


# Inflammatory biomarkers and radiologic measurements in never-smokers with COPD: A cross-sectional study from the CODA cohort

Chronic Respiratory Disease  
2018, Vol. 15(2) 138–145  
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DOI: 10.1177/1479972317736293  
journals.sagepub.com/home/crd  


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## Abstract

Various biomarkers have emerged as potential surrogates to represent various subgroups of chronic obstructive pulmonary disease (COPD), which manifest with different phenotypes. However, the biomarkers representing never-smokers with COPD have not yet been well elucidated. The aim of this study was to evaluate the associations of certain serum and radiological biomarkers with the presence of COPD in never-smokers. To explore the associations of serum and radiological biomarkers with the presence of COPD in never-smokers, we conducted a cross-sectional patient cohort study composed of never-smokers from the COPD in Dusty Areas (CODA) cohort, consisting of subjects living in dusty areas near cement plants in South Korea. Of the 131 never-smokers in the cohort, 77 (58.8%) had COPD. There were no significant differences in the number of subjects with high levels of inflammatory biomarkers (>90th percentile of never-smokers without COPD), including white blood cell count, total bilirubin, interleukin (IL)-6, IL-8, and C-reactive protein, or radiologic measurements (including emphysema index and mean wall area percentage) between never-smokers with COPD and those without COPD. However, the number of subjects with high uric acid was significantly higher in never-smokers with COPD than never-smokers without COPD (31.2% (24/77) vs. 11.1% (6/54);  $p = 0.013$ ). In addition, multivariate analysis revealed that high uric acid was significantly associated with the presence of COPD in never-smokers (adjusted relative risk: 1.63; 95% confidence interval: 1.21, 2.18;  $p = 0.001$ ). Our study suggests that high serum levels of uric acid might be a potential biomarker for assessing the presence of COPD in never-smokers.

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## Keywords

Serum and radiologic biomarker, uric acid, chronic obstructive pulmonary disease, never-smoker

Date received: 17 September 2016; accepted: 5 September 2017

## Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent and generally progressive airflow limitation, which is associated with an abnormal inflammatory response in the airways and the lungs to inhaled cigarette smoke and other noxious particles.<sup>1</sup> The heavy exposure to smoke is related to structural changes in the lung. The degree of emphysema and airway wall thickness can be measured by chest computed tomography (CT) scan and CT measurements have shown a significant correlation of emphysema and airway wall thickness with the degree of airflow obstruction in the context of COPD.<sup>2–4</sup>

COPD is also associated with low-grade systemic inflammation, which is potentially linked to the increased rate of extrapulmonary complications and comorbidities in COPD patients.<sup>5,6</sup> Indeed, numerous observational cohort studies have evaluated various inflammatory mediators, including interleukin (IL)-6, IL-8, fibrinogen, C-reactive protein (CRP), and white blood cell (WBC) count, to show the effect of systemic inflammation and its association with comorbidities and poor outcomes in patients with COPD.<sup>5,7,8</sup> Given that oxidative stress caused by environmental toxins, such as cigarette smoking and air pollutants, plays a central role in COPD pathogenesis, levels of uric acid and total bilirubin (TB), which possesses antioxidant properties, were assessed in patients with COPD and were found to have a significant negative association with the incidence of COPD and disease progression.<sup>9–11</sup> In particular, these biomarkers have the benefit of being measurable via relatively simple, inexpensive, and readily accessible blood tests.

Since cigarette smoking is the primary cause of COPD, these biomarkers have mainly been evaluated in smokers with and without COPD, using never-smokers as a control group. However, the proportion of never-smokers among patients with COPD is substantial. Moreover, this proportion is increasing and COPD imposes a large public health burden on the never-smoking population.<sup>12–15</sup> Consequently, the clinical characterization of COPD in never-smokers has begun to receive considerable attention and a recent study reported that never-smokers with COPD had

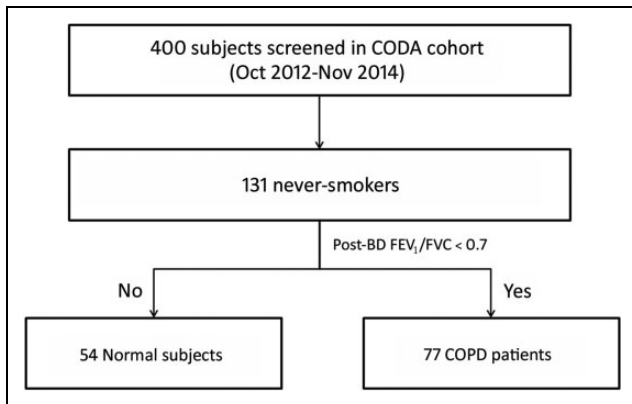
lower levels of inflammatory biomarkers when compared to smokers with COPD.<sup>16</sup> However a comprehensive comparison of levels of serum inflammatory biomarkers in never-smokers with COPD versus those in never-smokers without COPD has not been well described. Furthermore, there was no available study investigating whether never-smokers with COPD exhibit a different presentation with respect to airway wall thickness or emphysema compared with never-smokers without COPD. Thus, here we aimed to investigate whether serum inflammatory biomarkers and radiologic measurements were associated with the presence of COPD in never-smokers.

## Methods

### Study design

The COPD in Dusty Areas (CODA) study was a longitudinal observational study that was conducted on subjects living in dusty areas near cement plants in the Kangwon and Chungbuk provinces of South Korea.<sup>17</sup> The participants were recruited from six administrative districts of Korea where the cement plants were located. The administrative districts have areas of approximately 40–80 km<sup>2</sup> and 23,457 residents (participants from two districts are aged over 20 years and four districts are aged over 40 years). The cohort was composed of subjects with airflow limitation and healthy volunteers who agreed to undergo examination.

To explore the associations of serum and radiological biomarkers with COPD in never-smokers, we performed a cross-sectional study of never-smokers at the time of study enrollment who were recruited between October 2012 and November 2014 from the CODA cohort. Among the 400 patients in the CODA cohort, 131 subjects who had no smoking history were included in this study (Figure 1). All patients underwent pre- and post-bronchodilator (post-BD) spirometry to diagnose airflow limitation. Airflow limitation was defined as a post-BD forced expiratory volume in 1 s (FEV<sub>1</sub>)/forced vital capacity (FVC) of <70%, and the severity of airflow limitation was defined as follows: mild (FEV<sub>1</sub> ≥ 80% of the



**Figure 1.** Flow chart of study patients. BD: bronchodilator; FEV<sub>1</sub>: forced expiratory volume in 1 s; FVC: forced vital capacity; COPD: chronic obstructive pulmonary disease.

predicted value), moderate ( $50\% \leq \text{FEV}_1 < 80\%$  of the predicted value), severe ( $30\% \leq \text{FEV}_1 < 50\%$  of the predicted value), and very severe ( $\text{FEV}_1 < 30\%$  of the predicted value).<sup>1</sup> This study was approved by the Institutional Review Board of the Kangwon National University Hospital (IRB no. 2012-06-007), and written informed consent was provided by all participants.

### Clinical, laboratory, imaging, and quality of life measurements

The detailed methods adopted in the CODA study have been previously described.<sup>17,18</sup> The CODA study investigators collected the data detailed below via a questionnaire that was distributed to the study participants. Dyspnea and health-related quality of life were evaluated using the modified Medical Research Council (mMRC) dyspnea scale and the patient-reported COPD assessment test (CAT), respectively.

Volumetric CT scans were taken at full inspiration and expiration using a first-generation dual source CT system (Somatom Definition, Siemens Healthcare, Forchheim, Germany). The CT parameters used in CT scanner were as follows:  $16 \times 0.75 \text{ mm}^2$  collimation, 100 eff. milliampere-seconds (mAs), 140 peak kilovoltage (kVp), 0.9–1 beam pitch, and 0.6 mm section thickness. CT data were reconstructed using soft kernels. The CT images were obtained without the injection of a contrast medium. Imaging data were stored in the Digital Imaging and Communications in Medicine format, which is the international standard for interconnecting medical imaging devices on standard networks. We measured the emphysema index

(EI; the percentage of low attenuation area  $\leq 950$  Hounsfield units (HU, %LAA<sub>-950HU</sub>)) and mean wall area percentage ((WA%) of two segmental bronchi) using an in-house software program developed by the Korean obstructive lung disease study group.<sup>18–20</sup>

Spirometry was performed using an EasyOne Kit (NDD, Zurich, Switzerland) as recommended.<sup>21</sup> Serum concentrations of IL-6 and IL-8 were measured using commercially available ELISA kits (Cloud-Clone Corp., Houston, TX, USA) according to the manufacturer's instructions. The lower limits of quantification for IL-6 and IL-8 were 0.6 and 6.5  $\text{pg mL}^{-1}$ , respectively.

### Statistical analyses

Categorical variables are presented as a number (percentage), and continuous variables are presented as the mean  $\pm$  standard deviation or median with interquartile range (IQR), as appropriate. Categorical variables were compared using contingency chi-squared tests, and continuous variables were compared using the Mann–Whitney U test or Student's *t*-test, as appropriate. In our analysis of the relative risk of inflammatory biomarkers and EI in never-smokers with COPD versus never-smokers without COPD, we defined high levels of serum inflammatory biomarkers (WBC, TB, uric acid, CRP, IL-6, and IL-8) as >90th percentile of never-smokers without COPD. We categorized EI as 5% or 10%.<sup>22,23</sup> A modified Poisson regression model was used to determine the factors associated with the presence of COPD in never-smokers.<sup>24</sup> In the model, for each serum biomarker and radiologic measurement, we adjusted for age, sex, and body mass index (BMI), which were generally considered to be different between patients with COPD and those without COPD.<sup>25</sup> A two-sided *p* value of  $<0.05$  was regarded as statistically significant. All statistical analyses were performed using R Statistical Software (version 3.2.5; R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS Statistics for Windows, version 23.0 (Armonk, NY, USA).

## Results

### Patients

The baseline characteristics of the 131 subjects in the never-smoker cohort of the CODA study are summarized in Table 1. Of the 131 never-smokers, 77 (58.8%) had COPD. The median age was 73.0 years (IQR:

**Table 1.** Comparison of baseline characteristics between never-smokers without COPD and those with COPD.<sup>a</sup>

	Total (n = 131)	Never-smokers without COPD (n = 54; 41.2%)	Never-smokers with COPD (n = 77; 58.8%)	p
Age	73.0 (70.0, 77.0)	73.0 (69.0, 77.0)	74.0 (71.0, 78.0)	0.314
Female	95 (72.5)	38 (70.4)	57 (74.0)	0.793
BMI (kg m <sup>-2</sup> )	24.0 ± 3.1	23.9 ± 3.2	24.1 ± 3.1	0.682
Extra-pulmonary comorbidities				
Diabetes mellitus	16 (12.2)	7 (13.0)	9 (11.7)	1.0
Cerebrovascular disease	12 (9.2)	5 (9.3)	7 (9.1)	1.0
Malignancy	6 (4.6)	3 (5.6)	3 (3.9)	0.976
Chronic liver disease	5 (3.8)	2 (3.7)	3 (3.9)	1.0
Chronic kidney disease	3 (2.3)	2 (3.7)	1 (1.3)	0.772
Pulmonary comorbidities				
Asthma	30 (22.9)	11 (20.4)	19 (24.7)	0.575
Bronchiectasis	4 (3.1)	1 (1.9)	3 (3.9)	0.782
CAT score	18.0 (9.0, 26.0)	18.0 (9.0, 24.0)	19.0 (8.0, 26.0)	0.830
mMRC dyspnea scale				0.536
0	25 (19.1)	13 (24.1)	12 (15.6)	
1	56 (42.8)	22 (40.7)	34 (44.1)	
2	16 (12.2)	8 (14.8)	8 (10.4)	
3	26 (19.8)	9 (16.7)	17 (22.1)	
4	8 (6.1)	2 (3.7)	6 (7.8)	
Severity of airflow limitations				<0.001
Mild	46 (35.1)	—	46 (59.7)	
Moderate	30 (22.9)	—	30 (39.0)	
Severe	1 (0.8)	—	1 (1.3)	
Post-BD spirometry				
FVC (L)	2.6 (2.1, 3.1)	2.7 (2.2, 3.1)	2.4 (2.1, 3.4)	0.510
FVC (% predicted)	103.0 (93.5, 114.0)	100.5 (93.0, 113.0)	104.0 (94.0, 115.0)	0.583
FEV <sub>1</sub> (L)	1.7 (1.4, 2.1)	2.1 (1.7, 2.3)	1.5 (1.2, 1.9)	<0.001
FEV <sub>1</sub> (% predicted)	94.0 (80.6, 104.5)	99.5 (94.0, 115.0)	86.0 (72.0, 96.0)	<0.001
FEV <sub>1</sub> /FVC (%)	66.7 ± 9.4	75.5 ± 3.7	60.6 ± 6.6	<0.001

COPD: chronic obstructive pulmonary disease; BMI: body mass index; mMRC: modified Medical Research Council; BD: bronchodilator; FVC: forced vital capacity; FEV<sub>1</sub>: forced expiratory volume in 1 s; CAT: COPD assessment test.

<sup>a</sup>Categorical variables are presented as number (%) and continuous variables are presented as mean and standard deviation or median and interquartile range, as appropriate.

70.0–77.0 years), and 72.5% (*n* = 95) of subjects were female. The mean BMI was 24.0 ± 3.1 kg m<sup>-2</sup>. The common extrapulmonary comorbidities were diabetes mellitus (*n* = 16; 12.2%), followed by cerebrovascular disease (*n* = 12; 9.2%), malignancy (*n* = 6; 4.6%), and chronic liver disease (*n* = 5; 3.8%). The common pulmonary comorbidities were asthma (*n* = 30; 22.9%) and bronchiectasis (*n* = 4; 3.1%). The median CAT score was 18.0 (IQR: 9.0–26.0), and the mMRC dyspnea score was 0 in 25 (19.1%), 1 in 56 (42.8%), 2 in 16 (12.2%), 3 in 26 (19.8%), and 4 in 8 subjects (6.1%). The mean post-BD FEV<sub>1</sub>/FVC was 66.7% ± 9.4%, and the median post-BD FEV<sub>1</sub> (L; % predicted) was 1.7 L (94.0% predicted).

There were no significant differences in age, sex, BMI, the presence of extra-pulmonary comorbidities (diabetes mellitus, cerebrovascular disease, chronic kidney disease, chronic liver disease, and malignancy), the presence of pulmonary comorbidities (asthma and bronchiectasis), CAT score, mMRC dyspnea scale, or post-BD FVC (L; % predicted) between never-smokers with COPD and never-smokers without COPD. In contrast, the median post-BD FEV<sub>1</sub> (2.1 L (99.5% predicted) vs. 1.5 L (86.0% predicted); *p* < 0.001) and mean post-BD FEV<sub>1</sub>/FVC (75.5% ± 3.7% vs. 60.6% ± 6.6%; *p* < 0.001) values were significantly higher in never-smokers without COPD than never-smokers with COPD.

**Table 2.** Comparison of inflammatory biomarkers and radiologic measurements between never-smokers COPD and never-smokers with COPD.<sup>a</sup>

	Never-smokers without COPD (n = 54; 41.2%)	Never-smokers with COPD (n = 77; 58.8%)	p
<b>Measured values of inflammatory biomarkers</b>			
WBC ( $\times 10^9$ cells $L^{-1}$ )	6.5 (5.1, 7.5)	5.8 (4.8, 7.0)	0.156
TB (mg $dL^{-1}$ )	0.7 (0.6, 0.9)	0.8 (0.6, 1.0)	0.464
Uric acid (mg $dL^{-1}$ )	4.7 (3.7, 5.4)	4.7 (4.2, 5.9)	0.080
IL-6 (pg $mL^{-1}$ )	1.7 (0.5, 4.1)	1.1 (0.4, 2.8)	0.231
IL-8 (pg $mL^{-1}$ )	13.1 (6.0, 19.2)	12.3 (7.9, 18.9)	0.848
CRP (mg $dL^{-1}$ )	0.1 (0, 0.2)	0.1 (0, 0.1)	0.043
<b>High serum inflammatory biomarkers<sup>b</sup></b>			
WBC	6 (11.1)	8 (10.4)	1.0
TB	5 (9.3)	10 (13.0)	0.703
Uric acid	6 (11.1)	24 (31.2)	0.013
IL-6	6 (11.1)	8 (10.4)	1.0
IL-8	6 (11.1)	7 (9.1)	0.933
CRP	6 (11.1)	10 (13.0)	0.959
<b>Number of high inflammatory biomarkers</b>			
<2	47 (87.0)	62 (80.5)	0.456
$\geq 2$	7 (13.0)	15 (19.5)	
<b>Radiologic measurements</b>			
EI (%)	4.5 (1.3, 7.4)	3.7 (1.6, 9.9)	0.751
EI > 5%	24 (44.4)	31 (40.3)	0.766
EI > 10%	10 (18.5)	19 (24.7)	0.534
WA%	69.1 $\pm$ 5.1	67.8 $\pm$ 5.1	0.151

COPD: chronic obstructive pulmonary disease; WBC: white blood cell; IL: interleukin; TB: total bilirubin; CRP: C-reactive protein; EI: emphysema index; WA%: mean wall area percentage.

<sup>a</sup>Categorical variables are presented as number (%) and continuous variables are presented as mean and standard deviation or median and interquartile range, as appropriate.

<sup>b</sup>Defined as >90th percentile of never smokers without COPD.

### Comparison of biomarkers between never-smokers with or without COPD

As shown in Table 2, there were no significant differences in the median values of any of the measured inflammatory biomarkers, including WBC, TB, uric acid, IL-6, and IL-8, between never-smokers with COPD and those without COPD. In contrast, the median CRP level was significantly higher in never-

smokers without COPD than never-smokers with COPD (0.1 mg  $dL^{-1}$  (IQR: 0–0.2 mg  $dL^{-1}$ ) vs. 0.1 mg  $dL^{-1}$  (IQR: 0–0.1 mg  $dL^{-1}$ );  $p = 0.043$ ). There were no significant differences in the number of subjects with high serum WBC, TB, IL-6, IL-8, or CRP between the two groups. However, the number of subjects with high serum uric acid levels was significantly higher in the never-smokers with COPD than the never-smokers without COPD (31.2% (24/77) vs. 11.1% (6/54);  $p = 0.013$ ). With respect to the total number of high serum inflammatory biomarkers (<2 vs.  $\geq 2$ ), there was no significant difference between never-smokers with COPD and those without COPD. Moreover, no significant differences were observed for EI or WA% between the two groups.

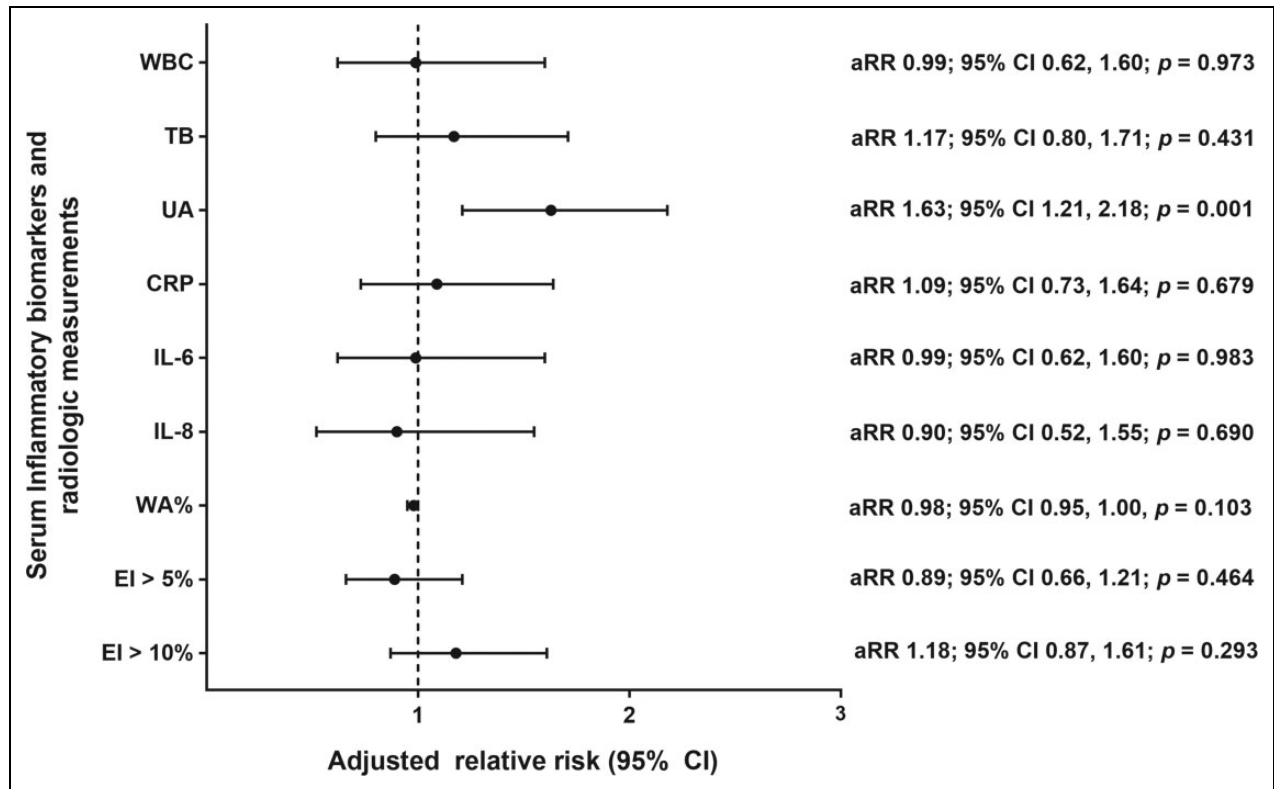
### Association of high-level serum inflammatory biomarkers and radiologic measurements with the presence of COPD in never-smokers

As shown in Figure 2, high serum uric acid was the only biomarker that was significantly associated with the presence of COPD in never-smokers (adjusted relative risk: 1.63; 95% confidence interval: 1.21 and 2.18;  $p = 0.001$ ). On the other hand, the other inflammatory biomarkers (high levels of WBC, TB, CRP, IL-6, and IL-8) or radiologic measurements (EI > 5%, EI > 10%, and WA%) showed no significant association with the presence of COPD in never-smokers.

### Discussion

In the present study, we compared serum inflammatory biomarkers and radiologic measurements between never-smokers with COPD and never-smokers without COPD using data from the CODA cohort study. The main finding of our study is that high serum uric acid was significantly associated with the presence of COPD in never-smokers, and that this association persisted even after adjustment for other covariates. However, there were no significant differences with respect to any of the other inflammatory biomarkers (high levels of WBC, TB, CRP, IL-6, and IL-8) or radiologic measurements (EI and WA%) between never-smokers with COPD and those without COPD.

Uric acid is an end-product molecule generated from purine degradation<sup>26</sup> that shows a complex response in patients with COPD which appears to be heavily influenced by smoking status. One cross-sectional study of smokers showed that serum



**Figure 2.** aRR of inflammatory biomarkers and radiologic measurements for the presence of COPD in never-smokers. Each serum biomarker (high levels of WBC, TB, uric acid, CRP, IL-6, and IL-8) and radiologic measurement (EI > 5%, EI > 10%, and WA%) was adjusted for age, sex, and BMI. aRR: adjusted relative risk; COPD: chronic obstructive pulmonary disease; WBC: white blood cell; TB: total bilirubin; CRP: C-reactive protein; IL: interleukin; BMI: body mass index; EI: emphysema index; WA%: mean wall area percentage; CI: confidence interval.

uric acid levels were reduced in severe COPD.<sup>27</sup> Another large population-based cohort study reported that lower serum uric acid levels were significantly associated with a higher rate of COPD development in current smokers.<sup>9</sup> In contrast, a population-based cross-sectional study in Japan observed an inverse association between serum uric acid levels and FEV<sub>1</sub> in healthy women, the majority of whom had little smoking history.<sup>28</sup> Although one large population-based cohort study showed that there was no statistically significant association between serum uric acid and COPD in non-smokers, an incidence of COPD among non-smokers tends to increase as uric acid levels elevate, especially in the highest quintiles of uric acid.<sup>9</sup> These results suggest that above certain level, the risk of COPD might increase with elevated uric acid among non-smoker. One in vivo study using human airway epithelial cells demonstrated that exposure to particulate matter (PM)<sub>10</sub>, a major component of air pollution, induced lung mucosal uric acid production and secretion, indicating that uric acid increases in the

lung in response to PM<sub>10</sub> exposure.<sup>29</sup> Since outdoor air pollution is another important risk factor of the development of COPD in never-smokers, our study with a highly specific group of patients, that is, those without smoking history, extends the findings of previous studies showing that high serum uric acid levels are specifically associated with the presence of COPD in never-smokers.

With the exception of uric acid, high levels of serum inflammatory biomarkers, including WBC, CRP, IL-6, and IL-8, were not shown to be associated with the presence of COPD in never-smokers. These findings are consistent with previous studies, which showed similar levels of WBC, CRP, and fibrinogen in never-smokers with COPD and never-smokers without COPD.<sup>16</sup> In addition, we did not identify any significant differences in radiologic measurements, including EI and WA%, between never-smokers with COPD and those without COPD. This lack of association might explain the distinctive characteristics of COPD in never-smokers that have been previously described (fewer symptoms, milder

disease severity, and a lower risk of cardiovascular comorbidities and lung cancer), compared with the characteristics seen in patients with a smoking history.<sup>16</sup> Our study also showed that never-smokers with COPD and never-smokers without COPD had similar respiratory symptoms (mMRC score) and CAT scores representing health-related quality of life. As the majority of never-smokers with COPD had mild-to-moderate airflow limitations in our study, more symptomatic never-smokers with severe grade of COPD might show a different pattern of inflammatory biomarker profiles and radiologic measurements, compared with never-smokers without COPD.

In our study, almost 59% of never-smokers had COPD, which is much higher than the prevalence of COPD in never-smokers reported in population-based studies with subjects aged  $\geq 40$  years.<sup>13,30</sup> Age is often regarded as a risk factor for COPD.<sup>1</sup> Considering that the median age was 73 years in our cohort, high prevalence of COPD might be due to a selection bias that people with old age or physical symptoms are more likely to participate in study. Given that asthma is a risk factor for COPD, another explanation could be the higher prevalence of bronchial asthma of 23% in our cohort than those in other studies conducted with Koreans: it was 5.4% in subjects with age  $>65$  years in a longitudinal study<sup>31</sup> and 13% of the Korean population with obstructive pattern of pulmonary function test had asthma according to the fourth and fifth Korean National Health and Nutrition Examination Survey.<sup>30</sup> Although genuine environmental factor, cement plants, would impact on airway disease resulting in increasing prevalence of COPD among never-smokers, further studies are necessary to evaluate the association.

There are several limitations of the present study. First, this study was performed in dusty areas near cement plants in South Korea. Thus, the patients enrolled in this study may have been subject to selection bias, and our results may not be generalizable to all never-smokers with COPD. However, since we enrolled controls in the same district, the amount of dust exposure should be the same between never-smokers with and without COPD. Thus, we believe that the study population used was appropriate for the purposes of this study. Second, the exact mechanism underlying the bidirectional association between uric acid levels and the presence of COPD according to smoking status has not been well elucidated. Thus, further studies are needed to investigate these issues. Finally, the possibility remains that the number of

patients was not sufficient to reach statistical significance regarding the negative associations between inflammatory biomarkers other than uric acid and the presence of COPD in never-smokers. Thus, further studies with larger sample sizes are needed to confirm the lack of associations between these biomarkers and the presence of COPD in never-smokers.

In conclusion, our study showed that high uric acid was independently associated with never-smokers with COPD, which suggests that uric acid might be a useful biomarker related to the presence of COPD in never-smokers.

### Author contributions

WJK and HYP contributed to this work equally.

### Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by a grant from the Ministry of Environment, Republic of Korea and Samsung Medical Center Foundation for Medical Research (SMX1151371). Hye Yun Park has received lecture fees from AstraZeneca, Novartis and Boehringer-Ingelheim.

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