria	<a href="#">#6b</a>	For matched studies, give matching criteria and number of exposed and unexposed	n/a (This is not a matched study.)
Variables	<a href="#">#7</a>	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources / measurement	<a href="#">#8</a>	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. Give information separately for for exposed and unexposed groups if applicable.	6-7
Bias	<a href="#">#9</a>	Describe any efforts to address potential sources of bias	8-9
Study size	<a href="#">#10</a>	Explain how the study size was arrived at	6
Quantitative variables	<a href="#">#11</a>	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7-9
Statistical methods	<a href="#">#12a</a>	Describe all statistical methods, including those used to control for confounding	8-9
Statistical methods	<a href="#">#12b</a>	Describe any methods used to examine subgroups and interactions	9
Statistical methods	<a href="#">#12c</a>	Explain how missing data were addressed	6

1	Statistical methods	<a href="#">#12d</a>	If applicable, explain how loss to follow-up was addressed	6
2				
3	Statistical methods	<a href="#">#12e</a>	Describe any sensitivity analyses	9
4				
5	<b>Results</b>			
6				
7	Participants	<a href="#">#13a</a>	Report numbers of individuals at each stage of study—eg numbers potentially	6
8			eligible, examined for eligibility, confirmed eligible, included in the study,	
9			completing follow-up, and analysed. Give information separately for for	
10			exposed and unexposed groups if applicable.	
11				
12				
13	Participants	<a href="#">#13b</a>	Give reasons for non-participation at each stage	6
14				
15	Participants	<a href="#">#13c</a>	Consider use of a flow diagram	6
16				
17	Descriptive data	<a href="#">#14a</a>	Give characteristics of study participants (eg demographic, clinical, social) and	10
18			information on exposures and potential confounders. Give information	
19			separately for exposed and unexposed groups if applicable.	
20				
21	Descriptive data	<a href="#">#14b</a>	Indicate number of participants with missing data for each variable of interest	n/a (There was no
22				missing data in the
23				final analysis)
24				
25				
26	Descriptive data	<a href="#">#14c</a>	Summarise follow-up time (eg, average and total amount)	10
27				
28	Outcome data	<a href="#">#15</a>	Report numbers of outcome events or summary measures over time. Give	10
29			information separately for exposed and unexposed groups if applicable.	
30				
31	Main results	<a href="#">#16a</a>	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and	10
32			their precision (eg, 95% confidence interval). Make clear which confounders	
33			were adjusted for and why they were included	
34				
35				
36	Main results	<a href="#">#16b</a>	Report category boundaries when continuous variables were categorized	10
37				
38	Main results	<a href="#">#16c</a>	If relevant, consider translating estimates of relative risk into absolute risk for a	n/a (We didn't
39			meaningful time period	calculate relative
40				risk)
41				
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43	Other analyses	<a href="#">#17</a>	Report other analyses done—e.g., analyses of subgroups and interactions, and	11
44			sensitivity analyses	
45				
46	<b>Discussion</b>			
47				
48	Key results	<a href="#">#18</a>	Summarise key results with reference to study objectives	11
49				
50	Limitations	<a href="#">#19</a>	Discuss limitations of the study, taking into account sources of potential bias or	13
51			imprecision. Discuss both direction and magnitude of any potential bias.	
52				
53				
54	Interpretation	<a href="#">#20</a>	Give a cautious overall interpretation considering objectives, limitations,	11-12
55			multiplicity of analyses, results from similar studies, and other relevant	
56			evidence.	
57				
58	Generalisability	<a href="#">#21</a>	Discuss the generalisability (external validity) of the study results	14
59				
60				

1 **Other**  
2 **Information**  
3

4 Funding [#22](#) Give the source of funding and the role of the funders for the present study and, 14  
5 if applicable, for the original study on which the present article is based  
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