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

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Abstract

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

***Methods*:** We reviewed the data of 8,035 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^2. 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 513 subjects (6.4%). An increase of 0.1 in FEV1/FVC was associated with a decreased risk of incident CKD (HR 0.84, CI 0.75-0.94, $P = 0.002$). Compared to the fourth quartile, the HR (95 % CI) of the first quartile of FEV1/FVC ratio was 1.35 (1.03-1.76, $P = 0.028$). 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 = 0.026).

***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 investigates 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 for analysis.

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

Introduction

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

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

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

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

Methods

Participants

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

Ethics statement

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

Exposure

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

Outcome

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

Measurements and other definitions

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

Copiague, NY, USA), and the average BP on both arms was used as the representative BP measure. Body mass index (BMI) was calculated by dividing the weight by the square of the height (kg/m^2). Waist circumference (WC) was measured at the narrowest point between the lower rib and the iliac crest (measured to the nearest 0.1 cm). Blood samples were examined for fasting for at least 8 hours. Hemoglobin levels and white blood cell (WBC) counts were analyzed using enzymatic methods with ADVIA 120 (Bayer Diagnostics, Tarrytown, NY, USA). Fasting glucose (FG), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), C-reactive protein (CRP), serum creatinine and blood urea nitrogen (BUN) levels were measured using ADVIA 1650 (Siemens, Tarrytown, NY, USA). Five components of metabolic syndrome (MetS) were defined according to the recommendations of the International Diabetes Federation.[27] First, elevated BP was defined as a systolic BP ≥130mmHg, a diastolic BP ≥85mmHg, treatment with anti-hypertensive drugs, or a previous diagnosis of hypertension by a physician. Second, elevated FG was defined as an FG level of ≥100 mg/dL, treatment with insulin or oral anti-diabetic drugs, or a previous diagnosis of diabetes by a physician. Third, increased TG was defined as TG ≥150 mg/dL, treatment with anti-dyslipidemic drugs, or a previous diagnosis of dyslipidemia by a physician. Fourth, reduced HDL-C levels were defined as HDL-C <40mg/dL in men and < 50mg/dL in women. Finally, central obesity was defined as WC ≥90cm in men and ≥80cm in women. MetS was defined as three or more of the five MetS components.[28]

Statistical analyses

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

were expressed as mean ± standard deviation (SD). Non-normally distributed continuous variables were described as medians with interquartile ranges (IQR). The *P*-trend was analyzed using linear regression for the normally distributed continuous variables, Jonckheere-Terpstra test for the non-normally distributed continuous variables, and the Cochran-Armitage test for the categorical variables. Survival curves were analyzed using Kaplan-Meier estimates, and differences among groups were tested using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression analysis. Both analyses were performed with the 'survival' package. In the Kaplan-Meier survival curve, the mean survival time of each FEV1/FVC ratio quartile group was truncated at 14 years and analyzed using the restricted mean survival time function with the 'survRM2' package. The proportional hazards assumption was verified by goodness-of-fit tests. Two variables, age and eGFR, violated proportional hazard assumption. Therefore, they were categorized by clinically important cutoffs (65 years for age and 90 mL/min/1.73m^2 for eGFR) and incorporated as strata in multivariate modeling after confirming the absence of interactions. Potential non-linear relationships between obstructive lung function and incident CKD were evaluated using restricted cubic spline curve analysis with the 'rms' package. A *P* value of <0.05 was considered statistically significant. Subgroup analysis was performed on clinically important variables, and continuous variables were divided into median values. Sensitivity analysis was presented using multivariate Cox regression analysis for percent-predicted FEV1.

Results

The 8,035 subjects had a mean ± SD age of 51.7 ± 8.7 years, and the proportions of men and current smokers were 48.3% and 41.2%, respectively. Mean ± SD BMI, WC, systolic BP, diastolic BP, and HDL-C level were 24.6 ± 3.1 kg/m^2, 82.6 ± 8.7 cm, 120.9 ± 18.1 mmHg, 80.2 ± 11.4 mmHg, and 44.7 ± 9.9 ml/dL, respectively, and median (IQR) of FG and TG levels were 82 (77-90) mg/dL and 134 (99-188) mg/dL, respectively. The mean ± SD of FEV1/FVC ratio, FEV1, and FVC were 0.80 ± 0.08, 96.8 ± 14.1%-predicted, and 96.9 ± 13.1%-predicted, respectively. Mean ± SD baseline eGFR was 94.9 ± 12.0 mL/min/1.73m^2. During a mean 11.7 years' follow-up, incident CKD developed in 513 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 ≥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, and FVC increased, while eGFR and 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 0.84 (0.75-0.94, $P = 0.002$). Compared to the fourth quartile, the HR (95% CI) of the first quartile of the FEV1/FVC

ratio was 1.35 (1.03-1.76, $P = 0.028$). 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.

In the subgroup analysis, MetS modified the effect of the FEV1/FVC ratio on incident CKD development (Figure 4). In detail, although an increased FEV1/FVC ratio was not associated with incident CKD development in people with MetS, it was independently associated with incident CKD development in those without MetS. There were no subgroups showing statistically significant effect modification. However, nonsmokers, low baseline eGFR, low CRP, low WBC, younger age, female sex, low BMI, non-raised HDL-C, BP, and FG were valid subgroups for the relationship between FEV1/FVC ratio and CKD development.

Discussion

Obstructive lung disease and CKD are both important chronic diseases in the modern world.[9, 29] Several recent studies have shown the relationship between obstructive lung disease and CKD.[17, 30] 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).[30] Huang et al. found that BA patients were more likely to develop CKD (HR 1.56, CI 1.48-1.64, P < 0.001).[17] The FEV1/FVC ratio called the Tiffeneau-pinelli index, has been used worldwide as a screening index for diagnosing obstructive lung function. The FEV1/FVC ratio is an easily applicable index because it does not require calculation of the predicted value.[3, 18] 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 ≥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 function, was not associated with incident CKD development. This may be because of possible inaccuracies in the prediction method attribute to race, age, and gender.[31] We used the formula proposed in 2005 based on the Korean population, but the demographics of Korea have been changed dramatically over the last15 years. Thus, a new estimation formula based on new demographics will be needed.[32] 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.[33] 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 FEV1 values. Since the FEV1/FVC ratio was particularly evident in groups without metabolic derangements, we propose that this ratio can be used as a spirometric index to be associated with future CKD development in a relatively healthy population.

To date, there have been no exact mechanisms for the potential renal hazard of airway obstruction. One possible explanation is the chronic hypoxia induced by airway obstruction. Chronic hypoxia may cause hypoxic renal damage, which is related to a decline in kidney function.[34] Atherosclerosis, a risk factor for CKD, is also associated with chronic hypoxia.[35] The systemic inflammation in obstructive lung diseases, including increased levels of tumor necrosis factor α and interleukin 6, may cause vascular calcification and protein-energy wasting, which can ultimately result in CKD development.[36]

Our study has several strengths. First, to our knowledge, this is the first prospective study using the FEV1/FVC ratio as the main index to predict CKD development. Second, a large number of participants and many confounders for the incident CKD were adjusted in this study. Third, using a non-linear analytic method, we found that incident CKD and the FEV1/FVC

ratio had a U-shaped relationship. This study also had several limitations. First, this was an observational study. Therefore, a causal relationship could not be ascertained, and the results should be interpreted with caution. Second, because of the large number of participants, we only obtained pre-bronchodilator measurements. Because of the low prevalence of airway diseases, however, we assumed that this limitation has little effect on the study results. Finally, the generalizability of the results is limited because the study was conducted in a single country with a single ethnicity.

In conclusion, decreased FEV1/FVC ratio was an independent risk factor for future CKD development. The relationship of this findings with incident CKD development was particularly valid in a relatively healthy population, suggesting that it may serve as an early predictor for CKD development. Future studies need to be conducted to confirm the results of this study.

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.

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Competing Interests: None declared.

Patient consent: Not required.

Ethics approval: Ethical Committee of Eulji Medical Center, Seoul, Korea.

Data sharing statement: No data are available.

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Figure legends

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

Figure 2. Kaplan-Meier CKD-free survival curves among four groups defined by the FEV1/FVC ratio. 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 FEV1/FVC ratio. FEV1, forced expiratory volume in 1 second; FVC, functional vital capacity. All covariates of model 2 shown in table 2 were used for adjustment. The solid line indicates the calculated line of association between the FEV1/FVC ratio and estimated hazard ratio. The shaded region represents the 95% confidential intervals for value of hazard ratio according to the FEV1/FVC ratio.

Figure 4. Subgroup analysis for the relationship between the FEV1/FVC ratio and the risk of incident CKD. FEV1, forced expiratory volume in 1 second; FVC, functional vital capacity; CKD, chronic kidney disease; BMI, body mass index; MetS, metabolic syndrome; HR, hazard ratio; CI, confidence interval. Adjusted beta and 95% CI were analyzed using Cox proportional hazards regression analysis. All covariates of model 2 shown in table 2 were used to adjustment.

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

	FEV1/FVC ratio groups (n = 8,035)				
	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)	*P*-trend
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^2)	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^2)	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 (×10^3/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

for normally distributed continuous variables, Mann-Whitney U tests for non-normally distributed continuous variable, and chi-square tests for categorical variables.

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

	Univariate	Model 1	Model 2
	HR (95% CI, *P*-value)	HR (95% CI, *P*-value)	HR (95% CI, *P*-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, *P*-value)	HR (95% CI, *P*-value)	HR (95% CI, *P*-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, *P*)	*P* 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.

Figure 1.

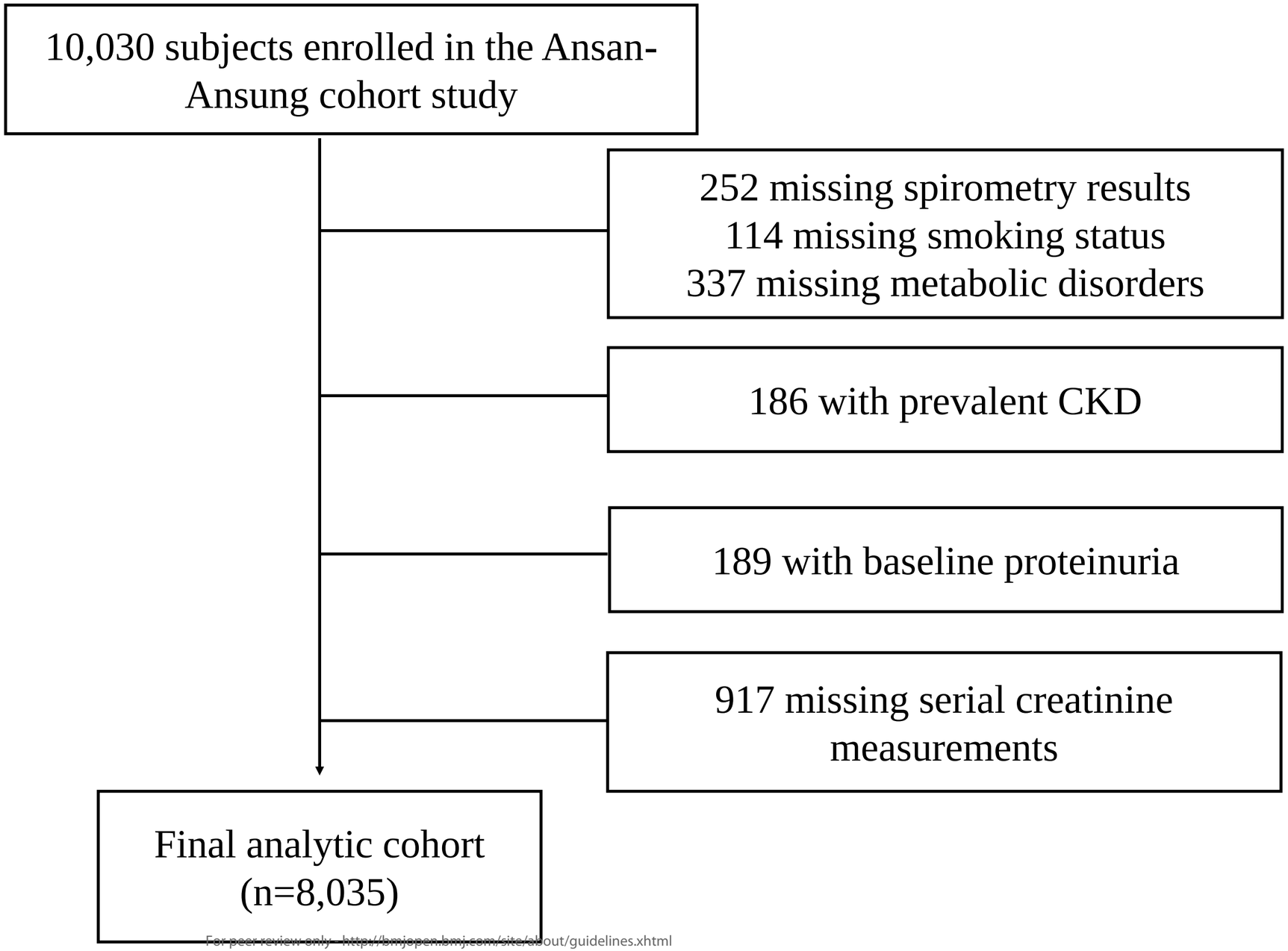


Figure 2.

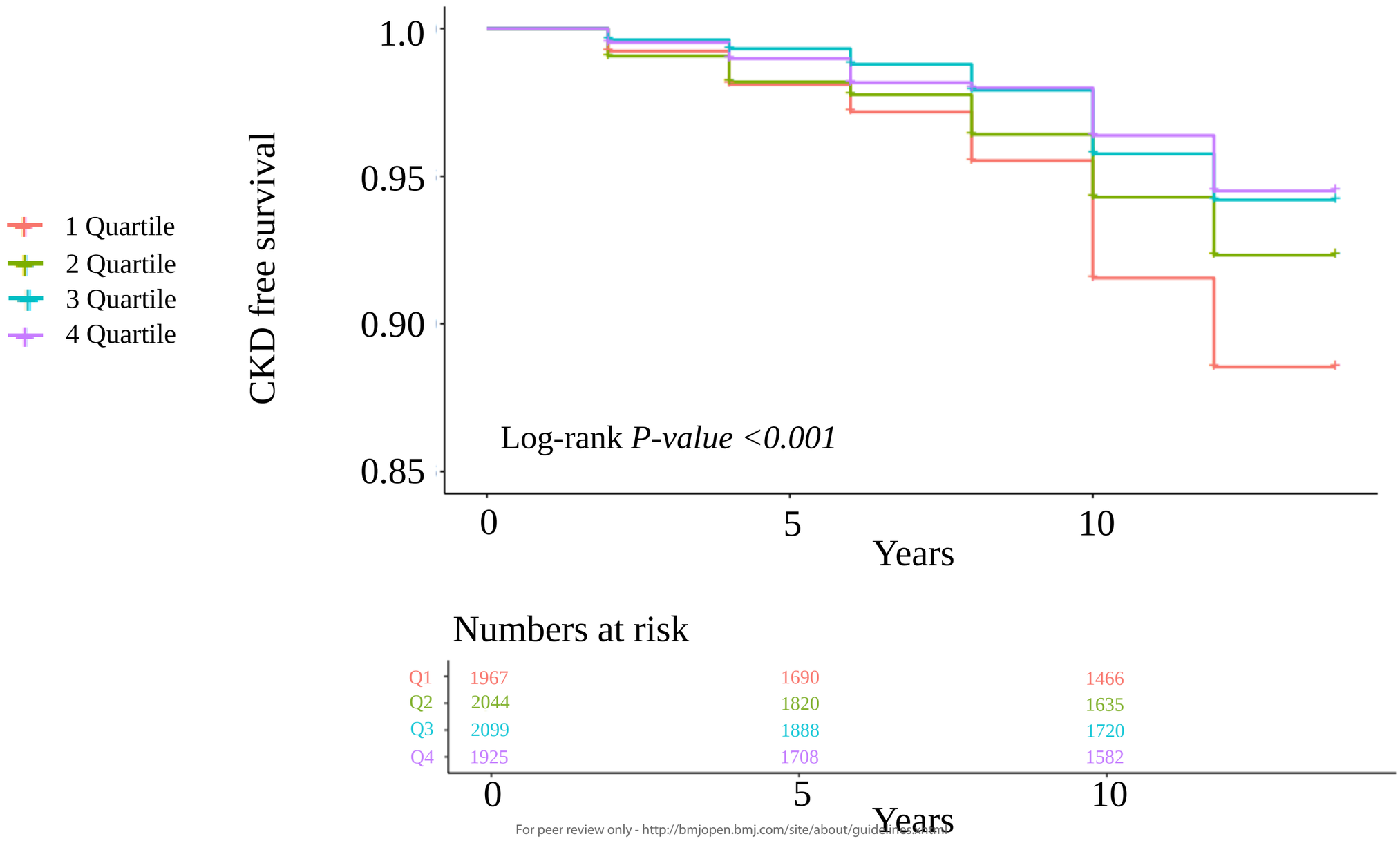


Figure 3.

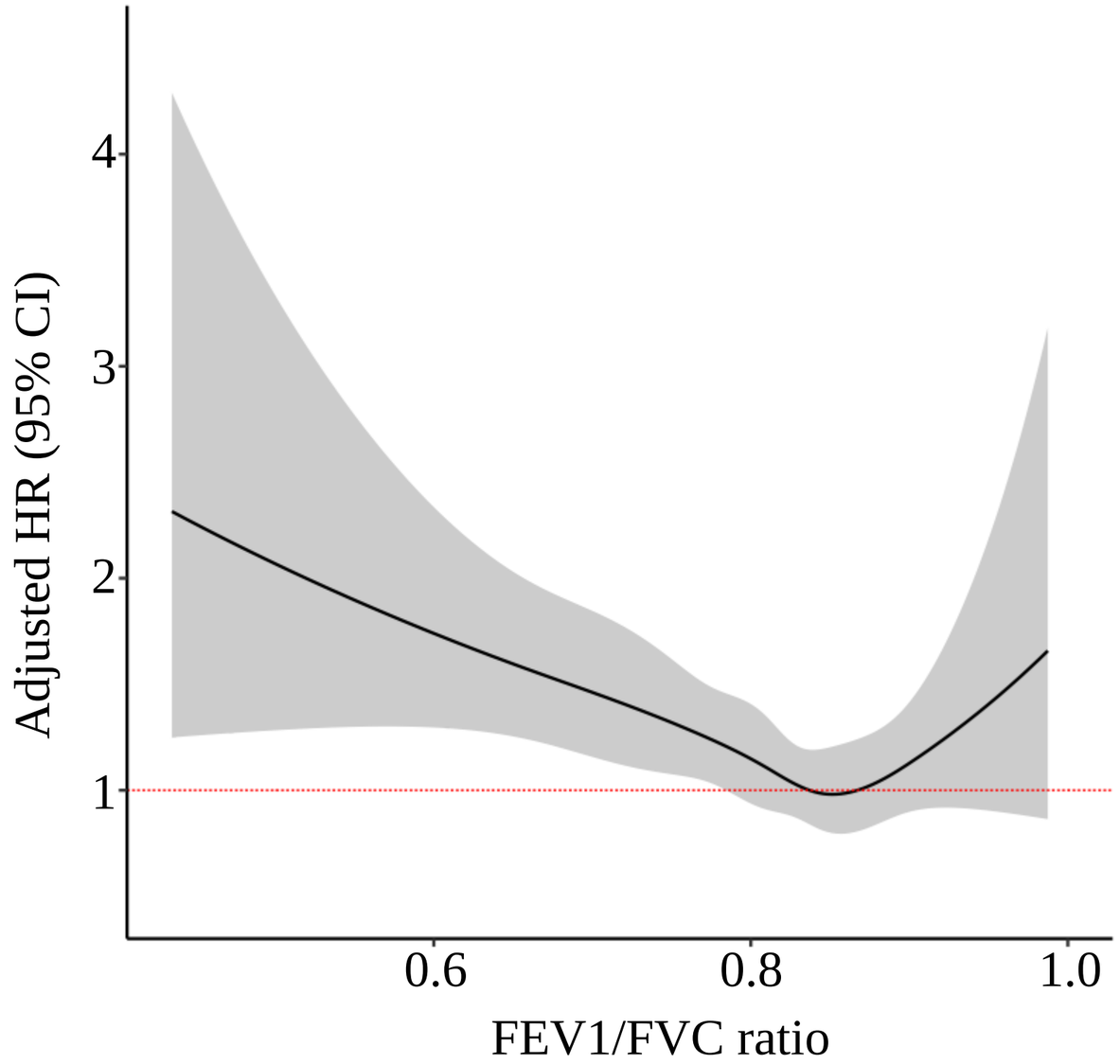
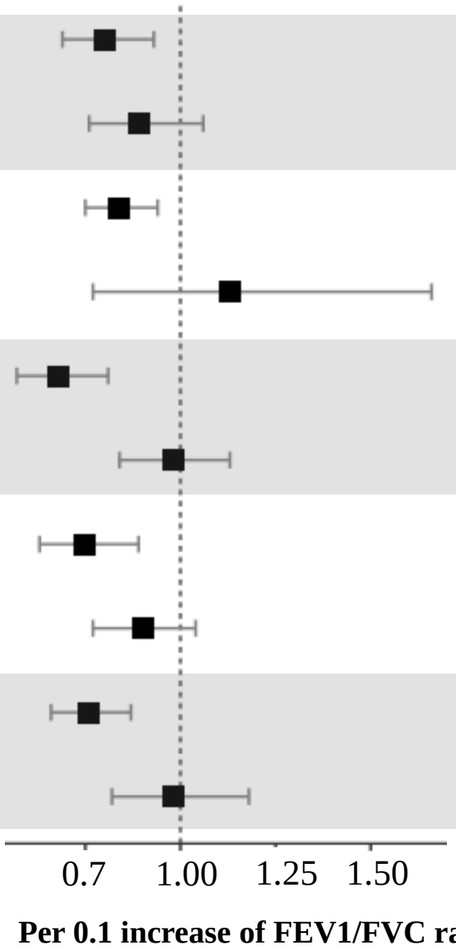


Figure 4.

Subgroup	No. of people	Adjusted HR (95% CI, *P*)	*P* for interaction
Current or past smoking	No (n=4,724)	0.80 (0.69-0.93, 0.004)	0.510
	Yes (n=3,311)	0.89 (0.76-1.06, 0.194)	
eGFR (mL/min/1.73^2)	< 96.5 (n=4,047)	0.84 (0.75-0.94, 0.003)	0.588
	≥ 96.5 (n=3,988)	1.13 (0.77-1.66, 0.532)	
CRP (mg/dL)	< 0.14 (n=3,916)	0.68 (0.57-0.81, < 0.001)	0.779
	≥ 0.14 (n=4,119)	0.98 (0.84-1.13, 0.759)	
WBC (x10^2/μL)	< 6.3 (n=3,945)	0.75 (0.63-0.89, < 0.001)	0.175
	≥ 6.3 (n=4,090)	0.90 (0.77-1.04, 0.164)	
MetS	No (n=5,450)	0.76 (0.66-0.87, < 0.001)	0.026
	YES (n=2,585)	0.98 (0.82-1.18, 0.833)	



Reporting checklist for cohort study.

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

Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	6
Statistical methods	#12e	Describe any sensitivity analyses	9
Results			
Participants	#13a	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. Give information separately for for exposed and unexposed groups if applicable.	6
Participants	#13b	Give reasons for non-participation at each stage	6
Participants	#13c	Consider use of a flow diagram	6
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	10
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	n/a (There was no missing data in the final analysis)
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	10
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	10
Main results	#16a	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	10
Main results	#16b	Report category boundaries when continuous variables were categorized	10
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a (We didn't calculate relative risk)
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	#18	Summarise key results with reference to study objectives	11
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.	13
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	11-12
Generalisability	#21	Discuss the generalisability (external validity) of the study results	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	14

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

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

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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^2. 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 investigates 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

for analysis.

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

Introduction

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

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

Several recent studies have reported the association between obstructive airway diseases and CKD.[17-19] Furthermore, the findings of obstructive spirometry pattern may also be associated with CKD.[20-22] Suzuki et al. reported that the prevalence of CKD increased with an increase in the obstructive spirometry grade.[20] Sumida et al. analyzed 14,946 participants of the Atherosclerosis Risk in Communities (ARIC) study and reported that the incidence of end-stage renal disease was higher in the lowest quartile of FEV1/FVC ratio than highest quartile with a hazard ratio (HR) and 95% confidence interval (CI) of 1.33 (1.03-1.73).[21] Although one Korean study also suggested that decreased FEV1/FVC ratio was associated with an increased risk of incident CKD, it was based on a single-center retrospective cohort, and the potential renal hazard associated with obstructive spirometry pattern needs to be tested in a prospective setting.[22] The aim of this study was, therefore, to investigate the relationship

between FEV1/FVC ratio and incident CKD using data from the community-based prospective Ansan-Ansung cohort in Korea.

Methods

Participants

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

Ethics statement

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

Exposure

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

Outcome

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

Measurements and other definitions

A standard interview regarding the participants' socio-demographic status and lifestyle was conducted by trained interviewers. High income was defined as the highest quintile of monthly household income (≥3 million won a month). Blood pressure (BP) was measured using a standard mercury sphygmomanometer (Baumanometer-Standby; W. A. Baum Co., Inc., Copiague, NY, USA), and the average BP on both arms was used as the representative BP measure. Body mass index (BMI) was calculated by dividing the weight by the square of the height (kg/m^2). Waist circumference (WC) was measured at the narrowest point between the lower rib and the iliac crest (measured to the nearest 0.1 cm). Blood samples were examined for fasting for at least 8 hours. Hemoglobin levels and white blood cell (WBC) counts were analyzed using enzymatic methods with ADVIA 120 (Bayer Diagnostics, Tarrytown, NY, USA). Fasting glucose (FG), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), C-reactive protein (CRP), serum creatinine and blood urea nitrogen (BUN) levels were measured using ADVIA 1650 (Siemens, Tarrytown, NY, USA). Five components of metabolic syndrome (MetS) were defined according to the recommendations of the International Diabetes Federation.[27] First, elevated BP was defined as a systolic BP ≥130mmHg, a diastolic BP ≥85mmHg, treatment with anti-hypertensive drugs, or a

previous diagnosis of hypertension by a physician. Second, elevated FG was defined as an FG level of ≥100 mg/dL, treatment with insulin or oral anti-diabetic drugs, or a previous diagnosis of diabetes by a physician. Third, increased TG was defined as TG ≥150 mg/dL, treatment with anti-dyslipidemic drugs, or a previous diagnosis of dyslipidemia by a physician. Fourth, reduced HDL-C levels were defined as HDL-C <40mg/dL in men and < 50mg/dL in women. Finally, central obesity was defined as WC ≥90cm in men and ≥80cm in women. MetS was defined as three or more of the five MetS components.[28]

Statistical analyses

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

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 ± SD age of 51.7 ± 8.7 years, and the proportions of men and current smokers were 48.2% and 41.1%, respectively. Mean ± SD BMI, WC, systolic BP, diastolic BP, and HDL-C level were 24.6 ± 3.1 kg/m^2, 82.6 ± 8.7 cm, 120.9 ± 18.1 mmHg, 80.2 ± 11.4 mmHg, and 44.7 ± 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 ± SD of FEV1/FVC ratio, FEV1, and FVC were 0.80 ± 0.08, 96.9 ± 14.1%-predicted, and 96.9 ± 13.1%-predicted, respectively. Mean ± SD baseline creatinine was 0.8 ± 0.2 mL/min/1.73m^2. 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 ≥ 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).

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

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

	FEV1/FVC ratio groups (n = 7,960)				
	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)	*P*-trend
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^2)	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 (×10^3/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

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, *P*-value)	HR (95% CI, *P*-value)	HR (95% CI, *P*-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.[9 29] Several recent studies have shown the relationship between obstructive lung disease and CKD.[17 30] 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).[30] Huang et al. found that BA patients were more likely to develop CKD (HR 1.56, CI 1.48-1.64, P < 0.001).[17] 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.[3 18] 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 ≥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.[31] We used the formula proposed in 2005 based on the Korean population, but the demographics of Korea have been changed dramatically over the last15 years. Thus, a new estimation formula based on new demographics will be needed.[32] 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.[33] 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

FEV1 values. The FEV1/FVC ratio was particularly evident in groups without metabolic derangements. This means that spirometry patterns in individuals with metabolic disorders may differ from those in healthy population. We propose that FEV1/FVC ratio can be used as a spirometric index to be associated with future CKD development in a relatively healthy population.

To date, there have been no exact mechanisms for the potential renal hazard of airway obstruction. One possible explanation is the chronic hypoxia induced by airway obstruction. Chronic hypoxia may cause hypoxic renal damage, which is related to a decline in kidney function.[34] Atherosclerosis, a risk factor for CKD, is also associated with chronic hypoxia.[35] The systemic inflammation in obstructive lung diseases, including increased levels of tumor necrosis factor α and interleukin 6, may cause vascular calcification and protein-energy wasting, which can ultimately result in CKD development.[36]

Our study has several strengths. First, to our knowledge, this is the first prospective study using the FEV1/FVC ratio as the main index to predict CKD development. Second, a large number of participants and many confounders for the incident CKD were adjusted in this study. Third, using a non-linear analytic method, we found that incident CKD and the FEV1/FVC ratio had a U-shaped relationship. The upper limit of FEV1/FVC is not clear, but most of those with FEV1/FVC above 0.9 had a decreased FVC % predicted. Neuromuscular disorders may cause high FEV1/FVC and be associated with incident CKD. Further study will be needed to clarify the clinical significance of high FEV1/FVC. This study also had several limitations. First, this was an observational study. Therefore, a causal relationship could not be ascertained, and the results should be interpreted with caution. Second, because of the large number of participants, we only obtained pre-bronchodilator measurements. Thirds, age was not included in the adjustment of Cox proportional hazard regression analysis. Age cannot be adjusted due to extreme violation of the proportional risk assumption. However, age was used to adjust for incident CKD. The superiority of further adjustment for already adjusted variable is not clear. Repeated adjustment of same variable can cause bias.[37] Because of the low prevalence of airway diseases, however, we assumed that this limitation has little effect on the study results. Finally, the generalizability of the results is limited because the study was conducted in a single country with a single ethnicity.

In conclusion, decreased FEV1/FVC ratio was an independent risk factor for future CKD development. The relationship of this findings with incident CKD development was particularly valid in a relatively healthy population, suggesting that it may serve as an early predictor for CKD development. Future studies need to be

conducted to confirm the results of this study.

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.

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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

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

Figure 4. Subgroup analysis for the relationship between the FEV1/FVC ratio and the risk of incident CKD. Adjusted beta and 95% CI were analyzed using Cox proportional hazards regression analysis. All covariates of model 2 shown in table 2 were used to adjustment. Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, functional vital capacity; CKD, chronic kidney disease; BMI, body mass index; MetS, metabolic syndrome; HR, hazard ratio; CI, confidence interval.

Figure S1. Kaplan-Meier CKD-free survival curves among four groups defined by age. Abbreviations: CKD, chronic kidney disease; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4.

Figure 1.

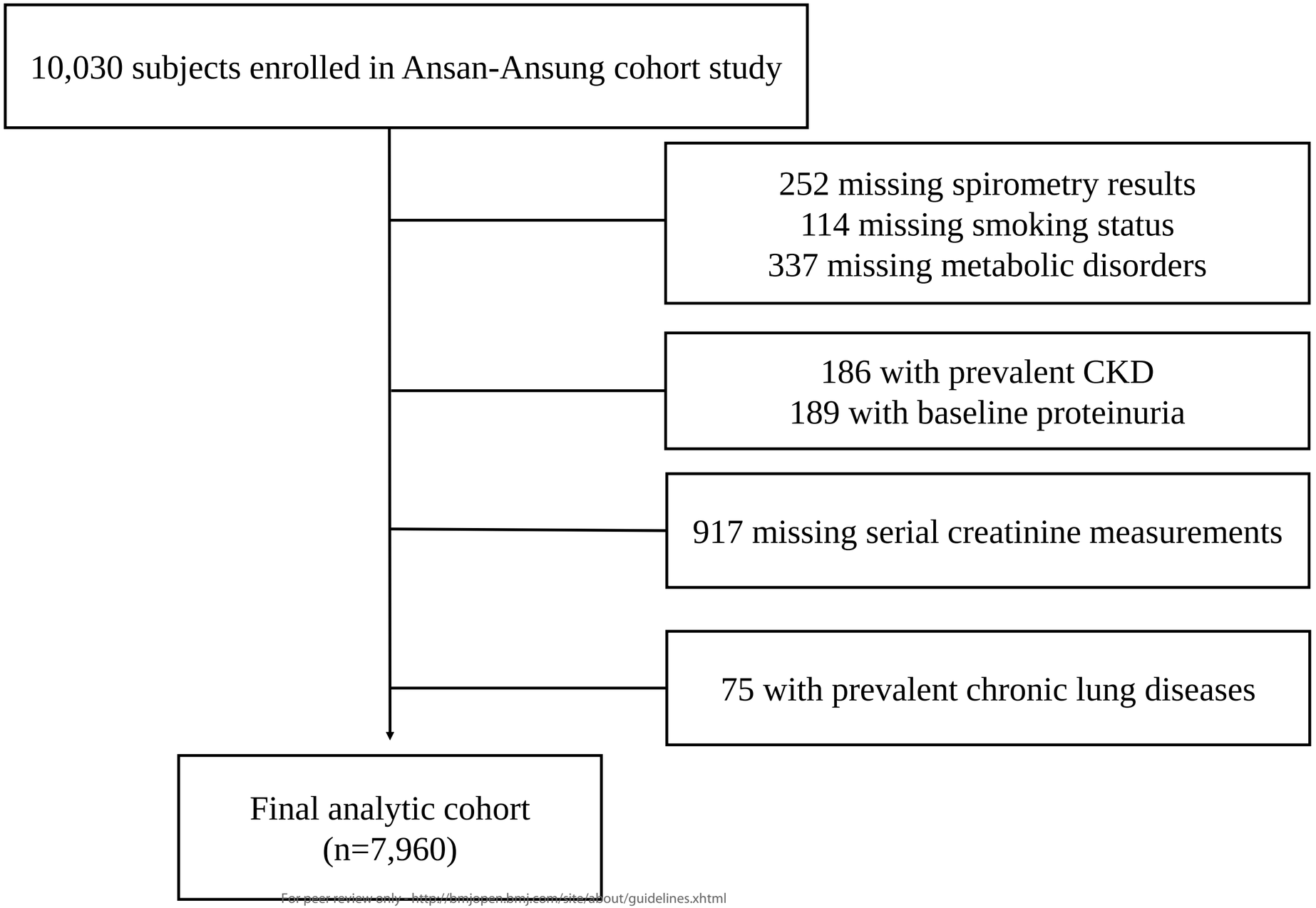

Figure 2.

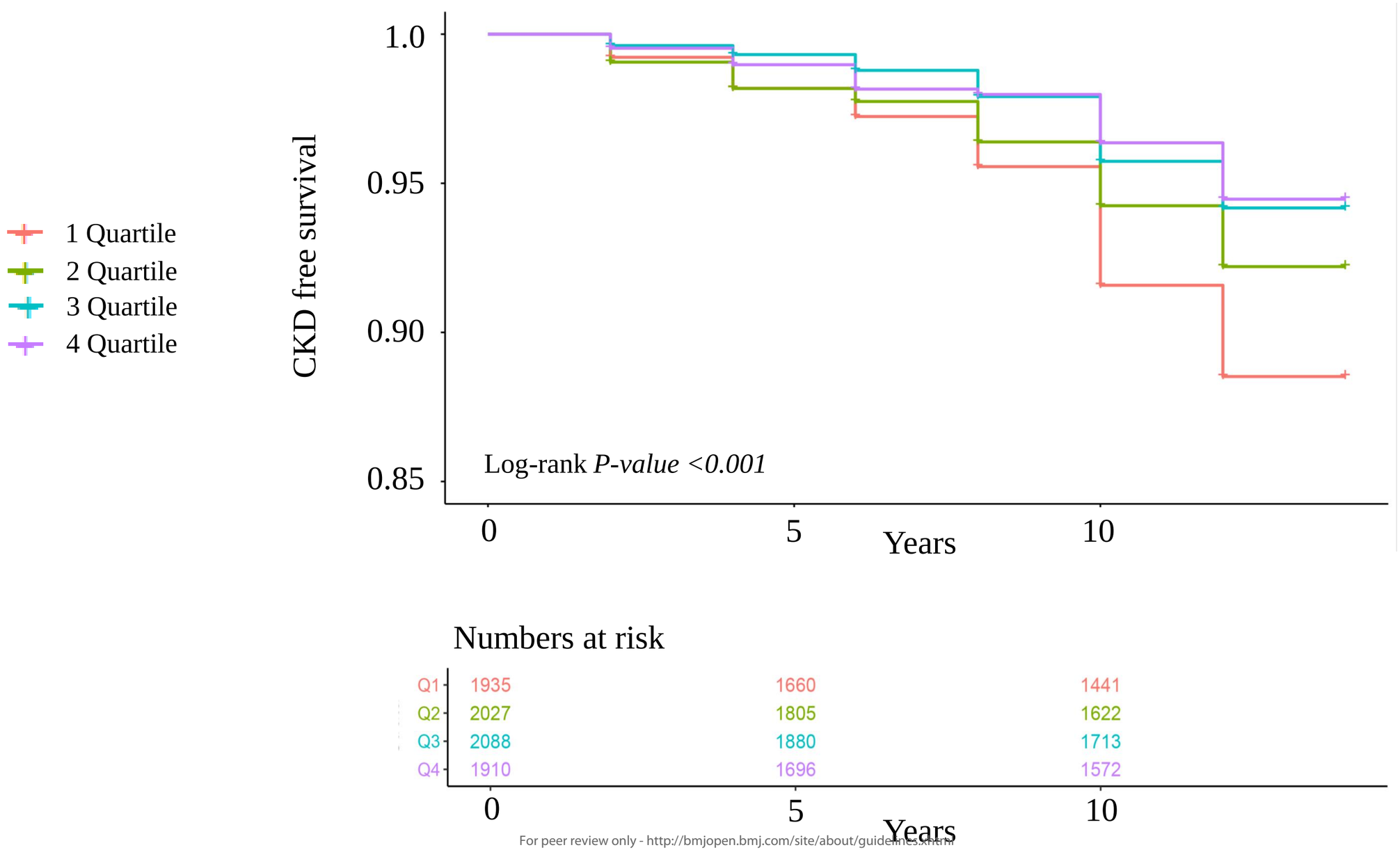

Figure 3.

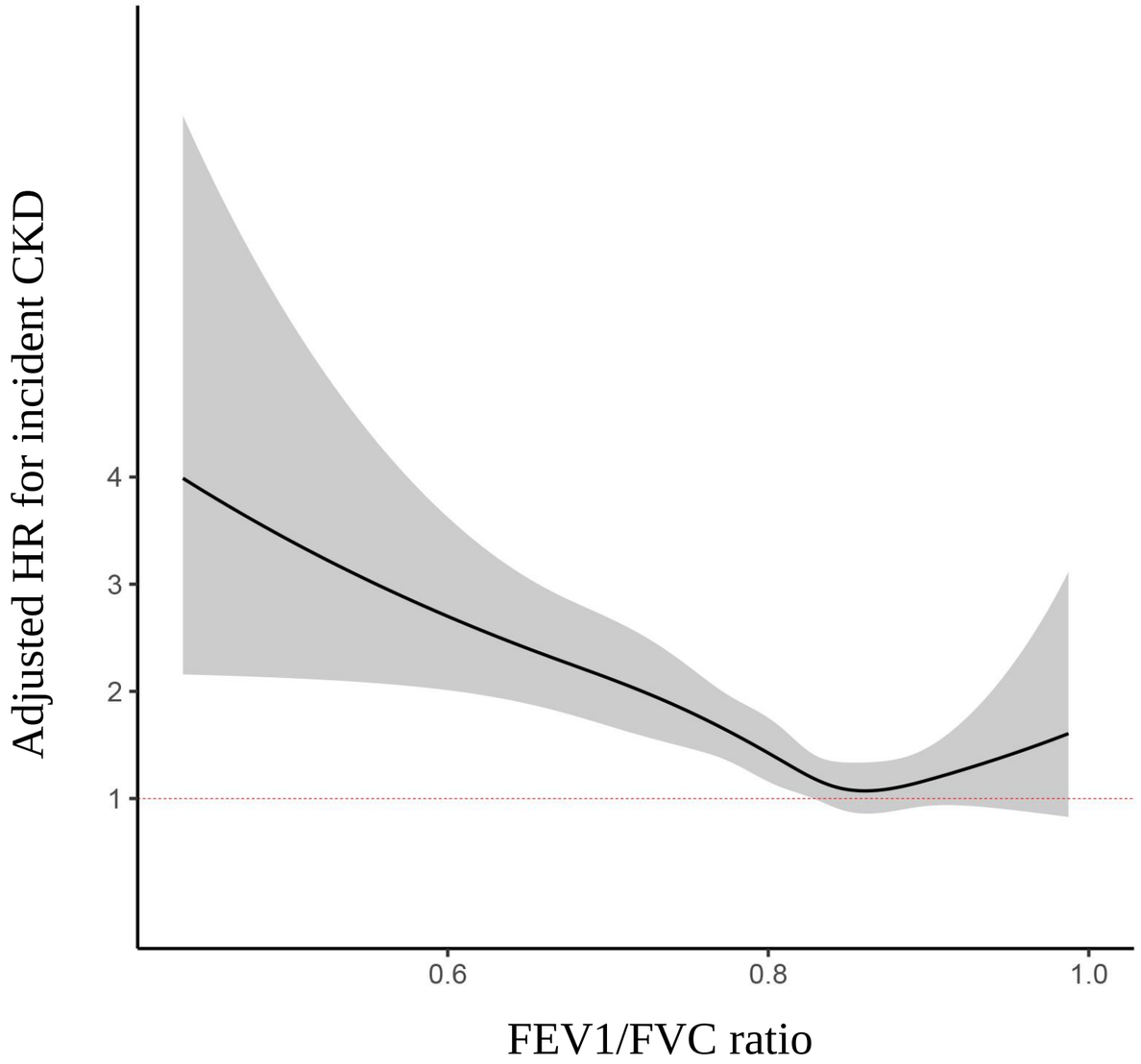

Figure 4.

Subgroup	No. of people	Adjusted HR (95% CI, *P*)	*P* for interaction
Current or past smoking	No (n=4,690)	0.71 (0.61-0.82, < 0.001)	0.455
	Yes (n=3,270)	0.77 (0.66-0.91, 0.002)	
eGFR (mL/min/1.73^2)	< 94 (n=4,045)	0.76 (0.68-0.86, 0.001)	-
	≥ 94 (n=3,915)	0.84 (0.62-1.14, 0.266)	
CRP (mg/dL)	< 0.14 (n=3,882)	0.61 (0.52-0.72, < 0.001)	0.847
	≥ 0.14 (n=4,119)	0.85 (0.73-0.98, 0.024)	
WBC (x10^2/μL)	< 6.3 (n=3,909)	0.65 (0.55-0.77, < 0.001)	0.056
	≥ 6.3 (n=4,090)	0.79 (0.68-0.91, 0.001)	
MetS	No (n=5,450)	0.66 (0.58-0.75, < 0.001)	0.018
	YES (n=2,585)	0.86 (0.72-1.02, 0.083)	

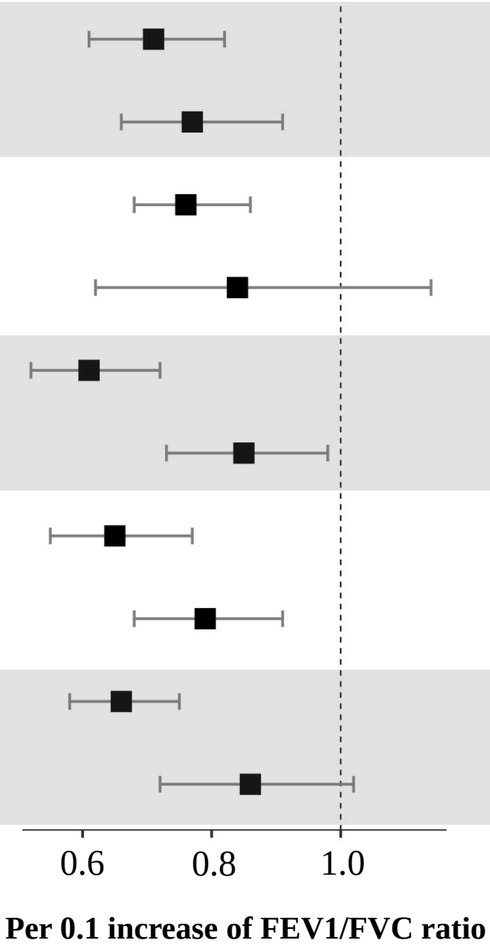

Figure S1.

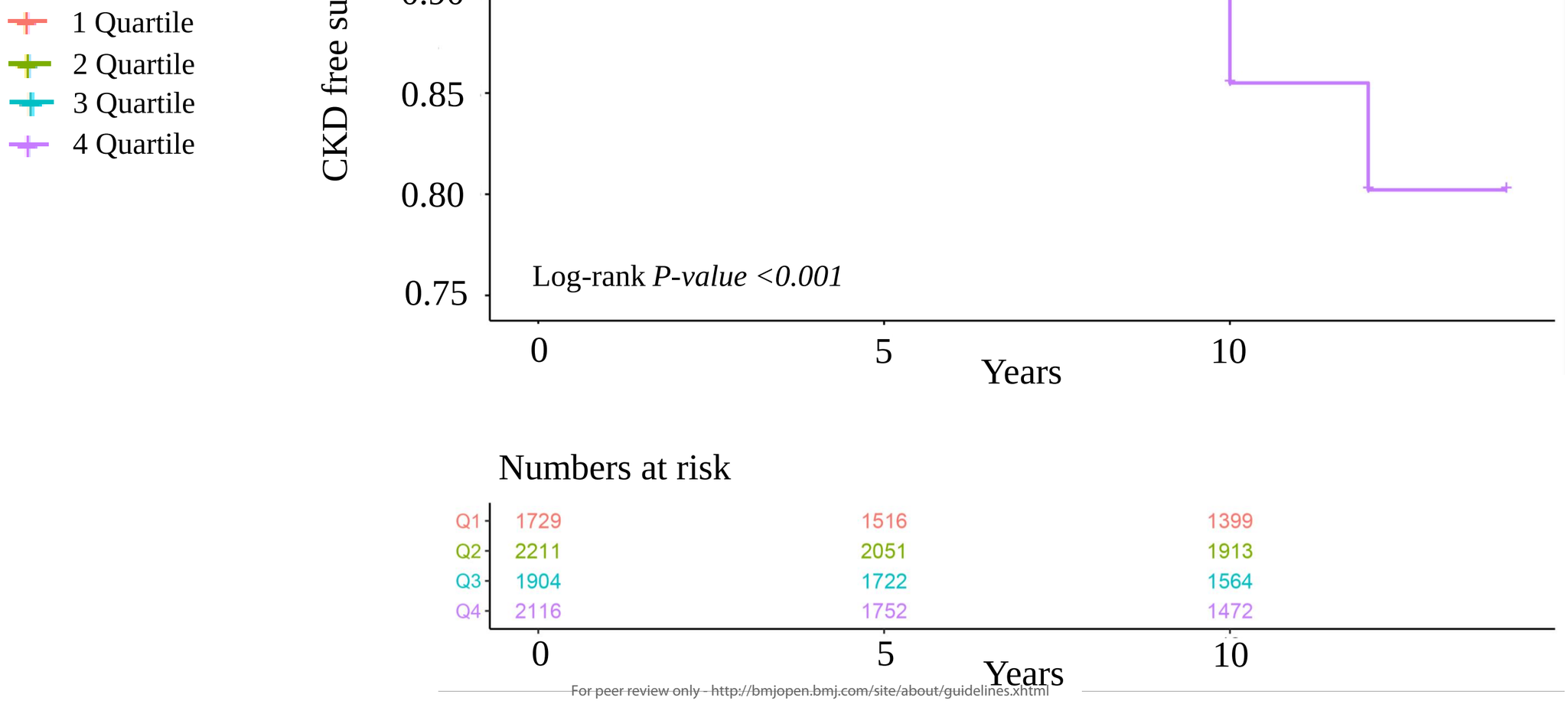

Table S1. Sensitivity analysis for the relationship between the %-predicted FEV1, FVC and the risk of incident CKD

	Univariate	Model 1	Model 2
	HR (95% CI, *P*-value)	HR (95% CI, *P*-value)	HR (95% CI, *P*-value)
%-predicted FEV1			
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)
%-predicted FVC			
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, *P*)	*P* 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
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	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	5
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	n/a (This is not a matched study.
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
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. Give information separately for for exposed and unexposed groups if applicable.	6-7
Bias	#9	Describe any efforts to address potential sources of bias	8-9
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7-9
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8-9
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	9
Statistical methods	#12c	Explain how missing data were addressed	6

Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	6
Statistical methods	#12e	Describe any sensitivity analyses	9
Results			
Participants	#13a	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. Give information separately for for exposed and unexposed groups if applicable.	6
Participants	#13b	Give reasons for non-participation at each stage	6
Participants	#13c	Consider use of a flow diagram	6
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	10
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	n/a (There was no missing data in the final analysis)
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	10
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	10
Main results	#16a	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	10
Main results	#16b	Report category boundaries when continuous variables were categorized	10
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a (We didn't calculate relative risk)
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	#18	Summarise key results with reference to study objectives	11
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.	13
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	11-12
Generalisability	#21	Discuss the generalisability (external validity) of the study results	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	14