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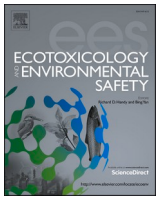

The effect of long-term exposure to a mixture of air pollutants on chronic obstructive pulmonary disease

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a major global cause of morbidity and mortality; however, evidence on the effects of air pollutant mixtures on COPD remains limited. This study assessed the impact of long-term exposure to multiple pollutants on COPD prevalence and identified vulnerable subgroups. We analyzed Korea National Health and Nutrition Examination Survey (2010–2017) data linked to 5-year moving average concentrations of CO, NO_2, SO_2, O_3, $PM_{2.5}$, and PM_{10}. Bayesian kernel machine regression (BKMR) estimated the combined effects of pollutants on COPD prevalence, with subgroup analyses performed according to sex, smoking status, and airflow limitation. Adjustments included age, sex, BMI, smoking status, and household income. Among 21,804 participants, 3515 had COPD. BKMR analysis showed that long-term exposure to a pollutant mixture was associated with increased COPD prevalence. O_3 and NO_2 were identified as the most influential pollutants (posterior inclusion probabilities > 0.50). Further analysis showed a significant increase in COPD risk with higher NO_2 and O_3 concentrations, particularly when other pollutants were at lower or median levels. Significant interactions were observed, particularly between SO_2 and CO, CO and O_3, and NO_2 and O_3. Subgroup analyses identified vulnerable populations, indicating stronger associations among females and never smokers and more pronounced effects in individuals with GOLD 2–4. These findings suggest that long-term exposure to multiple air pollutants could increase COPD risk, particularly for females, never smokers, and individuals with more severe COPD. Targeted interventions and policy measures are needed to reduce exposure, especially for these at-risk populations.

1. Introduction

Chronic respiratory diseases rank as the third leading cause of death globally, with chronic obstructive pulmonary disease (COPD) being the most prevalent (GBD Chronic Respiratory Disease Collaborators, 2020). COPD poses a significant public health burden, affecting an estimated 10.6 % of the population in 2020, with approximately 480 million cases reported worldwide (Boers et al., 2023). This burden is expected to increase considerably in the coming decades, with projections indicating a 23 % increase in cases among individuals aged 25 years and older, reaching nearly 600 million by 2050 (Boers et al., 2023). The impact of COPD is anticipated to be particularly pronounced among females and populations in low- and middle-income regions, exacerbating existing health disparities. Additionally, the economic burden of COPD is substantial, with global costs projected to surpass INT$4.3 trillion between 2020 and 2050 (Chen et al., 2023). Given these estimates, COPD represents not only a growing health crisis but also a significant economic challenge, underscoring the urgent need for targeted interventions and policy measures to mitigate its impact.

Although cigarette smoking has long been recognized as a significant risk factor for COPD, growing evidence suggests that environmental exposures, such as ambient air pollution, indoor pollutants, and

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occupational exposure, may also play a crucial role in its pathogenesis (Stolz et al., 2022). In particular, worsening air pollution is an increasing concern in East Asia due to socioeconomic factors and reliance on fossil fuel sources (Lelieveld et al., 2015). As air pollution continues to increase in this region, understanding its long-term impact on COPD has become even more crucial for shaping effective public health strategies and mitigating disease burden.

COPD is a heterogeneous lung condition characterized by chronic respiratory symptoms resulting from abnormalities in the airways and/or alveoli, leading to persistent and often progressive airflow obstruction (Agustí et al., 2023). Among the potential mechanisms through which air pollution may contribute to COPD pathophysiology, oxidative stress and inflammatory damage have been widely suggested to play important roles (Duan et al., 2020). Oxidative stress in airway smooth muscles can induce airway hyperresponsiveness and airflow obstruction (Saunders et al., 2022). However, despite these plausible biological mechanisms, epidemiological evidence on the chronic effects of air pollutants on COPD prevalence remains inconsistent (Atkinson et al., 2015; Doiron et al., 2019; Guo et al., 2018; Schikowski et al., 2014; Weichenthal et al., 2017). Large-scale studies have reported mixed findings. For example, the European Study of Chronic Air Pollution Effects (ESCAPE) found no significant association between long-term exposure to nitrogen dioxide (NO_2) or particulate matter (PM) and COPD prevalence, except among women (Schikowski et al., 2014). On the other hand, a Canadian cohort study demonstrated that long-term exposure to NO_2 and PM2.5 was associated with an increased incidence of COPD (Weichenthal et al., 2017). Similarly, a study in Taiwan reported an increased risk of COPD with prolonged PM2.5 exposure (Guo et al., 2018). Additionally, chronic air pollution has been linked to a greater decline in lung function, particularly in women and former smokers. These conflicting results underscore the need for more rigorous research with robust methodologies and long-term studies to better assess the impact of air pollution on COPD.

Previous studies have provided valuable insights into the relationship between air pollution and COPD. However, most of these studies have examined the effects of individual air pollutants, which may not fully capture the complex interactions among multiple pollutants. In reality, individuals are exposed to pollutant mixtures rather than isolated pollutants, and failing to account for these interactions could lead to an underestimation of the true health effects of air pollution. Furthermore, COPD is a heterogeneous disease, and its association with air pollution may vary according to sex, smoking status, and disease severity. Identifying populations that are more vulnerable to air pollution is crucial for developing targeted prevention strategies. Therefore, building on prior research, this study aimed to assess the combined effects of long-term exposure to multiple air pollutants using a mixture analysis approach. Additionally, subgroup analyses were performed to identify high-risk populations, providing insights that may help refine public health interventions and policies.

2. Methods

2.1. Study population

The Korea National Health and Nutrition Examination Survey (KNHANES), administered by the Korea Disease Control and Prevention Agency (KDCA), is a comprehensive, nationwide survey aimed at evaluating the health and nutritional status of the South Korean population. Utilizing a stratified, multistage probability sampling design, the KNHANES ensures a representative national sample. The survey comprises health examinations and interviews conducted in mobile examination units, as well as nutrition surveys conducted via household interviews. Our study analyzed data from 25,362 individuals aged 40 years or older who underwent lung function tests during KNHANES phases V to VII (2010–2017).

2.2. Ambient air pollution

The KNHANES dataset was linked to an air pollution database based on the participants' residential addresses (converted into latitude and longitude coordinates) and survey year. Air pollutant concentrations in the database were estimated using the Community Multiscale Air Quality (CMAQ) model (US EPA Model-3 CMAQ version 4.7.1), enhanced by data assimilation and multiple regression analysis. To evaluate long-term exposure, we calculated the 5-year moving average concentrations (0–1825 days) of PM_{10}, $PM_{2.5}$, SO_2, NO_2, CO, and O_3 preceding the survey year.

2.3. Pulmonary function

In the KNHANES, pulmonary function tests (PFTs) were conducted on participants aged 40 years and older. From July 2007 to June 2016, a dry rolling seal spirometer (Model 2130) was utilized for PFTs, and since June 2016, the Vyntus Spiro spirometer has been employed. Participants underwent testing between 2 and 8 times, with additional measurements taken as necessary contingent upon their cooperation and health status. Individuals with a forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio of less than 0.7 were classified as the COPD group (Agustí et al., 2023). Based on the degree of airflow limitation, subjects with COPD were divided into two groups: mild COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD] 1, FEV1 $\geq$ 80 %) and moderate-to-very severe COPD (GOLD 2–4, FEV1 $<$ 80 %). Individuals with a FEV1/FVC ratio of 0.7 or greater and an FVC equal to or exceeding 80 % of the predicted value were categorized as the non-COPD group. Individuals presenting a FEV1/FVC ratio of 0.7 or greater but with a FVC less than 80 % of the predicted value were classified as the restrictive lung disease group and excluded from our analysis.

2.4. Covariates

Our analysis considered the following covariates: age, sex, body mass index (BMI), smoking status, and household income. Age was divided into four groups: 40–49, 50–59, 60–69, and $>$ 70 years. BMI was calculated by dividing weight in kilograms by height in meters squared and was classified into three categories ($<$ 23, 23–24.9, $\geq$ 25). Smoking status, derived from survey responses, was categorized as current smoker, former smoker, or never smoker. Household income level was divided into quartiles (lowest quartile, lower middle quartile, upper middle quartile, highest quartile).

2.5. Statistical analysis

We performed a comprehensive descriptive analysis to elucidate the characteristics of the study subjects. Categorical variables are presented as frequencies with percentages, whereas continuous variables are expressed as means with standard deviations (SDs). Student's *t*-test was utilized for comparisons of normally distributed continuous variables, and chi-square (χ^2) test was applied to assess the distribution of categorical variables.

We analyzed the 5-year moving average concentrations for six air pollutants and determined their respective quartiles, mean, and standard deviation. To ensure comparability and account for differences in measurement units and scales, all air pollutant concentrations were standardized and scaled prior to analysis, allowing for a more consistent evaluation of their relative effects in the Bayesian kernel machine regression (BKMR) model.

We conducted Spearman's rank correlation analyses to evaluate the correlations between the six air pollutants. To assess the risk of COPD associated with six types of air pollutants, we employed the BKMR model with a probit link function to investigate the relationship between a pollutant mixture and binary outcomes. Posterior inclusion

probabilities (PIPs) were calculated to determine the relative contribution of each air pollutant to COPD. The overall effects of the air pollutant mixture were assessed by estimating the difference in the probability of COPD when all pollutants were set at each 5th percentile interval between the 25th and 75th percentiles, compared to the mixture at the 50th percentile. Univariate pollutant-response functions for each air pollutant within the mixture were analyzed with all other pollutants fixed at their 50th percentile. The effects of individual pollutants on COPD were examined by comparing outcomes when the pollutant was at its 25th and 75th percentiles, while holding all other pollutants at the 25th, 50th, or 75th percentile. Pairwise interactions between pollutants were explored using a bivariate model; the association of each pollutant with COPD was estimated while fixing a second pollutant at the 25th, 50th, or 75th percentile and the remaining pollutants at the 50th percentile. Model fitting was performed using 10,000 iterations of the Markov Chain Monte Carlo (MCMC) sampler.

Subgroup analyses for BKMR were conducted based on sex, smoking status, and COPD severity. Separate BKMR analyses were performed for male and female participants. Associations were evaluated for each smoking status category: current smoker, former smoker, and never smoker. COPD patients were also analyzed according to the level of airflow limitation, with one analysis including non-COPD and mild COPD (GOLD 1), and another analysis including non-COPD and moderate-to-very severe COPD (GOLD 2–4).

All analyses were conducted using R Statistical Software (version 4.3.0; R Core Team 2023), with the "bkmr" package utilized for BKMR analyses. Statistical significance was determined at a threshold of $P < 0.05$.

3. Results

3.1. Demographic characteristics

After applying the exclusion criteria, a total of 21,804 subjects were enrolled in this study from the KNHANES database (Fig. 1). Table 1 summarizes the characteristics of the study participants, comprising 3515 COPD subjects and 18,289 non-COPD subjects. When categorized according to COPD severity, there were 1671 cases of GOLD 1 and 1844 cases of GOLD 2–4 (Table S1). The mean age was higher in the COPD group than in the non-COPD group (65.6 ± 9.5 vs. 55.4 ± 10.3, $P < 0.001$). Males were more prevalent in the COPD group than in the non-COPD group (72.7 % vs. 37.6 %, $P < 0.001$). There was a higher proportion of current or former smokers in the COPD group (67.9 %) compared to the non-COPD group (35.3 %). Furthermore, in the COPD group, the proportion of participants with household income in the lowest quartile was the highest (33.2 %), whereas in the non-COPD group, the proportion in the highest quartile was the greatest (31.5 %).

Table S2 summarizes the concentration of air pollutants in the study.

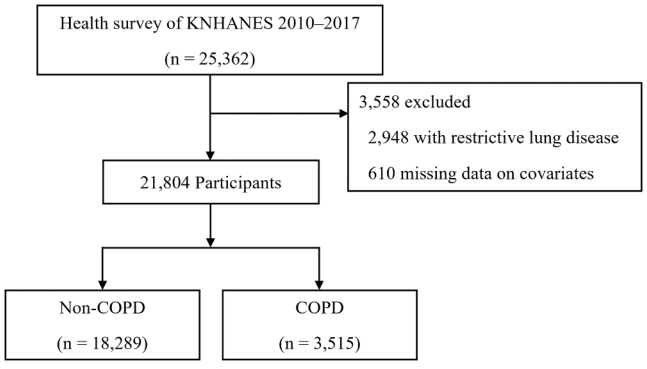

Fig. 1. Flowchart of the study participants. KNHANES, Korea National Health and Nutrition Examination Survey; COPD, chronic obstructive pulmonary disease.

Table 1
Baseline characteristics of participants.

Characteristics	Total (n = 21,804)	COPD (n = 3515)	Non-COPD (n = 18,289)	P-value
Age (years)	57.1 ± 10.8	65.6 ± 9.5	55.4 ± 10.3	< 0.001
Age group (years)				< 0.001
40–49	6364 (29.2)	232 (6.6)	6132 (33.5)	
50–59	6698 (30.7)	680 (19.3)	6018 (32.9)	
60–69	5278 (24.2)	1243 (35.4)	4035 (22.1)	
> 70	3464 (15.9)	1360 (38.7)	2104 (11.5)	
Sex				< 0.001
Male	9436 (43.3)	2554 (72.7)	6882 (37.6)	
Female	12,368 (56.7)	961 (27.3)	11,407 (62.4)	
BMI (kg/m^2)				< 0.001
< 23.0	13,457 (61.7)	2267 (64.5)	11,190 (61.2)	
23.0–24.9	7384 (33.9)	1091 (31.0)	6293 (34.4)	
≥ 25.0	963 (4.4)	157 (4.5)	806 (4.4)	
Smoking status				< 0.001
Current smoker	3843 (17.6)	1008 (28.7)	2835 (15.5)	
Former smoker	4999 (22.9)	1377 (39.2)	3622 (19.8)	
Never smoker	12,962 (59.5)	1130 (32.1)	11,832 (64.7)	
Household income				< 0.001
Lowest quartile	4287 (19.7)	1167 (33.2)	3120 (17.1)	
Lower middle quartile	5522 (25.3)	971 (27.6)	4551 (24.9)	
Upper middle quartile	5545 (25.4)	696 (19.8)	4849 (26.5)	
Highest quartile	6450 (29.6)	681 (19.4)	5769 (31.5)	
Pulmonary function				
FVC (%)	94.3 ± 10.5	89.6 ± 14.4	95.2 ± 9.4	< 0.001
FEV1 (%)	93.3 ± 13.2	78.2 ± 15.7	96.2 ± 10.3	< 0.001
FEV1/FVC (%)	76.9 ± 7.8	63.4 ± 6.9	79.5 ± 4.6	< 0.001

Data are presented as the mean ± SD or N (%).
COPD, chronic obstructive pulmonary disease; BMI, body mass index; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s.

The 5-year moving average concentrations were 50.44 μg/m^3 for PM_{10}, 25.20 μg/m^3 for $PM_{2.5}$, 0.005 ppm for SO_2, 0.02 ppm for NO_2, 0.49 ppm for CO, and 0.02 ppm for O_3 during the study period. The correlation coefficients among the air pollutants are presented in Fig. S1. The highest positive correlations were observed between PM_{10} and $PM_{2.5}$, CO and NO_2, and PM_{10} and CO, with correlation coefficients of 0.74, 0.74, and 0.73, respectively. O_3 exhibited strong negative correlations with CO, NO_2, and PM_{10}, with correlation coefficients of −0.83, −0.82, and −0.76, respectively.

3.2. Bayesian kernel machine regression (BKMR) model

Fig. 2 illustrates the overall combined effects of six air pollutants in the air pollutant mixture on COPD. The figure shows the outcome estimate differences when all air pollutants are set at a particular percentile, ranging from the 25th to 75th, compared to when all pollutants are fixed at the 50th percentile. A significant increasing trend in COPD prevalence was observed with an increasing concentration of the air pollutant mixture.

We examined the PIPs to assess the relative importance of each air pollutant in the association between exposure to the air pollutant mixture and COPD. Following the variable selection process in the BKMR model, O_3 and NO_2 were identified as key contributors, with PIPs exceeding 0.50 in more than 50 % of the MCMC iterations (Table S3).

The BKMR model demonstrated the univariate exposure-response relationship between individual air pollutants and COPD (Fig. S2). When each pollutant was fixed at the median level, the univariate exposure-response relationship demonstrated an upward trend in COPD prevalence for $PM_{2.5}$, CO, and NO_2. In contrast, O_3 exhibited a cubic polynomial curve, initially showing a decrease in COPD risk, followed by an increase, and then a sharp decrease.

We further explored the effects of exposure to a single air pollutant by assessing risk differences between the 75th and 25th percentiles,

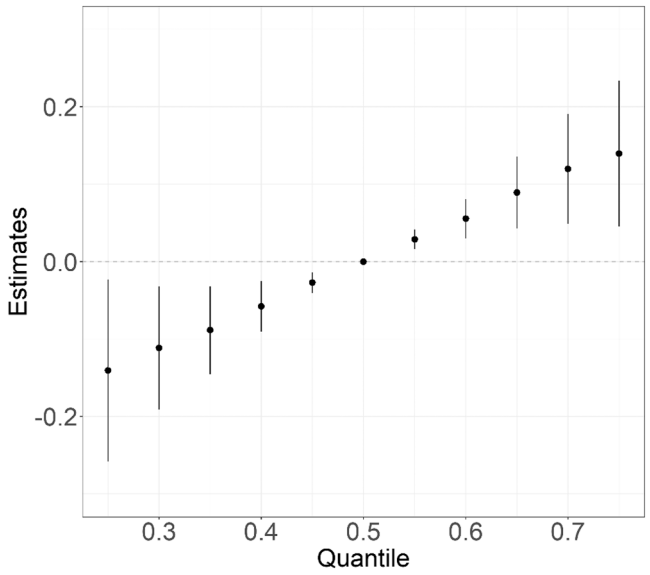

Fig. 2. Overall effects of a mixture of air pollutants on COPD. Estimates and 95 % confidence intervals are depicted by black dots with corresponding error bars. The model was adjusted for age, sex, BMI, smoking status, and household income.

while fixing other pollutants at the 25th, 50th, and 75th percentiles (Fig. S3). A significant increase in COPD risk was observed as the concentrations of NO_2 and O_3 increased from the 25th to the 75th percentile, while other pollutant concentrations were held constant at either the 25th or 50th percentiles.

Based on these findings, we assessed the interactions between air pollutants (Fig. S4). Each column represented environmental exposure 1, and each row represented exposure 2, with both set at the 25th, 50th, and 75th percentiles, while other exposures were fixed at their median levels. Potential interactions were identified between SO_2 and CO, CO and O_3, and NO_2 and O_3.

In sex-stratified BKMR analyses, a significant increasing trend in COPD risk was observed among females compared to males as the concentration of the air pollutant mixture was increased (Fig. 3). In smoking status-stratified BKMR analyses (current smoker, former smoker, and never smoker), a significant positive association between COPD and the concentration of the air pollutant mixture was identified among never smokers when all air pollutants exceeded the 50th percentile. An increasing trend was observed for current smokers; however, the association did not reach statistical significance. No significant association was observed for former smokers (Fig. 4). When stratified by disease severity, the association between air pollution and COPD was more pronounced among individuals with moderate-to-very severe COPD (GOLD 2–4) compared to those with mild COPD (GOLD 1) (Fig. 5).

4. Discussion

In this study, we found that long-term exposure to a mixture of air pollutants was associated with an increased prevalence of COPD. Among the pollutants analyzed, NO_2 and O_3 exhibited the strongest association with COPD prevalence, suggesting their potential role in disease progression. Additionally, we observed significant interactions between SO_2 and CO, CO and O_3, and NO_2 and O_3, indicating that pollutant interactions may influence COPD risk beyond the effects of individual pollutants. Subgroup analyses further revealed that the association between air pollution and COPD was more pronounced for females, never smokers, and individuals with more severe COPD (GOLD 2–4), highlighting the importance of identifying vulnerable populations. These findings emphasize the need to consider both pollutant interactions and population-specific susceptibility when assessing the impact of air pollution on COPD.

Epidemiological studies have long explored the relationship between air pollution and COPD, which have identified a strong association between $PM_{2.5}$ exposure and COPD prevalence (Doiron et al., 2019; Guo et al., 2018; Liu et al., 2017; Weichenthal et al., 2017). For example, studies in Taiwan and the UK reported that every 5 μg/m^3 increase in $PM_{2.5}$ was associated with 1.08-fold and 1.52-fold increases in COPD prevalence, respectively (Guo et al., 2018; Doiron et al., 2019). A meta-analysis of prospective longitudinal studies further demonstrated that a 10 μg/m^3 increase in $PM_{2.5}$ was associated with a 1.18 times higher incidence of COPD (Park et al., 2021). Ryu et al. suggested that $PM_{2.5}$ exposure could increase protease activity, contributing to COPD development (Ryu et al., 2022). Additionally, long-term O_3 exposure has been associated with an increased risk of COPD-related mortality in older adults (Kim et al., 2024).

However, most studies have assessed pollutants individually, potentially underestimating the broader impact of air pollutants as a mixture (Backhaus and Faust, 2012). Given the strong correlations and potential interactions among air pollutants, simultaneous exposure to multiple pollutants may modify their toxicities, leading to health effects that differ from the sum of individual effects (Silins and Högberg, 2011).

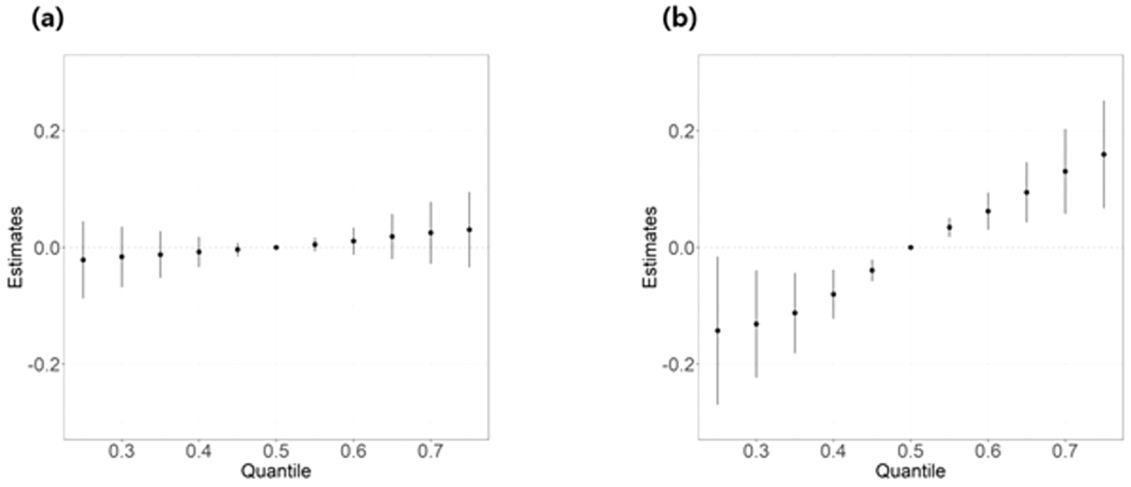

Fig. 3. Overall effects of a mixture of air pollutants on COPD stratified by sex: (a) males, (b) females. Estimates and 95 % confidence intervals are depicted by black dots with corresponding error bars. The model was adjusted for age, BMI, smoking status, and household income.

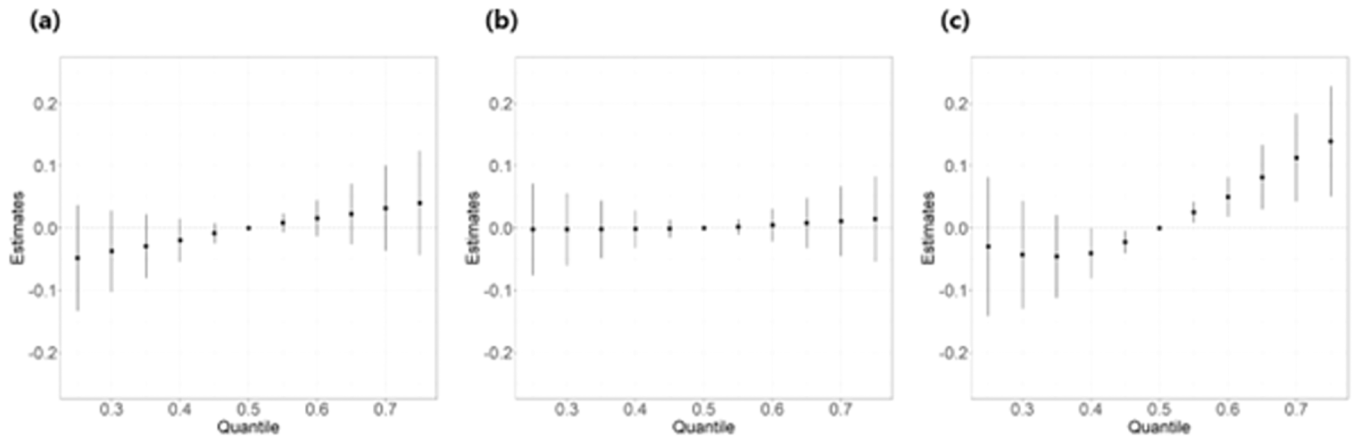

Fig. 4. Overall effects of a mixture of air pollutants on COPD stratified by smoking status: (a) current smoker, (b) former smoker, (c) never smoker. Estimates and 95 % confidence intervals are depicted by black dots with corresponding error bars. The model was adjusted for age, sex, BMI, and household income.

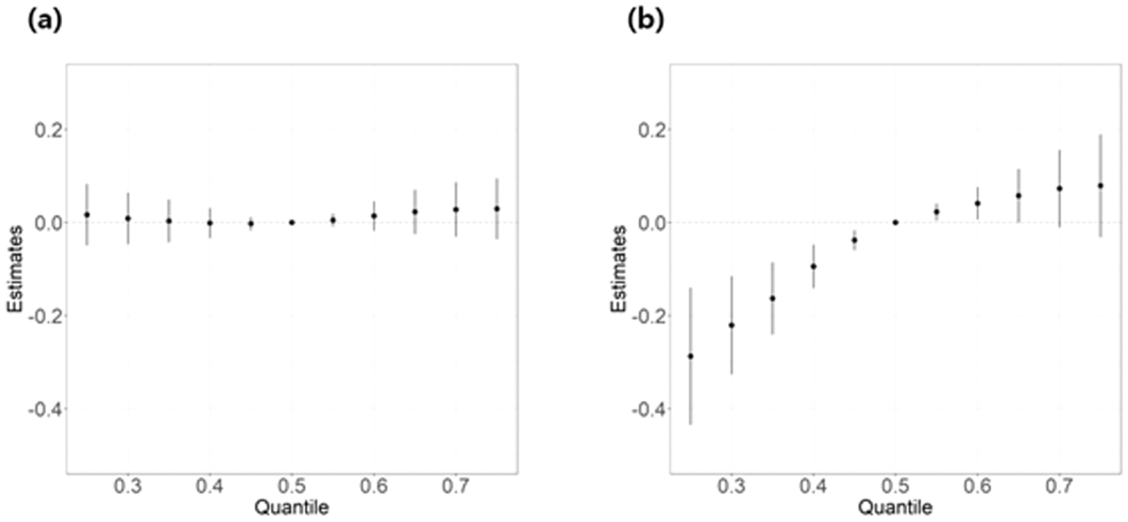

Fig. 5. Overall effects of a mixture of air pollutants on COPD stratified by the degree of airflow limitation: (a) GOLD 1, (b) GOLD 2, 3, and 4. Estimates and 95 % confidence intervals are depicted by black dots with corresponding error bars. The model was adjusted for age, sex, BMI, smoking status, and household income.

Furthermore, the health impact of each pollutant may depend on the concentration levels of others in the mixture (Fazakas et al., 2023), underscoring the need for a more comprehensive approach to evaluating the role of air pollution in COPD (Li et al., 2022).

To address this gap in research, we applied a mixture analysis approach to account for the correlations and interactions of pollutants when assessing their impact on COPD. Specifically, we employed BKMR, a non-parametric approach that can model complex, non-linear exposure-response relationships and identify key pollutants within a mixture. This method offers significant advantages over traditional single-pollutant models by allowing a more comprehensive assessment of cumulative and interactive effects. However, BKMR also has limitations, including its high computational demands due to reliance on MCMC algorithms and challenges in interpretability when compared to traditional regression models. Despite these constraints, BKMR provides valuable insights by detecting patterns that may not be identified using conventional methods. Our findings indicated that NO_2 and O_3 were the most significant pollutants; however, the contribution of $PM_{2.5}$ was relatively modest. Moreover, our analysis revealed a non-linear cubic polynomial relationship for O_3 exposure, reinforcing the importance of modeling non-linear effects when evaluating the health impact of air pollution. These findings, which cannot be obtained using traditional single-pollutant models, underscore the need for advanced mixture-based approaches that account for pollutant interactions and non-linearity, which can allow a more comprehensive assessment of the health effects of air pollution.

To the best of our knowledge, this is one of the few studies to apply a mixture analysis approach to examine the association between air pollution and COPD risk. A prior study by Kwon et al. (2024) also investigated air pollutant mixtures using quantile g-computation (qgcomp), a method that assumes linear or monotonic relationships when estimating overall mixture effects. Their findings, which demonstrated a significant association between long-term exposure to air pollutant mixtures and increased COPD risk, are consistent with our results. Although qgcomp offers a straightforward approach to estimating overall mixture effects, BKMR provides greater flexibility in capturing complex, non-linear relationships and pollutant interactions, allowing for a more nuanced understanding of exposure-response patterns. By leveraging BKMR, our study extends prior research by identifying key pollutants driving COPD risk, detecting interactions, and characterizing non-linear effects, thereby offering deeper insights into the health impact of air pollutant mixtures.

In addition to analyzing the overall association between air pollution and COPD, we conducted subgroup analyses according to sex, smoking status, and COPD severity considering that identifying vulnerable subpopulations is crucial for developing targeted strategies to reduce the

health impact of air pollution. Sex-stratified analyses revealed that air pollution had a stronger association with COPD prevalence among females than among males, suggesting that females may be more vulnerable to air pollution. This heightened susceptibility in females is unlikely to be explained by differences in smoking behavior, as the proportion of never smokers has been observed to be significantly higher among females than among males with COPD (Baek et al., 2024). Additionally, although biomass fuel exposure is a major risk factor for non-smoking-related COPD (Barnes, 2016), its use is minimal in Korea, making it an unlikely explanation for our findings. Instead, our results suggest that outdoor air pollutant mixtures may play a substantial role in COPD development among females. Several biological and physiological factors may contribute to this increased susceptibility. From an anatomical perspective, airway diameters are smaller in females than in males (Martinez et al., 2007). As a result, for the same level of air pollution, females may inhale higher concentrations of pollutants relative to the lung size, leading to greater airway damage (Chapman, 2004). Additionally, hormonal factors may play a role in sex differences in COPD susceptibility. Estrogen has been associated with lung function regulation (Cote and Chapman, 2009), and menopausal hypoestrogenism has been linked to lung function decline (Triebner et al., 2017). Although the exact mechanisms underlying sex differences in COPD susceptibility remain unclear, our findings support the hypothesis that females may be more vulnerable than males to the detrimental effects of air pollution. The results highlight the importance of considering sex differences in public health strategies aimed at reducing air pollution-related COPD risk.

Given that tobacco smoke exposure is a well-established major risk factor for COPD (Agustí et al., 2023; Stolz et al., 2022), we hypothesized that air pollution would have a stronger effect on COPD in smokers due to a potential synergistic effect between smoking and air pollution (Xu and Wang, 1998). However, our subgroup analyses revealed a stronger association between air pollution and COPD in never smokers than in current or former smokers, suggesting that individuals without prior long-term tobacco smoke exposure may be more susceptible to the harmful effects of air pollution. Chronic smoking induces sustained oxidative stress and inflammatory responses, which contribute to lung tissue damage (Agustí and Hogg, 2019) and abnormal lung repair (Hogg, 2004). As smoking and air pollution share common pathways in airway inflammation and pulmonary function decline, smoking might play a dominant role in smokers (Guo et al., 2018). Consequently, the additional exposure to air pollutants may not contribute to COPD risk to the same extent as in non-smokers, potentially masking the incremental effects of air pollution in this group. In contrast, never smokers may be more susceptible to the effects of air pollution. These findings are consistent with those of previous studies reporting a stronger association between air pollution and COPD in non-smokers (Doiron et al., 2019; Fisher et al., 2016; Schikowski et al., 2014). The mechanisms underlying COPD susceptibility in non-smokers remain unclear, and further prospective studies are needed to determine whether reducing exposure to air pollutants in this group could effectively lower COPD prevalence. Given that 25–45 % of COPD patients have never smoked (Salvi and Barnes, 2009) and that the proportion of never smokers with COPD is increasing, understanding the impact of air pollution on this growing population is crucial for public health strategies and disease prevention efforts (Ryu et al., 2024).

Additionally, we performed subgroup analyses according to COPD severity. Our findings demonstrated a stronger association between air pollution and COPD prevalence among patients with GOLD 2–4 compared to those with GOLD 1, suggesting that individuals with more severe COPD may be more vulnerable to the adverse effects of air pollution. A decline in FEV_1 is a crucial predictor of morbidity and mortality in COPD (Young et al., 2007) and is strongly associated with frequent acute exacerbations (Halpin et al., 2012; Makris et al., 2007). Given that previous large-scale cross-sectional studies have associated higher exposure to individual air pollutants with lower lung function (Doiron et al., 2019; Elbarbary et al., 2020), it is possible that long-term exposure to pollutant mixtures may accelerate lung function decline in COPD patients. For instance, Doiron et al. (2019) reported that a 5 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with an 83 mL decrease in FEV_1, and a 10 $\mu g/m^3$ increase in NO_2 corresponded to a 34 mL decrease. Considering these findings, patients with severe COPD may experience greater functional impairment when exposed to long-term air pollution, highlighting the urgent need for targeted air quality policies and protective measures for this high-risk population.

This study has several strengths, including the use of a nationwide representative dataset, an advanced mixture analysis approach to assess pollutant interactions and non-linear effects, and subgroup analyses to identify vulnerable populations, such as females, never smokers, and patients with severe COPD. However, several limitations should be considered when interpreting our findings. First, as the KNHANES is a cross-sectional survey and PFTs were conducted only once, there is a possibility that patients already diagnosed with COPD may have been included. This makes it difficult to confirm the causal relationship between air pollution and the incidence of COPD. Further prospective studies are necessary to elucidate more clearly the effect of air pollutant mixtures on COPD development. Second, we used the average air pollutant concentrations over the past 5 years based on the baseline residential address due to the cross-sectional nature of the KNHANES, which does not account for any changes in residence during this period. Third, patients with COPD who were treated with inhalers could have been misclassified as part of the non-COPD group. Lastly, the influence of indoor air pollution and occupational exposure was not considered, which could have introduced bias to the results.

5. Conclusions

The findings of our study provide strong evidence indicating that long-term exposure to a mixture of air pollutants may be associated with an increased risk of COPD. Additionally, we identified subpopulations of COPD patients, including females and never smokers, who may be particularly vulnerable to outdoor air pollution. These results highlight the critical need to reduce air pollution levels as part of COPD prevention strategies and emphasize the importance of targeted interventions to protect high-risk groups. Further research is needed to replicate these findings in prospective cohort studies and to elucidate the underlying mechanisms through which air pollution contributes to COPD progression, particularly in vulnerable subpopulations.

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of Chung-Ang University (1041078–20231007-HR-279). Informed consent was waived because the data analyses were performed retrospectively using anonymized data from the South Korean KNHANES database. The present study complied with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

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CRediT authorship contribution statement

Kim Chung Ho: Writing – original draft, Methodology, Formal analysis, Data curation. **Park Bomi:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Baek Moon Seong:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Moon Seong Baek reports financial support was provided by Chung Ang University Hospital. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Not applicable.

Consent for publication

Not applicable.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2025.117978.

Data availability

Data will be made available on request.

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