

# BMJ Open Is decreased lung function associated with chronic kidney disease? A retrospective cohort study in Korea

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## ABSTRACT

**Objective** There is some evidence that lung function and chronic kidney disease (CKD) may be related. We evaluated the impact of lung function on the development of CKD in a large-scale longitudinal study.

**Method** Retrospective longitudinal analyses were conducted among subjects who participated in comprehensive health check-ups at least four times during 7 years (between 2006 and 2012). We investigated the development of CKD during the follow-up period according to lung function status.

**Results** Ten thousand one hundred and twenty-eight individuals (mean age =51.2 years) without CKD at baseline were enrolled. During the mean follow-up of 5 years (58.5±14.4 months), 167 of the 10 128 subjects (1.6%) developed CKD. Multivariable Cox proportional hazards analyses adjusting for age, sex, body mass index, systolic blood pressure, fasting glucose, estimated glomerular filtration rate, uric acid, triglycerides, serum albumin, and the presence of diabetes and hypertension revealed that a decrease of 10% in the forced expiratory volume in 1s (FEV<sub>1</sub>)/forced vital capacity (FVC) ratio was associated with a 35% increase in the development of CKD during the follow-up. The incidence of CKD was higher in those with an FEV<sub>1</sub>/FVC ratio <0.8 compared with those with FEV<sub>1</sub>/FVC ratio ≥0.8 (HR=1.454; 95% CI 1.042 to 2.028, p=0.028).

**Conclusions** Limited airflow as measured by the FEV<sub>1</sub>/FVC ratio was associated with an increased risk of CKD.

## INTRODUCTION

Chronic kidney disease (CKD) is an increasing public health problem in Korea and is associated with significant morbidity and mortality.<sup>1–4</sup> CKD is linked to various other diseases, including hypertension, diabetes, atherosclerosis and metabolic syndrome (MetS).<sup>5</sup> Chronic obstructive pulmonary disease (COPD) is a systemic inflammatory disease.<sup>7</sup> It is known that cardiovascular disease, osteoporosis, diabetes and MetS are systemic effects caused by COPD and also its comorbidities.<sup>7,8</sup> Proinflammatory cytokines, including tumour necrosis factor  $\alpha$  and interleukin 6, induce insulin resistance by blocking signalling via the insulin receptor, thereby

## Strengths and limitations of this study

- The strengths of this study are the large sample and longitudinal nature of the study.
- This study is one of few studies on the relationship between lung function and chronic kidney disease development.
- Limitations of this study are its retrospective nature and failure to note symptoms of any airway disease.
- Another limitation of this study is that most patients had normal pulmonary function; thus it needs further study in patients with chronic obstructive pulmonary disease.

increasing the risk of type 2 diabetes and MetS in patients with COPD.<sup>8</sup> However, only a few studies have examined the association between renal function and lung function, and found that kidney dysfunction is more common in patients with COPD.<sup>9–13</sup> These studies suggest that CKD is associated with COPD. However, few studies have explored the relationship between lung function and the incidence of CKD. Thus, we examined cross-sectional and longitudinal associations between lung function, measured by calculating forced vital capacity (FVC), forced expiratory volume in 1s (FEV<sub>1</sub>), or the FEV<sub>1</sub>/FVC ratio, and the development of CKD after adjusting for other risk factors for CKD.

## METHODS

### Study population and data collection

This was a retrospective longitudinal cohort study. Many people undergo comprehensive health check-ups each year at the Samsung Medical Center. Initial data were obtained from 25 170 individuals who participated in comprehensive health check-ups at least four times over 7 years (between January 2006 and December 2012). The data from the first visits served as baseline data. In total, 15 042 subjects were excluded for the following reasons: (1)

missing pulmonary function test (n=3370), (2) age <20 years (n=7), (3) body mass index (BMI) <18.5 kg/m<sup>2</sup> (n=456), (4) CKD evident at baseline (n=965), (5) missing urine albumin/Cr ratio (n=6249) and (6) current smoker (n=3995). We excluded current smokers from this analysis because smoking itself has a significant effect on lung function. It would have been difficult to correctly evaluate the association between lung function and the development of CKD if we included current smokers in the study. A total of 10 128 individuals (mean age 51.2 years) without CKD at baseline were enrolled.

### Measurements

All subjects fasted overnight, and blood was collected subsequently. All laboratory tests were performed in the central certified laboratory of Samsung Medical Center. Anthropometric and other biochemical variables were measured as described previously.<sup>13</sup> We measured serum creatinine using the kinetic alkaline picrate method (Jaffe reaction; Roche Modular DP, Roche, Switzerland).

### Definition of development of CKD

The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.<sup>14</sup> CKD was defined as an eGFR <60 mL/min/1.73 m<sup>2</sup> in patients over 40 years old and eGFR <75 mL/min/1.73 m<sup>2</sup> in patients younger than 40 years old.<sup>15</sup>

### Statistical analysis

Data expressed as mean±SEM. Metabolic risk factors, the prevalence of diabetes and other clinical characteristics were compared between subjects who did and did not develop CKD. A Student's t-test was used to compare continuous variables, and the exact  $\chi^2$  test was used to detect differences between groups. Pearson's correlation analyses were used to generate correlation coefficients between eGFR and other factors. We used multivariable Cox proportional hazards analyses to estimate HRs with 95% CIs for the development of CKD during follow-up per 10% decrease in the FEV<sub>1</sub>/FVC ratio. We compared the development of CKD between two groups (FEV<sub>1</sub>/FVC ratio >0.8 vs FEV<sub>1</sub>/FVC ratio <0.8) during follow-up using the HRs for incidences of CKD estimated by Cox proportional hazards analysis. All statistical analyses were performed using Predictive Analytics Software (PASW) (V.17.0; SPSS, Chicago, Illinois, USA). A p value <0.05 was considered statistically significant.

### Patient and public involvement statement

This study was a retrospective study. Patients were not involved in this study.

## RESULTS

During the mean follow-up of 5 years (58.5±14.4 months), 167 of the 10 128 subjects (1.6%) developed CKD. The baseline characteristics of those with and without de novo CKD are shown in table 1. Those who

**Table 1** Baseline characteristics of all subjects by the development of chronic kidney disease (CKD)

	The subjects who developed CKD (n=167)	All other subjects (n=9961)	P values
Age (years)	60.0±0.8	51.0±0.1	<0.001
Sex (male, %)	134 (80.2%)	5749 (57.7%)	<0.001
BMI (kg/m <sup>2</sup> )	24.7±0.2	23.8±0.1	<0.001
SBP (mm Hg)	118.9±1.3	114.1±0.2	<0.001
DBP (mm Hg)	72.5±0.8	70.6±0.1	0.022
Total cholesterol (mg/dL)	191.8±2.7	192.7±0.3	0.733
Triglyceride (mg/dL)	142.9±5.7	122.4±0.7	<0.001
HDL cholesterol (mg/dL)	54.1±1.0	57.4±0.2	<0.001
Fasting glucose (mg/dL)	93.4±1.2	92.0±0.2	0.248
Haemoglobin A1c (%)	5.53±0.05	5.42±0.01	0.023
Albumin (mg/L)	4.25±0.02	4.31±0.01	0.001
Haemoglobin (g/dL)	14.7±0.1	14.4±0.1	<0.001
Urea (mg/dL)	15.36±0.29	13.47±0.04	<0.001
Creatinine (mg/dL)	1.09±0.01	0.90±0.01	<0.001
Uric acid (mg/dL)	5.92±0.11	5.15±0.01	<0.001
eGFR (mL/min per 1.73m <sup>2</sup> )	69.9±0.7	88.5±0.1	<0.001
hs-CRP (mg/L)	0.14±0.02	0.11±0.01	0.154
FVC (%)	93.4±0.9	95.1±0.1	0.076
FEV <sub>1</sub> (%)	100.7±1.2	103.1±0.1	0.046
FEV <sub>1</sub> /FVC ratio	0.77±0.52	0.81±0.06	<0.001
Diabetes mellitus (%)	14 (8.4%)	583 (5.9%)	0.182
Hypertension (%)	66 (40.7%)	1602 (16.1%)	<0.001

BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FEV<sub>1</sub>, forced expiratory volume in 1s; FVC, forced vital capacity; hs-CRP, high-sensitivity C reactive protein; SBP, systolic blood pressure.

developed CKD during the follow-up were significantly older and had a higher baseline BMI, higher triglyceride (Tg) levels and higher blood pressure (table 1). These subjects also had a lower baseline eGFR and FEV<sub>1</sub>/FVC ratio (table 1). In addition, the incidence of hypertension at baseline was higher in subjects who developed CKD (table 1).

The baseline eGFR correlated negatively with age, BMI, systolic blood pressure (SBP), total cholesterol, Hemoglobin A1c (HbA1c), uric acid, and high-sensitivity C reactive protein (hs-CRP). Conversely, eGFR correlated positively with High-density lipoprotein cholesterol

**Table 2** Correlation between the eGFR and risk factors for chronic kidney disease

Variable	eGFR (n=10 128)	
	Correlation coefficient	P values
Age (years)	-0.417	<0.001
BMI (kg/m <sup>2</sup> )	-0.153	<0.001
SBP (mm Hg)	-0.078	<0.001
Fasting glucose (mg/dL)	-0.032	0.840
Albumin (mg/dL)	-0.093	<0.001
Total cholesterol (mg/dL)	-0.063	<0.001
Triglyceride (mg/dL)	-0.053	<0.001
HDL cholesterol (mg/dL)	0.073	<0.001
HbA1c (%)	-0.062	<0.001
Uric acid (mg/dL)	-0.304	<0.001
hs-CRP (mg/L)	-0.018	0.030
Haemoglobin (g/dL)	-0.245	<0.001
Baseline FVC (%)	-0.033	<0.001
Baseline FEV <sub>1</sub> (%)	-0.034	<0.001
FEV <sub>1</sub> /FVC ratio	0.175	<0.001

BMI, body mass index; eGFR, estimated glomerular filtration rate; FEV<sub>1</sub>, forced expiratory volume in 1s; FVC, forced vital capacity; hs-CRP, high-sensitivity C reactive protein; SBP, systolic blood pressure.

(HDL-C) and the FEV<sub>1</sub>/FVC ratio (table 2). The hs-CRP level correlated negatively with FVC ( $r = -0.043$ ,  $p < 0.001$ ), FEV<sub>1</sub> ( $r = -0.041$ ,  $p < 0.001$ ) and FEV<sub>1</sub>/FVC ratio ( $r = -0.020$ ,  $p < 0.001$ ).

After adjustment for risk factors for CKD, including age, sex, BMI, eGFR, fasting glucose, haemoglobin, uric acid, serum albumin, Tg, SBP and the presence of diabetes and/or hypertension, the risk of developing CKD increased as the FEV<sub>1</sub>/FVC ratio decreased (table 3). The HR for the incidence of CKD with a 10% decrease in the FEV<sub>1</sub>/FVC ratio was 1.346. A lower baseline FEV<sub>1</sub>/FVC ratio was associated with the development of CKD even after adjusting for risk factors for CKD. We divided the subjects into two groups according to FEV<sub>1</sub>/FVC ratios (<0.8 and ≥0.8). The incidence of CKD was 2.8% and 1.0%, respectively. Age, sex, BMI, eGFR, SBP, levels of haemoglobin, albumin, uric acid, Tg, fasting glucose, the presence of diabetes and the hypertension-adjusted risk of developing CKD were higher in those with an FEV<sub>1</sub>/FVC ratio less than 0.8 compared with those with an FEV<sub>1</sub>/FVC ratio greater than 0.8 (HR=1.454; 95% CI 1.042 to 2.028,  $p = 0.028$ ; figure 1).

## DISCUSSION

We found that lower FEV<sub>1</sub>/FVC ratio was associated with an increased risk of CKD during the mean follow-up of 5

**Table 3** HR for incident chronic kidney disease by a 10 decrement in the FVC/FEV<sub>1</sub> ratio

Variable	HR (95% CI)	P values
Crude model (95% CI)	1 2.136 (1.787 to 2.552)	<0.001
Adjusted* (95% CI)	1	
Model 1	1 1.419 (1.126 to 1.788)	0.003
Model 2	1 1.384 (1.091 to 1.755)	0.007
Model 3	1 1.346 (1.062 to 1.705)	0.014

Multivariate model 1: adjusted for age, sex, body mass index and the estimated glomerular filtration rate.

Multivariate model 2: adjusted for the factors of model 1, systolic blood pressure and levels of haemoglobin, albumin, uric acid, triglyceride and fasting glucose.

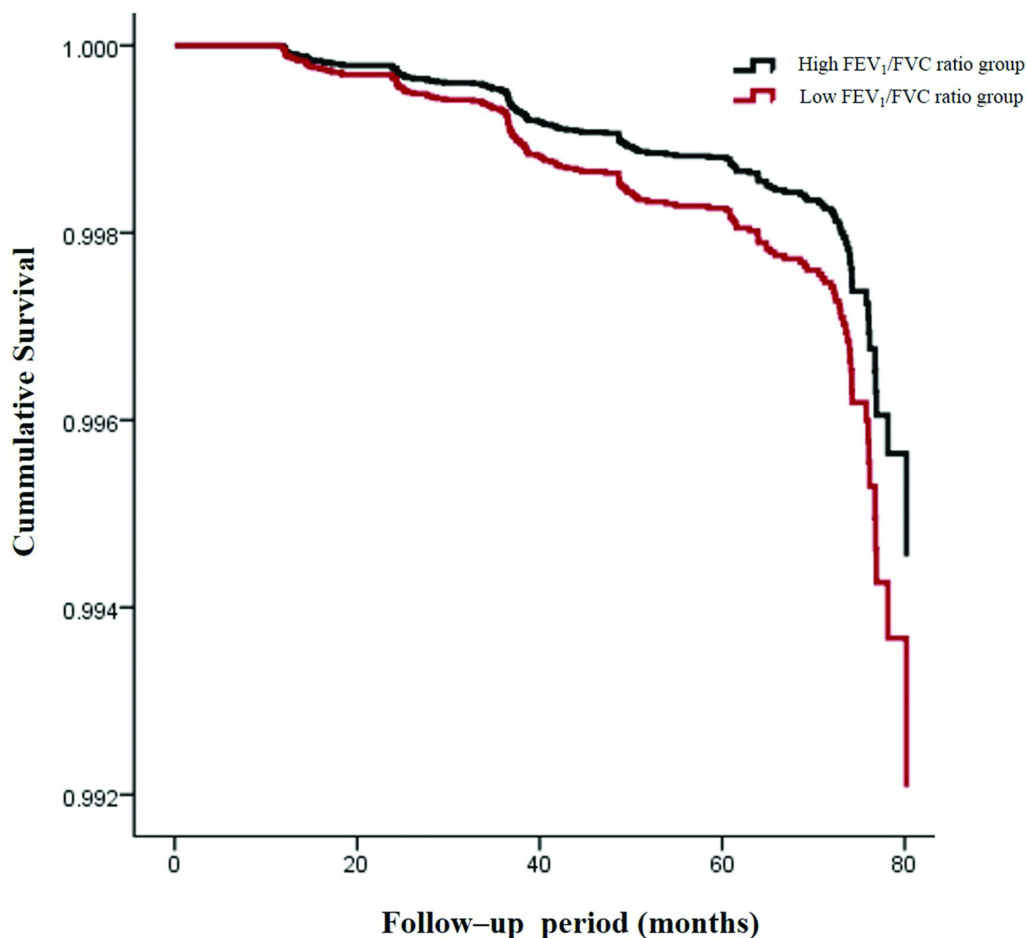
Multivariate model 3: adjusted for the factors of model 2 and the presence of diabetes or hypertension at baseline.

\*By multivariable Cox's proportional hazards analysis.

FEV<sub>1</sub>, forced expiratory volume in 1s; FVC, forced vital capacity.

years. The FEV<sub>1</sub>/FVC ratio (Tiffeneau Index) is an index of airflow limitation.<sup>16</sup> To the best of our knowledge, only a few studies have explored associations between lung function and CKD. Some studies found that kidney dysfunction was more common in patients with COPD.<sup>9-12</sup> Incalzi *et al* found that the prevalence of CKD is increased in patients with COPD, and CKD is a common comorbidity of COPD.<sup>9</sup> Van Gestel *et al* also found that COPD was associated with CKD in patients undergoing vascular surgery.<sup>10</sup> However, most of these studies were conducted in patients with COPD and had a cross-sectional design. Even less is known about the relationship between lung function and CKD incidence. Chen *et al* explored the association between COPD and CKD incidence using hospital records and found that the overall incidence of CKD was higher in patients with COPD than patients without COPD.<sup>11</sup> Our study also showed that subjects with a lower FEV<sub>1</sub>/FVC ratio were at increased risk of developing CKD. This remained true after adjusting for other known risk factors for CKD. Chen *et al* used insurance research data, which did not include information on the GFR, pulmonary function or laboratory test results.<sup>11</sup> Unlike Chen *et al*, we used the eGFR and pulmonary function test data to define CKD and pulmonary function.

Although our study results may be due to a causal relationship, there are some plausible explanations for this relationship. The lung dysfunction has risk factors in common with CKD including old age, smoking, diabetes, hypertension and obesity.<sup>17-19</sup> Patients with reduced lung function may have coexisting diabetes, MetS and/or hypertension, which are known risk factors for CKD.<sup>20 21</sup> We also found that those who developed CKD were more likely to have hypertension and/or dyslipidaemia at baseline and more likely to be older. Baseline age, BMI, HbA1c level and SBP negatively correlated with eGFR. However, reduced lung function (FEV<sub>1</sub>/FVC ratio) at



**Figure 1** Cumulative survival curve for incident chronic renal failure from values of  $FEV_1/FVC$  ratio. The data are adjusted for age, sex, smoking status, body mass index, estimated glomerular filtration rate, systolic blood pressure, levels of haemoglobin, albumin, uric acid, triglyceride and fasting glucose, and the presence of diabetes and/or hypertension at baseline. Cox's proportional hazards regression model was employed to draw the curves.  $FEV_1$ , forced expiratory volume in 1s; FVC, forced vital capacity.

baseline was associated with CKD development after adjusting for these risk factors although the HR decreases after adjusting other risk factors, and baseline  $FEV_1/FVC$  also positively correlated with eGFR. This implies that lung function affects CKD development. Hypoxaemia or increased oxidative stress caused by decreased lung function could contribute to the development of CKD. Accumulating evidence suggests that renal hypoxia is a key player in the progression of CKD.<sup>22</sup> Chronic renal hypoxia is closely linked to capillary rarefaction, which affects tubular epithelial cells, fibroblasts and inflammatory cells, resulting in tubulointerstitial fibrosis.<sup>23</sup> Increased oxidative stress could also contribute to the onset of CKD. Oxidative stress increases the generation of advanced glycation end products (AGEs), which in turn interact with receptors for AGEs (RAGE).<sup>24</sup> AGEs were increased in patients with COPD,<sup>24</sup> and one recent study showed that pulmonary and renal endothelial cell injury was linked to increased endothelial AGEs and RAGE.<sup>25</sup> These studies were done in patients with COPD or COPD animal models, and lung function in our study group was near normal. The attenuated association between  $FEV_1/FVC$

and the development of CKD after adjustment for other factors might be explained by the difference in lung function status of subjects in our study and those of other studies.

Systemic inflammation may also be a link between lung dysfunction and CKD. COPD is a systemic inflammatory disease.<sup>26</sup> Low-grade systemic inflammation was noted in subjects with airflow obstructions.<sup>26</sup> High serum CRP concentrations have been reported in patients with COPD.<sup>27</sup> Thus, COPD is a systemic inflammatory disease involving the lungs. Inflammation also plays a role in the development of CKD and is associated with increased levels of inflammatory and procoagulant biomarkers, including CRP and fibrinogen.<sup>28</sup> Inflammation may trigger the development of CKD in those with lung dysfunction. To understand why lung function was associated with the development of CKD, we explored the association between hs-CRP levels and lung function. The hs-CRP level was negatively associated with the  $FEV_1/FVC$  ratio. This indicates that inflammation may play a role in the relationship between lung dysfunction and CKD.

Our study has certain limitations. First, all subjects were volunteers, self-scheduling comprehensive health examinations (sometimes annually) for at least 5 years, implying that they were more concerned about their health and therefore not representative of the general population. Second, we used the CKD-EPI equation to estimate GFR, because the Modification of Diet in renal disease (MDRD) equation was developed in subjects with CKD and underestimated GFR.<sup>20</sup> So the incidence of CKD was low, and we did not assess proteinuria. Thus, we did not analyse the relationship between lung function and proteinuria. Third, the work was retrospective in nature and the symptoms of any airway disease were not noted. Prospective studies are needed to further define these relationships.

We confirmed that the incidence of CKD is increased in patients with airflow limitation, as measured by the FEV<sub>1</sub>/FVC ratio. CKD is associated with mortality and morbidity. Therefore, it is important to recognise the relationship between reduced lung function and CKD development in clinical practice.

## CONCLUSION

Limited airflow as measured by the FEV<sub>1</sub>/FVC ratio was associated with an increased risk of CKD. This implies that common pathogenic mechanisms exist between a decline in lung function and the development of CKD. The baseline FEV<sub>1</sub>/FVC ratio could be helpful for identifying individuals at risk for CKD.

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