Received: 19 September 2023 | Accepted: 30 January 2024

DOI: 10.1111/resp.14687

ORIGINAL ARTICLE

Official Journal of the Asian Pacific Society of Respirology
Respirology
APSR
WILEY

Combined effect of changes in NO_2, O_3, $PM_{2.5}$, SO_2 and CO concentrations on small airway dysfunction

Hyun Woo Lee[1] | Hyo Jin Lee[1] | Sohee Oh[2] | Jung-Kyu Lee[1] | Eun Young Heo[1] | Deog Kyeom Kim[1]

[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University College of Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, Korea

[2]Medical Research Collaborating Center, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, Korea

Correspondence
Hyun Woo Lee
Email: athrunzara86@snu.ac.kr

Associate Editor: Alexander Larcombe;
Senior Editor: Paul King

Abstract

Background and Objective: When multiple complex air pollutants are combined in real-world settings, the reliability of estimating the effect of a single pollutant is questionable. This study aimed to investigate the combined effects of changes in air pollutants on small airway dysfunction (SAD).

Methods: We analysed Korea National Health and Nutrition Examination Survey (KNHANES) V–VIII database from 2010 to 2018 to elucidate the associations between annual changes in air pollutants over a previous 5-year period and small airway function. We estimated the annual concentrations of five air pollutants: NO_2, O_3, $PM_{2.5}$, SO_2 and CO. Forced expiratory flow between 25% and 75% of vital capacity ($FEF_{25\%–75\%}$) <65% was defined as SAD. Using the quantile generalized-Computation (g-Computation) model, the combined effect of the annual changes in different air pollutants was estimated.

Results: A total of 29,115 individuals were included. We found significant associations between SAD and the quartiles of annual changes in NO_2 (OR = 1.10, 95% CI = 1.08–1.12), O_3 (OR = 1.03, 95% CI = 1.00–1.05), $PM_{2.5}$ (OR = 1.03, 95% CI = 1.00–1.05), SO_2 (OR = 1.04, 95% CI = 1.02–1.08) and CO (OR = 1.16, 95% CI = 1.12–1.19). The combined effect of the air pollutant changes was significantly associated with SAD independent of smoking (OR = 1.31, 95% CI = 1.26–1.35, *p*-value <0.001), and this trend was consistently observed across the entire study population and various subgroup populations. As the estimated risk of SAD, determined by individual-specific combined effect models, increased and the log odds for SAD increased linearly.

Conclusion: The combined effect of annual changes in multiple air pollutant concentrations were associated with an increased risk of SAD.

KEYWORDS
air pollutants, air pollution, environmental exposure, lung diseases, respiratory function tests

INTRODUCTION

Air pollution is widely recognized as one of the major causes of impaired lung function. Particulate matter <2.5 μm ($PM_{2.5}$) has been linked to a decrease in forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC), as well as an increased incidence of chronic obstructive pulmonary disease (COPD).[1–3] Exposure to nitrogen dioxide (NO_2) has been associated with a reduced FEV_1 or FVC, a decline in the FEV_1/FVC ratio and an increased prevalence of asthma and COPD.[1,4,5] Ozone (O_3) exposure is related to small airway dysfunction (SAD).[6] In particular, the impact of O_3 exposure on decreased FEV_1 and FVC has been more significant in children compared to adults.[7,8] Elevated levels of carbon monoxide (CO) have been related with decreased FEV_1 in both asthma and COPD patients,[9,10] as well as reduced peak expiratory flow rate (PEFR) and increased variability in asthmatic individuals.[11,12] Increased levels of sulphur dioxide (SO_2) have shown associations with decreased FEV_1, FVC and forced expiratory flow at 25%–75% ($FEF_{25\%–75\%}$) in elderly populations.[2]

Most previous studies have focused on the individual effects of each air pollutant on lung function. However, the estimated effect of a single air pollutant is not realistic in a real-world situation where several complex air pollutants are mixed. A comparison between a single-pollutant model and a two-pollutant model revealed that two air pollutants exhibited the presence of synergistic or antagonistic effects

on emergency room visits.[13] Therefore, it is crucial to consider the interactions and combined effects of multiple air pollutants for a comprehensive assessment of lung function in real-world atmospheric environments.

The aim of this study was to investigate whether the combined effects of changes in air pollutants over a 5-year period were associated with SAD.

SUMMARY AT A GLANCE

The combined effect of annual changes in NO_2, O_3, $PM_{2.5}$, SO_2 and CO concentrations were associated with an increased risk of small airway dysfunction.

METHODS

Study design and eligibility criteria

Our observational study used the database of the Korea National Health and Nutrition Examination Survey (KNHANES) V–VIII from 2010 to 2018, which is a nationwide surveillance system designed to assess the health status of a representative sample of the Korean population.[14] We included individuals who had information on air pollutants for the previous 5 years and spirometric profiles, which were publicly available in KNHANES website.[15] Spirometric evaluations were performed only in the adults aged 40–80 years. Individuals with any missing data were excluded from the study.

Lung function

Lung function tests were conducted once per individual from 2010 to 2018, following 5 years of air pollutant observation, in accordance with the 2005 ATS/ERS standards for spirometry. Each individual underwent three measurements, and the largest FVC and FEV_1 values were selected. $FEF_{25\%–75\%}$ value was taken from the blow with the largest sum of FEV_1 and FVC. We defined $FEF_{25\%–75\%}$ (% of predicted value) <65% as SAD based on the previous studies.[16,17]

Exposure assessment

We obtained annual average concentrations of NO_2, O_3, $PM_{2.5}$, SO_2 and CO that individuals had been exposed to over a 5-year period (2010–2018) using the KNHANES V–VIII database. These concentrations were predicted based on the subjects' home addresses. The detailed methodology for estimating ambient air pollution was previously described.[18] In brief, the concentrations of air pollutants were derived from a validated chemical transport model known as the Community Multiscale Air Quality (CMAQ) model (United States Environmental Protection Agency [US EPA] Model-3 CMAQ version 4.7.1). This model involved analysing gas and aerosol chemical reactions and advection diffusion equations based on meteorological and emission modelling data.[19,20] Data assimilation was additionally applied to generate NO_2, O_3, SO_2 and CO concentrations. For $PM_{2.5}$ data, satellite data and multiple regression model were used. The residential address data were annually updated on a 1 km grid for $PM_{2.5}$ and a 9 km grid for NO_2, O_3, SO_2 and CO. More detailed information on measuring each air pollutant can be obtained through the 'Guidelines for Using Air Pollution Databases' section through the following link (URL: https://knhanes.kdca.go.kr/knhanes/sub09/sub09_03.do). Finally, we computed β-coefficients from the linear mixed model to estimate the annual changes in air pollutant concentrations across all addresses for each subject over the five-year period, based on previous studies.[21–23]

Statistical analysis

We performed univariable and multivariable linear regression models to assess the association between the annual changes in air pollutant concentrations and $FEF_{25\%–75\%}$ (% of predicted value) as continuous variables. Additionally, we used univariable and multivariable logistic regression models to evaluate whether the annual change in air pollutant concentrations were associated with SAD as a categorical variable. Since the scales and data distributions varied across the air pollutants, we estimated the effect of each air pollutant change for a quartile increment. Supporting Information is provided for more detailed understanding through continuous variable analyses with annual changes in each air pollutant.

The relationships between the annual changes in different air pollutants were depicted using scatter plots, with the coefficient of determination (R^2) provided. Variance inflation factor (VIF) <4 was considered as low collinearity. The combined effect of the annual changes in NO_2, O_3, $PM_{2.5}$, SO_2 and CO concentrations was estimated using a quantile generalized-Computation (g-Computation) model, with equal quartile increments for each air pollutant change. The 'qgcomp' package in R was utilized for this model. In the quantile g-Computation model, the annual changes in air pollutants were transformed into categorical quartile variables. The summed weight of a quartile increment of the air pollutant changes was estimated for $FEF_{25\%–75\%}$ (% of predicted value) or SAD in multivariable linear or logistic models. The detailed methodology on the quantile g-Computation model was previously published.[24,25] Additionally, the log (OR) for SAD was calculated using a generalized additive model, combining the weighted quartiles of change in air pollutants into a single continuous variable for individual patients. The R statistical software, version 4.1.2 (R Core Team, Vienna, Austria), was used for all statistical analyses.

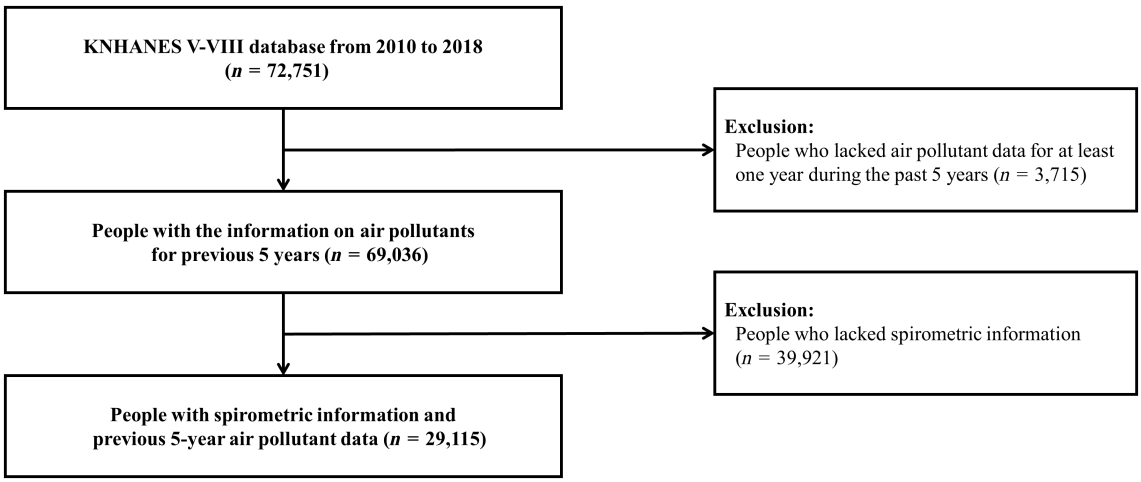

FIGURE 1 The flow diagram of inclusion for the study population.

TABLE 1 Baseline characteristics of people in KNHANES V–VIII database from 2010 to 2018.

	Total (n = 29,115)
Age, mean (SD)	57.6 (10.9)
Female, *n* (%)	16,338 (56.1)
BMI, mean (SD)	24.2 (3.1)
Smoking status	
Never smoker, *n* (%)	16,927 (58.1)
Ex-smoker, *n* (%)	6661 (22.9)
Current smoker, *n* (%)	4991 (17.1)
Comorbidities	
Asthma, *n* (%)	958 (3.3)
COPD, *n* (%)	197 (0.7)
History of pulmonary tuberculosis, *n* (%)	1498 (5.1)
History of lung cancer, *n* (%)	41 (0.1)
Blood test	
White blood cell, /μL, mean (SD)	6090 (1720)

Abbreviations: COPD, chronic obstructive pulmonary disease; SAD, small airway dysfunction.

TABLE 2 Initial concentration and annual change of air pollutants for 5 years.

	Total (n = 29,115)
Initial concentration of air pollutants	
NO_2, ppb, median (IQR)	22.5 (17.3–34.1)
O_3, ppb, median (IQR)	24.9 (22.3–27.7)
$PM_{2.5}$, μg/m^3, median (IQR)	24.7 (23.0–26.7)
SO_2, ppb, median (IQR)	4.7 (4.0–5.4)
CO, ppb, median (IQR)	503.2 (421.2–557.7)
Annual change of air pollutants	
Annual change of NO_2, ppb/year, median (IQR)	−0.01 (−0.22–0.25)
Annual change of O_3, ppb/year, median (IQR)	0.37 (0.11–0.57)
Annual change of $PM_{2.5}$, μg/m^3/year, median (IQR)	−0.17 (−0.51–0.17)
Annual change of SO_2, ppb/year, median (IQR)	−0.10 (−0.16–-0.02)
Annual change of CO, ppb/year, median (IQR)	−4.13 (−9.22–0.25)

Abbreviation: IQR, interquartile range.

RESULTS

Among the 72,751 individuals who received the KNHANES V–VIII surveys, 69,036 had data on the air pollutants for the previous 5 years (Figure 1). Within this population, 29,115 had the information on their spirometric profiles.

Baseline characteristics

The baseline characteristics of a total of 29,115 individuals are summarized in Table 1. Among them, 12,496 (42.2%) were identified with SAD. Individuals with SAD were older, had a higher proportion of males, higher BMI and higher rates of smoking compared to those without SAD (Table S1 in the Supporting Information). Individuals with SAD also had a higher prevalence of comorbidities such as asthma, COPD, history of pulmonary tuberculosis and history of lung cancer. Blood tests indicated a higher white blood cell count in those with SAD.

Annual changes of air pollutants

Initial concentrations and annual changes of air pollutants were described in Table 2 and Table S2 in the Supporting Information. We found that individuals with SAD were exposed to higher initial concentrations of air pollutants such as NO_2, $PM_{2.5}$, SO_2 and CO compared to those without SAD (p-value<0.001, Table S3 in the Supporting Information). The median annual changes for NO_2, O_3, $PM_{2.5}$ and CO were

TABLE 3 Association between quartiles of air pollutant changes and small airway dysfunction.

	Univariable OR (95% CI)	Multivariable OR (95% CI)
Age ≥65 years old	3.37 (3.20–3.56)	3.58 (3.38–3.79)
Female	0.35 (0.33–0.37)	0.42 (0.39–0.45)
BMI ≥25	1.02 (0.97–1.07)	0.94 (0.89–0.99)
Smoking status (reference: never smoker)		
Ex-smoker	2.69 (2.54–2.85)	1.33 (1.22–1.45)
Current smoker	2.19 (2.05–2.33)	1.42 (1.30–1.56)
Asthma	2.23 (1.95–2.55)	2.05 (1.77–2.38)
COPD	4.05 (2.96–5.66)	2.03 (1.42–2.95)
History of pulmonary tuberculosis	2.09 (1.88–2.32)	1.70 (1.51–1.91)
History of lung cancer	7.78 (3.52–20.56)	4.99 (2.11–13.85)
White blood cell, 1000/μL	1.09 (1.08–1.11)	1.02 (1.00–1.03)
Annual change of NO_2, /quartile	1.10 (1.08–1.12)	1.10 (1.08–1.12)
Annual change of O_3, /quartile	1.06 (1.09–1.42)	1.03 (1.00–1.05)
Annual change of $PM_{2.5}$, /quartile	1.02 (1.00–1.04)	1.03 (1.00–1.05)
Annual change of SO_2, /quartile	1.06 (1.04–1.09)	1.04 (1.02–1.08)
Annual change of CO, /quartile	1.18 (1.16–1.20)	1.16 (1.12–1.19)

Note: The multivariable analyses included the following covariables: age, gender, BMI, smoking status, asthma, COPD, history of pulmonary tuberculosis, history of lung cancer and white blood cell counts. In each subgroup analysis, other covariables except for the category variable were adjusted for.
Abbreviation: COPD, chronic obstructive pulmonary disease.

TABLE 4 Combined effects of air pollutant changes on small airway dysfunction in total population and subgroup populations.

	Univariable OR (95% CI)	Multivariable OR (95% CI)
Total	1.33 (1.28–1.38)	1.31 (1.26–1.35)
Age		
≥65 years old	1.40 (1.29–1.52)	1.39 (1.27–1.52)
<65 years old	1.31 (1.25–1.37)	1.31 (1.26–1.36)
Sex		
Male	1.48 (1.36–1.62)	1.46 (1.34–1.60)
Female	1.24 (1.14–1.35)	1.23 (1.12–1.34)
BMI		
≥25	1.39 (1.28–1.50)	1.34 (1.24–1.45)
<25	1.29 (1.23–1.36)	1.27 (1.22–1.33)
Smoking status		
Never smoker	1.27 (1.17–1.38)	1.25 (1.15–1.36)
Ex-smoker	1.51 (1.39–1.63)	1.50 (1.41–1.59)
Current smoker	1.40 (1.28–1.52)	1.38 (1.27–1.49)
Comorbidities		
With asthma	1.60 (1.32–1.93)	1.62 (1.34–1.96)
Without asthma	1.33 (1.30–1.35)	1.30 (1.28–1.32)
With COPD	1.53 (0.68–3.43)	1.77 (0.92–3.40)
Without COPD	1.33 (1.26–1.40)	1.31 (1.25–1.37)
With history of pulmonary tuberculosis	1.71 (1.46–2.01)	1.63 (1.41–1.88)
Without history of pulmonary tuberculosis	1.32 (1.29–1.37)	1.30 (1.27–1.33)
With history of lung cancer	2.85 (0.10–78.79)	0.83 (0.03–27.15)
Without history of lung cancer	1.33 (1.29–1.36)	1.31 (1.28–1.34)
White blood cell		
≥6000/μL	1.35 (1.28–1.44)	1.37 (1.29–1.45)
<6000/μL	1.29 (1.22–1.36)	1.26 (1.21–1.31)

Note: The combined effect of air pollutant changes was estimated for an equal quartile increment of each air pollutant change. The multivariable analyses included the following covariables: age, gender, BMI, smoking status, asthma, COPD, history of pulmonary tuberculosis, history of lung cancer and white blood cell counts. In each subgroup analysis, other covariables except for the category variable were adjusted for.

significantly different between the two groups, with larger increases or smaller decreases of median concentrations associated with SAD (p-value <0.001). In addition, a larger increase or a smaller decrease of NO_2, O_3, $PM_{2.5}$, SO_2 and CO was found in the group with SAD compared those without SAD.

Linear relationship with $FEF_{25\%–75\%}$

The linear relationships between $FEF_{25\%–75\%}$ and air pollutant changes were summarized in Table S4 and Table S5 in the Supporting Information. $FEF_{25\%–75\%}$ showed significant linear relationships with the quartiles of NO_2, O_3, $PM_{2.5}$, SO_2 and CO changes and the annual change of the individual air pollutants in univariable analyses. In multivariable analyses, $FEF_{25\%–75\%}$ was significantly negatively associated with an increase of 1 quartile in the annual change of NO_2 ($\beta = -2.04$ [95% CI $= -2.43$ to -1.65]), $PM_{2.5}$ ($\beta = -2.68$ [95% CI $= -3.07$ to -2.29]), SO_2 ($\beta = -2.92$ [95% CI $= -3.31$ to -2.53]) and CO ($\beta = -4.78$ [95% CI $= -5.21$ to -4.36]).

There were weak associations between annual changes of different air pollutants (Table S6 in the Supporting Information). The combined effect of air pollutant changes was significantly associated with $FEF_{25\%–75\%}$ after adjusting covariables ($\beta = -12.7$ [95% CI $= -13.2$ to -11.9], Table S7 in the Supporting Information). The combined effect of air pollutant changes on $FEF_{25\%–75\%}$ was consistently observed across different demographic and clinical subgroups, except for those with the history of lung cancer. The contributions of individual air pollutant changes to the combined effect on $FEF_{25\%–75\%}$ were as follows: CO = 37.7%, SO_2 = 22.9%, $PM_{2.5}$ = 21.1%, NO_2 = 16.2% and O_3 = 2.1% (Figure S1 in the Supporting Information).

Association with SAD

Significant relationships between SAD and air pollutant changes were found in multivariable analyses (Table 3). SAD was significantly associated with an increase of

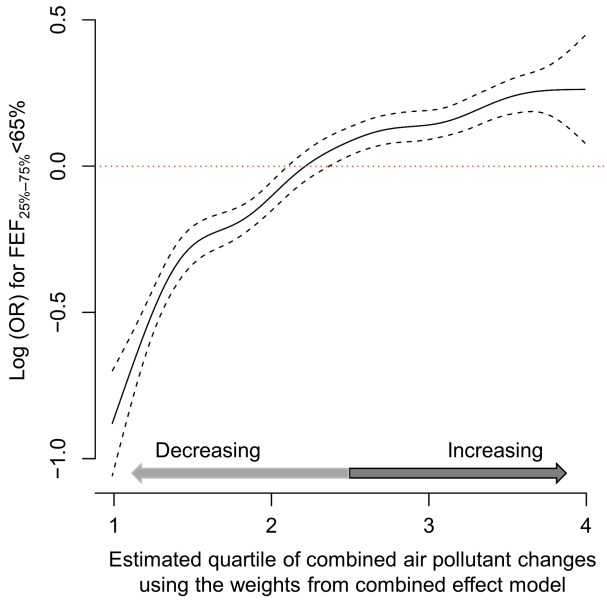

FIGURE 2 The weighted effect of changes in air pollutants on small airway dysfunction. The log (OR) for $FEF_{25\%-75\%}$ <65% was calculated in the generalized additive model by combining the weighted quartiles of change in air pollutants into a single continuous variable for individual patients.

1 quartile in the annual change of NO_2 (OR = 1.10 [95% CI = 1.08–1.12]), O_3 (OR = 1.03 [95% CI = 1.00–1.05]), $PM_{2.5}$ (OR = 1.03 [95% CI = 1.00–1.05]), SO_2 (OR = 1.04 [95% CI = 1.02–1.08]) and CO (OR = 1.16 [95% CI = 1.12–1.19]). In addition, annually increased concentrations of NO_2, O_3, $PM_{2.5}$ and CO were associated with a higher risk of SAD (Table S8 in the Supporting Information).

The combined effect of air pollutant changes was significantly associated with SAD after adjusting covariables (OR = 1.31 [95% CI = 1.26–1.35], Table 4). The combined effect of air pollutant changes on SAD was consistently observed across different demographic and clinical subgroups, except for those with COPD or the history of lung cancer. The contributions of individual air pollutant changes to the combined effect on SAD were as follows: CO = 47.8%, NO_2 = 28.1%, $PM_{2.5}$ = 8.4%, O_3 = 8.2% and SO_2 = 7.6% (Figure S2 in the Supporting Information). In the combined effect model, third or fourth quartile of combined air pollutant changes showed an increased risk of SAD, while first or second quartile of them showed a decreased risk of SAD (Figure 2).

DISCUSSION

Our findings indicate that the impact of changes in air pollutant concentrations over time is of great importance on SAD. Our study revealed significant associations between annual changes in NO_2, O_3, $PM_{2.5}$, SO_2 and CO concentrations and SAD. While the included subjects predominantly comprised females with a normal BMI, exhibiting distinct characteristics from Western cohort populations, the combined effect of the air pollutant changes on SAD remained consistent across various demographic and clinical subgroups, emphasizing its robustness.[26,27] When assessing SAD risk based on individual exposure to air pollutants using a combined effect model, we observed a nearly linear relationship in log odds for SAD occurrence according to the estimated risk. This suggests that as the combined effect increases, the risk of SAD increases linearly. Our results underscore the importance of considering the combined effects of multiple air pollutants and their changes over time for a comprehensive assessment of small airway function in real-world atmospheric conditions.

Despite the clinical relevance of SAD, its association with air pollutants has not received sufficient attention to date. SAD affects approximately 43.5% of the general population and is recognized as a risk factor for chronic airway diseases such as asthma, COPD and bronchiectasis.[16,27–29] The presence of SAD also increases the risk of acute exacerbations in individuals with chronic airway diseases.[30] Few studies have reported on the combined effects of different air pollutants on SAD. In a pilot prospective study, exposure to various air pollutants was associated with an increased risk of SAD.[31] However, given that the concentrations of various air pollutants changed annually, there have been uncertainties regarding the specific combined impacts of these changes on SAD. Our study provided evidence that the increased concentrations of multiple air pollutants may contribute to the pathogenesis of SAD.

Our study suggests that when calculating the individual effects of air pollutants in a simple manner, there is a possibility of overestimating the overall effect of all air pollutants on SAD. Among the 31,362 individuals without COPD, the combined effect of CO, NOx, $PM_{2.5}$, PM_{10} and SO_2 was associated with the incidence of COPD.[32] In the analysis of the combined effect of NO_2, O_3, $PM_{2.5}$, SO_2 and CO on children with asthma, each 1-quartile increase in the combined effect was associated with a 13% increase in emergency room visits.[33] In a recent study, the combined effect of air pollutants had an impact on cardiopulmonary mortality, with $PM_{2.5}$ being identified as the major contributor.[34] The World Health Organization currently provides the estimates of the combined effect of ambient air pollution and household air pollution on all-cause mortality, revealing distinct differences in attributable death rates across countries.[35] Analysing the combined effect of individual air pollutants and their respective contributing proportions will become increasingly important.

$FEF_{25\%-75\%}$ has been widely used as a marker for SAD due to its sensitivity and potential to detect early pathological changes.[36,37] It has been reported that an increase in $PM_{2.5}$ or PM_{10} concentrations is associated with a decrease in $FEF_{25\%-75\%}$.[2,38–40] Additionally, an increase in NO_2 and SO_2 has been associated with a decrease in $FEF_{25\%-75\%}$.[41] Moreover, exposure to a higher carbon content, leading to increased airway macrophage

exposure, is also associated with a decrease in $FEF_{25\%-75\%}$.[40] We also observed a similar pattern where increases in NO_2, O_3, $PM_{2.5}$, CO and SO_2 were temporally associated with a decrease in $FEF_{25-75\%}$ across multiple groups. $FEF_{25\%-75\%}$ may serve as a sensitive indicator of early changes in chronic airway diseases in response to air pollutant changes. However, $FEF_{25\%-75\%}$ can be highly variable, poorly reproducible and influenced by FVC.[42] These limitations should be acknowledged in the interpretation of results.

In this study, several strengths contribute to the robustness and reliability of our findings. Firstly, the utilization of the KNHANES database provides a nationally representative sample, enhancing the generalizability of our results. Secondly, the application of novel statistical methods, such as the quantile g-Computation model, allows for a comprehensive analysis of the combined effects of multiple air pollutants on small airway. This methodological approach adds depth to our understanding, especially in the context of real-world atmospheric environments where various complex air pollutants coexist. Thirdly, our study is distinguished by its meticulous adjustment for confounding factors, including information on smoking status.

Our study has several limitations. First, due to the nature of retrospective study design, unmeasured confounding factors (e.g., blood eosinophil count) were not fully controlled in our analysis. Additionally, underlying lung conditions such as COPD or asthma were assessed based on subjects' self-reports, which introduces the possibility of underestimating the true prevalence.[43] Second, the information on lung function measurements before exposure to air pollutants was not available, which prevented us from analysing the combined effect of air pollutant changes on lung function changes. Third, this study was conducted under the assumption that air pollutants would exhibit linear changes over a 5-year period in each specific region. Our results may not be generalizable to regions where air pollutant concentrations exhibit dynamic annual variations. Fourth, the transformation of annual changes in the air pollutant concentrations into quartiles for estimating the combined effect made the interpretation of our results challenging.

In conclusion, we found that the annual changes in air pollutant concentrations were associated with SAD. The combined effect of air pollutant changes showed consistent associations with SAD across different demographic and clinical subgroups. This finding emphasized the importance of considering measures to improve combined effects by reducing multiple air pollutants simultaneously, rather than focusing solely on reducing a specific air pollutant, in policy considerations.

AUTHOR CONTRIBUTIONS

Hyun Woo Lee: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); software (equal); supervision (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **Hyo Jin Lee:** Data curation (equal); writing – review and editing (equal). **Sohee Oh:** Formal analysis (equal); methodology (equal); software (equal); writing – review and editing (equal). **Jung-Kyu Lee:** Investigation (equal); methodology (equal); writing – review and editing (equal). **Eun Young Heo:** Investigation (equal); methodology (equal); writing – review and editing (equal). **Deog Kyeom Kim:** Investigation (equal); methodology (equal); writing – review and editing (equal).

FUNDING INFORMATION

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in at https://knhanes.kdca.go.kr/knhanes/sub09/sub09_04.do.

HUMAN ETHICS APPROVAL DECLARATION

We followed the ethical guidance of the Declaration of Helsinki in 1975. The Institutional Review Board (IRB) Committee of Seoul National University-Seoul Metropolitan Government (SNU-SMG) Boramae Medical Center approved the present study protocol (IRB No. 07-2023-18). The Korean Centers for Disease Control and Prevention obtained written informed consent from each person prior to the survey.

ORCID

Hyun Woo Lee https://orcid.org/0000-0003-4379-0260
Jung-Kyu Lee https://orcid.org/0000-0001-5060-7255
Eun Young Heo https://orcid.org/0000-0003-3803-4903
Deog Kyeom Kim https://orcid.org/0000-0001-9379-8098

REFERENCES

1. Doiron D, de Hoogh K, Probst-Hensch N, Fortier I, Cai Y, De Matteis S, et al. Air pollution, lung function and COPD: results from the population-based UK Biobank study. Eur Respir J. 2019;54:54.
2. Chen CH, Wu CD, Chiang HC, Chu D, Lee KY, Lin WY, et al. The effects of fine and coarse particulate matter on lung function among the elderly. Sci Rep. 2019;9:14790.
3. Park J, Kim HJ, Lee CH, Lee CH, Lee HW. Impact of long-term exposure to ambient air pollution on the incidence of chronic obstructive pulmonary disease: a systematic review and meta-analysis. Environ res. 2021;194:110703.
4. Dauchet L, Hulo S, Cherot-Kornobis N, Matran R, Amouyel P, Edmé JL, et al. Short-term exposure to air pollution: associations with lung function and inflammatory markers in non-smoking, healthy adults. Environ Int. 2018;121:610–9.
5. Anenberg SC, Mohegh A, Goldberg DL, Kerr GH, Brauer M, Burkart K, et al. Long-term trends in urban NO(2) concentrations and associated paediatric asthma incidence: estimates from global datasets. Lancet Planet Health. 2022;6:e49–58.
6. Niu Y, Yang T, Gu X, Chen R, Meng X, Xu J, et al. Long-term ozone exposure and small airway dysfunction: the China

Pulmonary Health (CPH) study. Am J Respir Crit Care Med. 2022; 205:450–8.
7. Holm SM, Balmes JR. Systematic review of ozone effects on human lung function, 2013 through 2020. Chest. 2022;161:190–201.
8. Kopp MV, Bohnet W, Frischer T, Ulmer C, Studnicka M, Ihorst G, et al. Effects of ambient ozone on lung function in children over a two-summer period. Eur Respir J. 2000;16:893–900.
9. Canova C, Torresan S, Simonato L, Scapellato ML, Tessari R, Visentin A, et al. Carbon monoxide pollution is associated with decreased lung function in asthmatic adults. Eur Respir J. 2010;35: 266–72.
10. Silkoff PE, Zhang L, Dutton S, Langmack EL, Vedal S, Murphy J, et al. Winter air pollution and disease parameters in advanced chronic obstructive pulmonary disease panels residing in Denver, Colorado. J Allergy Clin Immunol. 2005;115:337–44.
11. Park JW, Lim YH, Kyung SY, An CH, Lee SP, Jeong SH, et al. Effects of ambient particulate matter on peak expiratory flow rates and respiratory symptoms of asthmatics during Asian dust periods in Korea. Respirology. 2005;10:470–6.
12. Penttinen P, Timonen KL, Tiittanen P, Mirme A, Ruuskanen J, Pekkanen J. Ultrafine particles in urban air and respiratory health among adult asthmatics. Eur Respir J. 2001;17:428–35.
13. Rodríguez-Villamizar LA, Rojas-Roa NY, Fernández-Niño JA. Short-term joint effects of ambient air pollutants on emergency department visits for respiratory and circulatory diseases in Colombia, 2011–2014. Environmental Pollut. 2019;248:380–7.
14. Kweon S, Kim Y, Jang MJ, Kim Y, Kim K, Choi S, et al. Data resource profile: the Korea National Health and Nutrition Examination Survey (KNHANES). Int J Epidemiol. 2014;43:69–77.
15. https://knhanes.kdca.go.kr/knhanes/sub09/sub09_03.do [last access date: 2023.06.26].
16. Xiao D, Chen Z, Wu S, Huang K, Xu J, Yang L, et al. Prevalence and risk factors of small airway dysfunction, and association with smoking, in China: findings from a national cross-sectional study. Lancet Respir Med. 2020;8:1081–93.
17. Ciprandi G, Capasso M, Tosca M, Salpietro C, Salpietro A, Marseglia G, et al. A forced expiratory flow at 25-75% value <65% of predicted should be considered abnormal: a real-world, cross-sectional study. Allergy Asthma Proc. 2012;33:e5–8.
18. Koo YS. Roadmap development for research on the health impact of ambient air pollution and establishment of ambient air pollution dataset for national survey and cohort data [last access 2023.10.01]. National Center for Medical Information and Knowledge. Available from: https://library.nih.go.kr/ncmiklib/synap/skin/doc.html?fn=9ddc6dba43dc96dff055d7095f0e667873536a91e07ac070357f7a423748a290&rs=/romsn/ncmik/st1/synap/202310&fileKey=86718 2020.
19. Choi D, Yun H, Koo Y. A development of air quality forecasting system with data assimilation using surface measurements in East Asia. Available from: https://www.jekosae.or.kr/_common/do.php?a=full&b=41&bidx=1416&aidx=18367
20. Koo Y, Choi D, Yun H, Yoon G, Lee J. A development of PM concentration reanalysis method using CMAQ with surface data assimilation and MAIAC AOD in Korea. J Korean Soc Atmos Environ. 2020;36: 558–73.
21. Lee Y, Shindell DT, Faluvegi G, Wenig M, Lam Y, Ning Z, et al. Increase of ozone concentrations, its temperature sensitivity and the precursor factor in South China. Tellus B Chem Phys Meteorol. 2014;66:23455.
22. Fann N, Coffman E, Timin B, Kelly JT. The estimated change in the level and distribution of PM(2.5)-attributable health impacts in the United States: 2005-2014. Environ Res. 2018;167: 506–14.
23. González-Pardo J, Ceballos-Santos S, Manzanas R, Santibáñez M, Fernández-Olmo I. Estimating changes in air pollutant levels due to COVID-19 lockdown measures based on a business-as-usual prediction scenario using data mining models: a case-study for urban traffic sites in Spain. Sci Total Environ. 2022;823:153786.
24. Keil AP, Buckley JP, O'Brien KM, Ferguson KK, Zhao S, White AJ. A quantile-based g-Computation approach to addressing the effects of exposure mixtures. Environ Health Perspect. 2020;128:47004.
25. Xu J, Shi Y, Chen G, Guo Y, Tang W, Wu C, et al. Joint effects of long-term exposure to ambient fine particulate matter and ozone on asthmatic symptoms: prospective cohort study. JMIR Public Health Surveill. 2023;9:e47403.
26. Ioachimescu OC, Stoller JK. Assessing small airway disease in GLI versus NHANES III based spirometry using area under the expiratory flow-volume curve. BMJ Open Respir Res. 2019;6: e000511.
27. Postma DS, Brightling C, Baldi S, Van den Berge M, Fabbri LM, Gagnatelli A, et al. Exploring the relevance and extent of small airways dysfunction in asthma (ATLANTIS): baseline data from a prospective cohort study. Lancet Respir Med. 2019;7:402–16.
28. Hogg JC, Chu F, Utokaparch S, Woods R, Elliott WM, Buzatu L, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. N Engl J Med. 2004;350:2645–53.
29. Everaerts S, McDonough JE, Verleden SE, Josipovic I, Boone M, Dubbeldam A, et al. Airway morphometry in COPD with bronchiectasis: a view on all airway generations. Eur Respir J. 2019;54: 1802166.
30. Kraft M, Richardson M, Hallmark B, Billheimer D, Van den Berge M, Fabbri LM, et al. The role of small airway dysfunction in asthma control and exacerbations: a longitudinal, observational analysis using data from the ATLANTIS study. Lancet Respir Med. 2022;10:661–8.
31. Niyatiwatchanchai N, Pothirat C, Chaiwong W, Liwsrisakun C, Phetsuk N, Duangjit P, et al. Short-term effects of air pollutant exposure on small airway dysfunction, spirometry, health-related quality of life, and inflammatory biomarkers in wildland firefighters: a pilot study. Int J Environ Health Res. 2023;33(9):850–63.
32. Hendryx M, Luo J, Chojenta C, Byles JE. Air pollution exposures from multiple point sources and risk of incident chronic obstructive pulmonary disease (COPD) and asthma. Environ Res. 2019; 179:108783.
33. Winquist A, Kirrane E, Klein M, Strickland M, Darrow LA, Sarnat SE, et al. Joint effects of ambient air pollutants on pediatric asthma emergency department visits in Atlanta, 1998-2004. Epidemiology. 2014; 25:666–73.
34. Huang W, Zhou Y, Chen X, Zeng X, Knibbs LD, Zhang Y, et al. Individual and joint associations of long-term exposure to air pollutants and cardiopulmonary mortality: a 22-year cohort study in Northern China. Lancet Reg Health West Pac. 2023;36:100776.
35. https://www.who.int/data/gho/data/themes/topics/indicator-groups/indicator-group-details/GHO/joint-effects-of-air-pollution [last access date: 2023.06.26].
36. Alobaidi NY, Almeshari M, Stockley J, Stockley RA, Sapey E. Small airway function measured using forced expiratory flow between 25% and 75% of vital capacity and its relationship to airflow limitation in symptomatic ever-smokers: a cross-sectional study. BMJ Open Respir Res. 2022;9:e001385.
37. Qin R, An J, Xie J, Huang R, Xie Y, He L, et al. FEF(25-75)% is a more sensitive measure reflecting airway dysfunction in patients with asthma: a comparison study using FEF(25-75)% and FEV(1). J Allergy Clin Immunol Pract. 2021;9:3649–59.e6.
38. Yang T, Chen R, Gu X, Xu J, Yang L, Zhao J, et al. Association of fine particulate matter air pollution and its constituents with lung function: the China Pulmonary Health study. Environ Int. 2021;156: 106707.
39. Islam T, Gauderman WJ, Berhane K, McConnell R, Avol E, Peters JM, et al. Relationship between air pollution, lung function and asthma in adolescents. Thorax. 2007;62:957–63.

40. Kulkarni N, Pierse N, Rushton L, Grigg J. Carbon in airway macrophages and lung function in children. N Engl J Med. 2006;355:21–30.
41. Havet A, Hulo S, Cuny D, Riant M, Occelli F, Cherot-Kornobis N, et al. Residential exposure to outdoor air pollution and adult lung function, with focus on small airway obstruction. Environ Res. 2020; 183:109161.
42. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26:948–68.
43. Yoo KH, Kim YS, Sheen SS, Park JH, Hwang YI, Kim SH, et al. Prevalence of chronic obstructive pulmonary disease in Korea: the fourth Korean National Health and Nutrition Examination Survey, 2008. Respirology. 2011;16:659–65.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Lee HW, Lee HJ, Oh S, Lee J-K, Heo EY, Kim DK. Combined effect of changes in NO_2, O_3, $PM_{2.5}$, SO_2 and CO concentrations on small airway dysfunction. Respirology. 2024;29(5):379–86. https://doi.org/10.1111/resp.14687